Title
Methodological Issues in Exposure Assessment for Studies of Childhood Leukemia

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Publication Date
2010

Peer reviewed|Thesis/dissertation

Methodological Issues in Exposure Assessment for Studies of Childhood Leukemia

by

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A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Epidemiology

in the

Graduate Division

of the

University of California, Berkeley

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Fall 2010

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ABSTRACT

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This dissertation examined several methodological aspects of case control studies potentially influencing the association of environmental exposures with the risk of childhood leukemia. These aspects included the role of SES and racial distribution on subjects' participation, the role of selection bias on the association between EMF and childhood leukemia, as well as reproducibility of self-reports of household pesticide exposure. The research presented in this dissertation was made possible by the Northern California Childhood Leukemia Study, an ongoing population-based case-control study, which commenced in 1995. Results of meta-analyses suggest that in interview based case-control studies, cases were more likely to be non-White than White with an overall OR of 1.37 (95% CI 1.13, 1.67). In contrast, in the record-based studies cases, compared to controls, were less likely to be non-White than White, with an overall OR of 0.81 (95% CI 0.72,0.91). Results also indicated that SES was inversely associated with childhood leukemia while using interview based study design while positive association was observed while using record based study design.

Chapter Four of this dissertation examined the association between childhood leukemia and extremely low frequency of magnetic fields (measured by wire coding) with an emphasis on selection bias. Results indicated that the observed risk estimate depends on the selected control group. The odds ratios (OR) for developing childhood leukemia in the high-current configurations category were 1.43 (95% confidence interval (CI): 0.91, 2.26) compared to the first choice participant controls, while no associations were observed when compared to non-first choice participant controls (OR=1.06, 95% CI: 0.71-1.60) or first choice non-participant controls (OR=1.06, 95% CI: 0.71-1.57). Overall, no association was found between childhood leukemia and EMF as measured by wire configuration codes. Ideal (participating and non-participating) cases assigned to high-current configurations experience a non-significant increased risk of childhood leukemia, when compared to the ideal controls (OR=1.18, 95% CI: 0.85-1.64).

Chapter Five assessed the reproducibility of maternal-reported household use of pesticides and potential differential recall between cases and controls. Results indicated that the Kappa statistics ranged from 0.31 to 0.61 (fair to substantial agreement), with 9 out of the 12 tests indicating moderate agreement. The percent positive agreement ranged from 46-80% and the percent negative agreement from 54-95%. Results indicated

that the reliability of self-reported exposures for all pesticide categories using the three reliability measures did not differ markedly for cases and controls as confirmed by bootstrap analysis.

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ACKNOWLEDGEMENTS

I owe my deepest gratitude to my advisor, Prof. Patricia Buffler. It would have been next to impossible to write this dissertation without her help and guidance. Her encouragement, advice and support from the beginning to the end enabled me to write all the papers presented in this dissertation. I am, and will always be, extremely grateful for the opportunity to have had Prof. Buffler as my mentor for the past five years.

I am also grateful to Prof. Steve Selvin for advising me on the Biostatistics part of the research presented in this dissertation. His kindness and humor lifted my spirit on many occasions. My deepest gratitude is also owed to Dr. Catherine Metayer, whose contributions to all parts of the papers presented in this dissertation cannot be overstated. A sincere thank you goes to Dr.Gabor Mezei from Electric Power Research Institute for his wise comments and advice on the fields of epidemiological methods and low frequency magnetic fields. I thank Prof. Ronald Lee for being on my dissertation and oral exam committee and for his great advice along the way.

I thank all the staff of the Northern California Childhood Leukemia Study, especially Jeffery Chang, Melinda Aldrich, Neela Guha, Kevin Urayama, Monique Does, Barbara Rizzo, Magee Mooney, Anand Chokkalingam, Alice Kang, and Karen Bartley.

I would like to thank the most important people in my life, my loving family. A heartfelt thank you goes to my dear husband Alex, my parents Jette and Nathan Aharon and two brothers Yaniv and Oded for their unconditional love and support. I'd like to thank my little son, Elliot, who had to spend many days without me while I was working on this dissertation. He will always share a part of my heart, and I dedicate this dissertation to him.

This work was supported by the Electrical Power Research Institute (EP-P20634/C10044) and the National Institute of Environmental Health Sciences (PS42 ES04705, R01 ES09137).

CHAPTER ONE

Overview on Childhood Leukemia and Potential Bias in Exposure Assessment: Characteristics of the Northern California Childhood Leukemia Study and Research Questions

CHILDHOOD LEUKEMIA

Childhood leukemia is the most common childhood cancer (0–14 years of age), with more than 3,250 cases diagnosed annually in the United States (1). Childhood leukemia is a heterogeneous disease and consists of 75-80% acute lymphoblastic leukemia (ALL), 20% acute myeloid leukemia (AML), 2% chronic myeloid leukemia (CML), and rarely chronic lymphocytic leukemia (CLL) (2). Recently, greater heterogeneity of childhood leukemias has been recognized, and they have been subclassified according to their cytogenetics (3).

Incidence of ALL peaks at 2–3 years of age to 80 per million and decreases to a rate of 20 per million for 8-10 year olds. Leukemia rates are substantially higher for white children than for black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 (1). Incidence has shown a modest increase, less than 1% annually, between 1975 and 2002 in the U.S. This increase occurred mostly between 1975 and 1988 during which the incidence increased an average of 1.3% per year (1, 4, 5). The incidence of childhood leukemia in the U.S. stabilized between 1988 and 2002, during which time the annual percent change was 0.2% (5). However, the annual percent change between 2003 and 2007 was 0.6% (6).

Childhood leukemia is a cancer of immature lymphoid or myeloid progenitor cells derived from clonally expanded dysregulated cells that have encountered a series of catastrophic alterations within key regulatory genes (7). Acute leukemia is heterogeneous, characterized by different genetic and chromosomal abnormalities, with differing frequency by age (8). The two step model for childhood leukemia proposes that leukemia development occurs after both a first mutation, usually a chromosomal translocation occurring in utero, and a second mutation occurring after birth (8, 9). Chromosomal translocations are commonly present in childhood leukemia and many of the chromosomal translocations are present before birth (10). The most frequent translocations associated with ALL and AML are *TEL-AML1* [t(12;21), 20% of ALL] and AML1-ETO [t(8;21), 15% of AML], respectively (10).

The etiology of childhood leukemia remained largely unknown, with recognized risk factors explaining less than 10% of the cases (11). The difficulty in finding the etiology arises from the fact that pediatric leukemia, like most cancers, have multifactoral etiologies involving gene environment interaction (11). Established risk factors for ALL include sex, age, race, ionizing radiation, chemotherapeutic agents, and several genetic syndromes, but these together account for only a small proportion of childhood ALL cases diagnosed (12-14).

Other potential risk factors that have received some attention in the scientific literature include parental smoking (15, 16), alcohol consumption (17) (18), preconceptual paternal occupational exposure to solvents (19), hydrocarbons, reduced exposure and occurrence of common infections during childhood and allergies (20-23), socioeconomic factors, electromagnetic fields (24, 25), and pesticides (26, 27). The latter three will be further discussed in this dissertation.

ELECTROMAGNETIC FIELDS AND CHILDHOOD LEUKEMIA

The association between extremely low-frequency (ELF) magnetic field (MF) and childhood leukemia has been extensively studied since the first publication in 1979 by Wertheimer and Leeper (28). Since then, more than 25 epidemiological studies have been conducted on this topic, with major improvements in exposure assessment over time. A summary of these studies is presented in Table 1. Most of these studies were included in two pooled analyses published in 2000 by Greenland et al. (29) and Ahlbom et al. (30), including original data from 15 and nine studies, respectively. Greenland et al. indicated no association between childhood leukemia and MF levels less than 0.3 μT, but reported a statistically significant 1.7-fold increased risk for MF levels over 0.3 μT, compared to reference MF levels less than 0.1 μT. Based on four studies with both wire code and MF measurement data (31-34), the summary effect estimate for VHCC (very high current configurations) vs. LCC (low current configurations) was elevated after adjusting for MF levels (OR=1.6; 95% CI: 1.2–2.3) (29). The second pooled analysis by Ahlbom et al. used more restrictive inclusion criteria and similar to the results by Greenland et al., indicated no apparent association between MFs and childhood leukemia below MF exposure level of 0.4 μT. However, the summary odds ratio for exposure >0.4 μT as compared with exposure <0.1 μT was 2.1 (95% CI: 1.3 -3.3) (30).

Following these two pooled analysis in 2002, the International Agency for Research on Cancer (IARC) classified power-frequency magnetic field as a possible human carcinogen (group 2B) (35). In addition, the International Commission for Non-Ionizing Radiation Protection (ICNIRP) Standing Committee on Epidemiology concluded that among all the health outcomes evaluated in epidemiological studies of ELF-MF, the strongest evidence for an association exists between childhood leukemia and post-natal exposure to MFs at levels greater than 0.4 μT (36).

In 2005, Draper et al. reported an association between childhood leukemia and proximity of home address at birth to high voltage (transmission) power lines (37). The authors reported that compared with those who lived > 600 m from a power line at birth, children who lived within 200 m had a relative risk of leukemia of 1.69 (95% CI 1.13 to 2.53). Given the large size (9700 cases) of the study, the risk estimates were stable, and selection bias due to the differential participation among cases and controls was avoided since contact with the subjects was not necessary.

Despite the suggestive epidemiological findings and the IARC classification, there is no supporting biological evidence in either cellular or animal experimental studies to support the epidemiological observation. Hence, it remains uncertain whether the observed association between childhood leukemia and MF is causal. Among alternative explanations are the role of confounding factors, measurement errors, and selection bias. Confounding effects of socioeconomic status (SES), residential mobility, residence type, viral contacts, and traffic density have been raised as possible explanations for the observed associations (38-41).

Despite extensive research, no single confounder or set of confounders has been identified that could explain the observed association (41, 42). Selection bias has been suggested as a potential explanation in several studies. The assessment of selection bias,

however, requires considerable resources as well as early planning in study design and therefore is difficult to assess.

To our knowledge, only two studies to date have assessed the role of selection bias in the association between childhood leukemia and MF. Hatch et al. estimated the risk of acute lymphoblastic leukemia (ALL) for four levels of wire configuration codes, and compared analyses with and without partial participant controls (controls for whom no indoor-measurements were available) (41). The OR associated with living in homes with VHCC increased by 23% when partial participants were excluded from the model. The authors conclude that while confounding alone is unlikely to be an important source of bias, selection bias may be more of a concern, particularly in light of the generally low response rates among controls in case-control studies (41). A recent publication by Mezei et al. evaluated the role of selection bias in the 1999 Canadian case-control study of childhood leukemia and residential magnetic field exposure (33, 43). The authors reported that the risk estimates for childhood leukemia in the highest exposure category were 1.6 (95% CI: 1.0, 2.6) when the actual participant controls (first choice and non-first choice) were used and lower [1.3 ;95% CI: 0.8, 2.1] when the prefered more representative first-choice controls (participant and non-participant) were used (43).

Other studies reported an association between SES and wire codes. For example, Gurney et al. assessed the relationship between family income and wire codes and found that lower family income tended to be associated with higher wire codes (39). 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 et al. reported that people who changed addresses more frequently (high residential mobility) were more likely to live at an address with higher wire codes (40). Published studies to date have shown some evidence of selection bias, but the role of selection bias cannot entirely be confirmed on the basis of these studies alone.

PESTICIDES AND CHILDHOOD LEUKEMIA

Household exposure to pesticides has also been associated with childhood leukemia. Nearly all the case–control studies that investigated this exposure (19, 44-51) reported significant associations, with odds ratios close to two. A summary of these studies is presented in Table 2. In 1998 Zahm and Ward published a review on pesticides and childhood cancer and concluded that there is a positive associations between childhood leukemia and parental pesticide exposure before and during pregnancy and childhood exposure to household insecticides (26). A recent review by Infante-Rivard concluded that recent epidemiologic studies are consistent with those reviewed previously (27), by Zahm and Ward

A study previously published by the Northern California Childhood Leukemia Study (NCCLS) reported a positive association between childhood leukemia and household use of pesticides (44). In that study, Ma et al. reported that cases were exposed indoors to more pesticides than were the controls and that the highest odds ratio (OR) was seen for these exposures during pregnancy (OR = 2.2; 95% confidence interval

(CI): 1.3–3.6) (44). The authors also reported that more frequent indoor exposure to insecticides (but not herbicides) was associated with a higher risk, consistent with a dose response relationship.

One type of bias that is repeatedly discussed by previous studies on childhood leukemia and self-reports of pesticides exposure is recall bias. Differential recall of past pesticide exposure by cases and controls became a growing concern because the general public is increasingly aware of the potential toxicity and carcinogenicity of pesticides, and the effects of this recall has not been assessed.

SOCIOECONOMIC STATUS AND CHILDHOOD LEUKEMIA

Numerous epidemiological studies have examined the association between socioeconomic status (SES) and childhood leukemia, providing inconsistent results. Interview or questionnaire-based studies tend to show inverse associations and registry-based studies generally produced positive associations. In spite of these inconsistent results, in 1999, the National Cancer Institute (NCI) classified high SES as a 'known risk factor' for acute lymphoblastic leukemia (ALL) (1).

Individual-level measures of family income (18, 33, 52-57) mother's education (18, 33, 53, 55-62) and parental education (18, 19, 33, 53, 55-57, 62-65) found to be consistently associated with childhood leukemia in the inverse direction, with higher rates associated with lower SES levels. However, the results of studies of childhood leukemia and ecologic-level measures of SES indicate that almost all of the studies of SES and childhood leukemia shows a positive association (66-72), few reported mixed results (73-75), and only two indicated an inverse association (76, 77). The difference in the direction of association between the individual-level data and the ecological-level data could be explained by a potential effect of selection bias in the case controls studies. Selection bias related to SES might be a major factor responsible for the heterogeneous results, with interview based case-control studies including most cases, but only a selected subset of all relevant controls.

Nevertheless, SES is not only correlated with differential participation, but it is also often correlated with and may even be a surrogate for certain environmental exposures. SES has been shown in childhood leukemia studies to be associated with environmental factors such as pesticide use (78), traffic density (79) and exposure to VHCC. With SES being frequently related to study participation and risk factors, matching for SES factors or adjusting for them in the statistical analysis becomes increasingly challenging for investigators.

METHODOLOGICAL CHALLENGES IN CHILDHOOD LEUKEMIA CASE-CONTROL STUDIES

Because malignant neoplasms in children are rare, most epidemiologic studies have been case-control in design. Case-control studies are prone to a number of biases, notably due to differences between cases and controls in collection of exposure information and selection of study subjects. Sources of bias resulting from methodological features of study design and analysis can be classified in a variety of ways and usually classified into three main categories: confounding bias, selection bias and information (recall and measurement) bias. This dissertation will focus mostly on selection bias and information (recall) bias.

A major challenge of case-control studies is the rigorous selection of controls (80). In case-control studies, the distribution of exposure among controls should be representative of the exposure in the study base, the population which gave rise to the cases. Socio-demographic differences between the controls providing data and targeted controls for selection in the study base can lead to selection bias. Selection bias typically occurs when case and control selection or participation is differential based on their exposure status or based on some other characteristics related to exposure (81).

Selection bias refers to a distortion in the estimate of effect resulting from the manner in which subjects are selected for the study population. Among the many sources of selection bias are flaws in study design, most notably concerning the choice of groups to be compared and the choices of the sampling frame (82).

Selection bias has been repeatedly discussed by expert review panels (35, 83, 84) as the most likely candidate for providing a non-causal explanation for the apparent association between EMF and childhood leukemia. In its 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.

Another major challenge of interview-based case-control studies is misclassification of exposure information, which can be differential or nondiferential. Information bias refers to a distortion in the estimate of effect due to differential measurement error or misclassification of subjects on one or more variables (82). Major sources of information bias include invalid measurement, incorrect diagnosis criteria, and omissions, imprecision, or other inadequacies in recorded data (82) that differ by case-control status.

Information bias includes recall bias, also called reporting bias or differential recall. Recall bias occurs when recall of prior exposures is misclassified differentially for those with and without disease (85). Recall bias can distort the measure of association between exposure and disease by any magnitude and direction. This distortion is frequently difficult to predict (86). For example, it is recognized that parents of cases might be more motivated to search for causes or specific events that occurred in the past and either over report an experience or recall trivial events, whereas a parent of a healthy child may simply not remember or may believe an exposure to be unimportant. It is difficult to evaluate the direction of the resulting bias, if it exists, because cases could over or under report the exposure depending on whether recognition of past exposure or

guilt about that exposure took precedence (47). Moreover, the possibility of case mothers reporting their pesticide exposure more accurately than control mothers cannot be excluded (47).

NORTHERN CALIFORNIA CHILDHOOD LEUKEMIA STUDY

The Northern California Childhood Leukemia Study (NCCLS) is an ongoing case-control study which commenced in 1995. A detailed description of the NCCLS design has been published elsewhere (16, 87). In brief, the study recruited children with leukemia from hospitals in 35 counties in Northern and Central California, using rapid case ascertainment procedures to report cases usually within 72 hours after diagnosis. Medical records of all cases are abstracted and reviewed expeditiously by an expert hematologist to confirm diagnosis and subtype classification. For each case, one or two control subjects were randomly selected from birth certificates through the California Office of Vital Records, matched on date of birth, sex, Hispanic ethnicity, and maternal race. Although case ascertainment is hospital-based, a comparison with all population-based cases recorded by the statewide California Cancer Registry (2000) confirms that the NCCLS protocol successfully identified 95% of all age-eligible newly diagnosed childhood leukemia cases among residents of the 5-county San Francisco metropolitan area and 76% of such cases in the other 30 counties (88). Participating controls in the NCCLS were determined to be representative of the sampled population by parental age, parental education, and mother's reproductive history; characteristics which indicate a reduced potential for selection bias (87).

Eligibility criteria for cases and controls include: 1) residence in the 35-county study area; 2) less than 15 years of age at the time of case diagnosis (referent date for controls); 3) availability of an English or Spanish-speaking biological parent; and 4) no previous diagnosis of cancer.

All data collection instruments are available in English and Spanish. Data are primarily collected using a personal interview conducted at the home of the respondent in either English or Spanish. Questionnaires to obtain epidemiologic data were developed after consulting with established investigators in the field of childhood leukemia. The questionnaire has been tailored to obtain information relevant to the ethnically diverse California population and to focus specifically on the timing and types of exposures of interest to this study.

The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, the Institutional Review Board (IRB) of the National Institutes of Health and the IRBs of all the participating hospitals and institutions. A written informed consent was obtained from the parents or legal guardian of all participating subjects.

RESEARCH QUESTIONS TO BE ADDRESSED IN THIS DISSERTATION

1. To compare racial differences in childhood cancer incidence estimated by case-control studies with incidence data from population-based registries (Chapter Two).

2. To compare the association between SES and childhood leukemia using individual-level data and ecological-level data (Chapter Three).

3. To assess whether selection bias may explain the observed epidemiologic association between electromagnetic fields and childhood leukemia (Chapter Four).

4. To assess the reliability of maternal-reported household use of pesticides and potential differences in reliability by case-control status and by socio-demographic characteristics (Chapter Five).

REFERENCES

1. Ries LG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al. Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995. Bethesda, MD: National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. 1999.

2. Pui CH. Childhood leukemia. New York: Cambridge University Press. 1999.

3. Scelo G, Metayer C, Zhang L, Wiemels JL, Aldrich MC, Selvin S et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. Environ Health Perspect 2009;117:133-9.

4. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 1999;91:1051-8.

5. Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L. SEER Cancer Statistics Review, 1975-2002. Bethesda, MD: National Cancer Institute. 2005.

6. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER). Finding Cancer Statistics. National Cancer Institute; Bethesda, MD. 2003. (http://seer.cancer.gov/). (Accessed May 5, 2010).

7. Pui CH. Childhood leukemias. N Engl J Med 1995;332:1618-30.

8. Greaves M. Childhood leukaemia. BMJ 2002;324:283-7.

9. Rossig C, Juergens H. Aetiology of childhood acute leukaemias: current status of knowledge. Radiat Prot Dosimetry 2008;132:114-8.

10. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 2003;3:639-49.

11. Buffler PA, Kwan ML, Reynolds P, Urayama KY. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. Cancer Invest 2005;23:60-75.

12. Sandler DP, Ross JA. Epidemiology of acute leukemia in children and adults. Semin Oncol 1997;24:3-16.

13. Smith M, Ries L, Gurney J, Ross J. Leukemia. In: Ries L, Smith M, Gurney J, Linet M, Tamra T, Young J, GR B, eds. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute, SEER Program, 1999:17-34.

14. Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect 2007;115:138-45.

15. Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS et al. Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. Leuk Res 2009;33:250-8.

16. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 2006;163:1091-100.

17. Infante-Rivard C, El-Zein M. Parental alcohol consumption and childhood cancers: a review. J Toxicol Environ Health B Crit Rev 2007;10:101-29.

18. Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. J Natl Cancer Inst 1996;88:24-31.

19. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res 1989;49:4030-7.

20. Ma X, Buffler PA, Wiemels JL, Selvin S, Metayer C, Loh M et al. Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev 2005;14:1928-34.

21. Chang JS, Metayer C, Fear NT, Reinier K, Yin X, Urayama K et al. Parental social contact in the work place and the risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2007;97:1315-21.

22. Chang JS, Wiemels JL, Buffler PA. Allergies and childhood leukemia. Blood Cells Mol Dis 2009;42:99-104.

23. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer 2006;6:193-203.

24. Feychting M, Floderus B, Ahlbom A. Parental occupational exposure to magnetic fields and childhood cancer (Sweden). Cancer Causes Control 2000;11:151-6.

25. Schuz J, Ahlbom A. Exposure to electromagnetic fields and the risk of childhood leukaemia: a review. Radiat Prot Dosimetry 2008;132:202-11.

26. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev 2007;10:81-99.

27. Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect 1998;106 Suppl 3:893-908.

28. Wertheimer N, Savitz DA, Leeper E. Childhood cancer in relation to indicators of magnetic fields from ground current sources. Bioelectromagnetics 1995;16:86-96.

29. 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;11:624-34.

30. 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;83:692-8.

31. Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune WT, Friedman DR et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. N Engl J Med 1997;337:1-7.

32. London SJ, Thomas DC, Bowman JD, Sobel E, Cheng TC, Peters JM. Exposure to residential electric and magnetic fields and risk of childhood leukemia. Am J Epidemiol 1991;134:923-37.

33. McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli JJ et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol 1999;149:831-42.

34. Savitz DA, Wachtel H, Barnes FA, John EM, Tvrdik JG. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol 1988;128:21-38.

35. IARC, Non-ionizing radiation, Part 1: Static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monogr Eval Carcinog Risks Hum 2002;80:1-395.

36. Ahlbom IC, 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 6:911-33.

37. 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.

38. Feychting M, Ahlbom A, Savitz D. Electromagnetic fields and childhood leukemia. Epidemiology 1998;9:225-6.

39. Gurney JG, Davis S, Schwartz SM, Mueller BA, Kaune WT, Stevens RG. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. Epidemiology 1995;6:31-5.

40. Jones TL, Shih CH, Thurston DH, Ware BJ, Cole P. Selection bias from differential residential mobility as an explanation for associations of wire codes with childhood cancer. J Clin Epidemiol 1993;46:545-8.

41. Hatch EE, Kleinerman RA, Linet MS, Tarone RE, Kaune WT, Auvinen A et al. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? Epidemiology 2000;11:189-98.

42. Kheifets L, Swanson J, Greenland S. Childhood leukemia, electric and magnetic fields, and temporal trends. Bioelectromagnetics 2006;27:545-52.

43. Mezei G, Spinelli JJ, Wong P, Borugian M, McBride ML. Assessment of selection bias in the Canadian case-control study of residential magnetic field exposure and childhood leukemia. Am J Epidemiol 2008;167:1504-10.

44. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110:955-60.

45. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 2006;63:131-4.

46. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 1999;10:481-7.

47. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y et al. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environ Health Perspect 2007;115:1787-93.

48. 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;151:639-46; discussion 647-50.

49. 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:1943-8.

50. Alderton LE, Spector LG, Blair CK, Roesler M, Olshan AF, Robison LL et al. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: a report from the Children's Oncology Group. Am J Epidemiol 2006;164:212-21.

51. Pombo-de-Oliveira MS, Koifman S. Infant acute leukemia and maternal exposures during pregnancy. Cancer Epidemiol Biomarkers Prev 2006;15:2336-41.

52. Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J et al. Diagnostic X-ray and ultrasound exposure and risk of childhood cancer. Br J Cancer 1994;70:531-6.

53. Groves FD, Gridley G, Wacholder S, Shu XO, Robison LL, Neglia JP et al. Infant vaccinations and risk of childhood acute lymphoblastic leukaemia in the USA. Br J Cancer 1999;81:175-8.

54. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol 2002;155:603-13.

55. Green LM, Miller AB, Agnew DA, Greenberg ML, Li J, Villeneuve PJ et al. Childhood leukemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. Cancer Causes Control 1999;10:233-43.

56. Brondum J, Shu XO, Steinbuch M, Severson RK, Potter JD, Robison LL. Parental cigarette smoking and the risk of acute leukemia in children. Cancer 1999;85:1380-8.

57. Ma X, Buffler PA, Selvin S, Matthay KK, Wiencke JK, Wiemels JL et al. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2002;86:1419-24.

58. Dockerty JD, Elwood JM, Skegg DC, Herbison GP. Electromagnetic field exposures and childhood cancers in New Zealand. Cancer Causes Control 1998;9:299-309.

59. Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). Cancer Causes Control 2000;11:547-53.

60. Petridou E, Kassimos D, Kalmanti M, Kosmidis H, Haidas S, Flytzani V et al. Age of exposure to infections and risk of childhood leukaemia. Bmj 1993;307:774.

61. Rosenbaum PF, Buck GM, Brecher ML. Early child-care and preschool experiences and the risk of childhood acute lymphoblastic leukemia. Am J Epidemiol 2000;152:1136-44.

62. Thompson JR, Gerald PF, Willoughby ML, Armstrong BK. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: a case-control study. Lancet 2001;358:1935-40.

63. Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W et al. A population-based case-control study of childhood leukemia in Shanghai. Cancer 1988;62:635-44.

64. Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991;68:1351-5.

65. Perrillat F, Clavel J, Auclerc MF, Baruchel A, Leverger G, Nelken B et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. Br J Cancer 2002;86:1064-9.

66. Dickinson HO, Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: the Seascale cluster. Br J Cancer 1999;81:144-51.

67. Browning D, Gross S. Epidemiological studies of acute childhood leukemia. A survey of Cuyahoga county, Ohio. Am J Dis Child 1968;116:576-85.

68. Githens JH, Elliot FE, Saunders LH. The Relation of Socioeconomic Factors to Incidence of Childhood Leukemia. Public Health Rep 1965;80:573-8.

69. Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. Bmj 1993;306:743-8.

70. McWhirter WR. The relationship of incidence of childhood lymphoblastic leukaemia to social class. Br J Cancer 1982;46:640-5.

71. Pinkel D, Nefzger D. Some epidemiological features of childhood leukemia in the Buffalo, N. Y., area. Cancer 1959;12:351-8.

72. Richardson S, Monfort C, Green M, Draper G, Muirhead C. Spatial variation of natural radiation and childhood leukaemia incidence in Great Britain. Stat Med 1995;14:2487-501.

73. Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Community lifestyle characteristics and risk of acute lymphoblastic leukaemia in children. Lancet 1990;336:1461-5.

74. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;30:1428-37.

75. Muirhead CR. Childhood leukemia in metropolitan regions in the United States: a possible relation to population density? Cancer Causes Control 1995;6:383-8.

76. McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. Br J Cancer 1999;80:1844-51.

77. Reynolds P, Elkin E, Scalf R, Von Behren J, Neutra RR. A case-control pilot study of traffic exposures and early childhood leukemia using a geographic information system. Bioelectromagnetics 2001;Suppl 5:S58-68.

78. Gunier RB, Harnly ME, 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;109:1071-8.

79. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith D. Traffic patterns and childhood cancer incidence rates in California, United States. Cancer Causes Control 2002;13:665-73.

80. Rudant J, Clavel J, Infante-Rivard C. Selection bias in case-control studies on household exposure to pesticides and childhood acute leukemia. J Expo Sci Environ Epidemiol 2009.

81. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol 1996;25:1107-16.

82. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research: Principles and Quantitive Methods. John Willey & Sons, INC. Canada. 1982.

83. Portier CJ. NIEHS Working Group Report, NIH Publication No. 98-3981 NIH 1998.

84. National Radiologic Protection: ELF Electromagnetic Fields and the Risk of Cancer: Report of an Advisory Group on Non-ionising Radiation National Radiological Protection Board 2001.

85. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol 1990;43:87-91.

86. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol 2006;35:370-84.

87. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915-21.

88. Ma X, Urayama K, Chang J, Wiemels JL, Buffler PA. Infection and pediatric acute lymphoblastic leukemia. Blood Cells Mol Dis 2009;42:117-20.

89. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979;109:273-84.

90. Fulton JP, Cobb S, Preble L, Leone L, Forman E. Electrical wiring configurations and childhood leukemia in Rhode Island. Am J Epidemiol 1980;111:292-6.

91. Myers A, Clayden AD, Cartwright RA, Cartwright SC. Childhood cancer and overhead powerlines: a case-control study. Br J Cancer 1990;62:1008-14.

92. Olsen JH, Nielsen A, Schulgen G. Residence near high voltage facilities and risk of cancer in children. BMJ 1993;307:891-5.

93. Verkasalo PK, Pukkala E, Hongisto MY, Valjus JE, Jarvinen PJ, Heikkila KV et al. Risk of cancer in Finnish children living close to power lines. Bmj 1993;307:895-9.

94. Tynes T, Haldorsen T. Electromagnetic fields and cancer in children residing near Norwegian high-voltage power lines. Am J Epidemiol 1997;145:219-26.

95. Tomenius L. 50-Hz electromagnetic environment and the incidence of childhood tumors in Stockholm County. Bioelectromagnetics 1986;7:191-207.

96. Feychting M, Ahlbom A. Magnetic fields and cancer in children residing near Swedish high-voltage power lines. Am J Epidemiol 1993;138:467-81.

97. Michaelis J, Schuz J, Meinert R, Menger M, Grigat JP, Kaatsch P et al. Childhood leukemia and electromagnetic fields: results of a population-based case-control study in Germany. Cancer Causes Control 1997;8:167-74.

98. Study UCC. Exposure to power-frequency magnetic fields and the risk of childhood cancer. Lancet 1999;354:1925-31.

99. Schuz J, Grigat JP, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukaemia: results from a German population-based case-control study. Int J Cancer 2001;91:728-35.

100. 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;119:643-50.

101. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health 1995;85:249-52.

102. Schreinemachers DM. Cancer mortality in four northern wheat-producing states. Environ Health Perspect 2000;108:873-81.

103. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001;61:2542-6.

104. Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. Environ Health Perspect 2001;109:193-6.

105. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup Environ Med 2003;60:901-9.

106. Flower KB, Hoppin JA, Lynch CF, Blair A, Knott C, Shore DL et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect 2004;112:631-5.

107. Rull RP, Gunier R, Von Behren J, Hertz A, Crouse V, Buffler PA et al. Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. Environ Res 2009;109:891-9.

108. Ward MH, Colt JS, Metayer C, Gunier RB, Lubin J, Crouse V et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. Environ Health Perspect 2009;117:1007-13.

Table 1. Studies on electric and magnetic fields, measured by wire configuration codes, and childhood leukemia, 1979-2009

Author, Location, Year	Study population	Residence	Study design	Cancer Cases/controls	Wire codes odds ratio (95% CI)
Wertheimer & Leeper, Denver, 1979 (89)	Cases: death 1950-1973. Controls: birth certificates. < 19 years	Residence at time of diagnosis	Case control	 All cancers (328/328) Leukemia (136/136) Brain tumors (57/57)	LCC: reference HCC 2.11 (1.60-1.80) 2.98 (1.78-4.98) 2.40 (1.03-5.41)
Fulton, Rhode Island, USA, 1980 (90)	Cases: Rhode Island Hospital. Controls: birth certificates.< 20 years	Cases: all lifetime residences Controls: birth residence	Case control	 Leukemia (119/240)	LCC: reference HCC 1.08 (0.62-1.89)
Savitz, Denver, USA, 1988 (34)	Cases: The Colorado Central Cancer Registry. death 1976-1983. Controls: RDD. < 15 years	Residence at time of diagnosis	Case control	 All cancers (320/259) Leukemia (97/259) Brain tumors (59/259)	Underground: reference VHCC 2.20 (0.93-5.21) 2.75 (0.94-8.04) 1.94 (0.47-7.95)
Myers, Yorkshire, England, 1990 (91)	Cases: Yorkshire Childhood Cancer Registry, death 1970-1979. Controls: birth certificates. < 15 years	Residence at time of birth	Case control	 All cancers (374/588)	>25m: reference <25m 1.10 (0.47-2.57)
London, Los Angeles, USA, 1991 (32)	Cases: Los angeles County Cancer Surveillance Program 1980-1987. Controls: friends and RDD. < 10 years	Residence at time of diagnosis	Case control	 Leukemia (211/205)	Underground: reference VHCC 2.15 (1.08-4.26)
Olsen, Denmark, 1993 (92)	Cases: Danish cancer registry, 1960-1986. Controls: registry. < 15 years	Historically calculated fields	Case control	 All cancers (1,707/4,788) Leukemia (833/1,666) Brain tumors (624/1,872)	<0.4μT: reference ≥0.4 μT 5.6 (1.6-19) 6.0 (0.8-44) 6.0 (0.8-44)
Verkasalo, Finland, 1993 (93)	Cases: Finnish cancer registry, 1974-1990. < 17 years	Historically calculated fields, residence within 500m	Cohort	 All cancers (140) Leukemia (35) Brain tumors (39)	<0.01μT: reference ≥0.2 μT 1.5 (1.74-2.7) 1.6 (0.32-4.5) 2.3 (0.75-5.4)

Author, Location, Year	Study population	Residence	Study design	Cancer Cases/controls	Wire codes odds ratio (95% CI)
Tynes, Norway, 1997 (94)	Cases: Cancer Registry of Norway, 1965-1989. Controls: from matched cohort. < 15 years	Historically calculated fields	Nested CC		<0.05μT: reference
					≥0.14 μT
				All cancers (12/51)	0.9 (0.5-18)
				Leukemia (1/14)	0.3 (0.0-21)
				Brain tumors (4/23)	0.7 (0.2-21)
					≥101m: reference
					> 51m
				All cancers (51/164)	0.9 (0.9-18)
				Leukemia (14/63)	0.3 (0.4-16)
				Brain tumors (9/55)	0.6 (0.3-13)
Linet, 9 mid-Athlantic and Midwestern States, USA, 1997 (31)	Cases: Children's Cancer Group, 1989-1993. Controls: RDD. < 15 years	Residence > 5 years before diagnosis	Case control		Underground and VLCC: reference
					VHCC
				Leukemia (402/402)	0.88 (0.48-1.63)
McBride, Canada , 1999 (33)	Cases: cancer registries, 1990-1994. Controls: province health insurance rolls. < 15 years	Wire code of residence 2 yr before diagnosis	Case control		Underground: reference
					VHCC
				Leukemia (303/309)	0.77 (0.37-1.60)
Green, Canada, 1999 (55)	Cases: Hospital for Sick Children, 1985-1993. Controls: telephone marketing lists. < 15 years	Wire code	Case control		VLCC: reference
					OHCC+VHCC
				Leukemia (79/125)	0.6 (0.2-1.5)
Mezei, Canada, 2008 (43)	Cases: cancer registries, 1990-1994. Controls: province health insurance rolls. < 15 years	Wire code of residence 2 yr before diagnosis	Case control		VLCC and OLCC: reference
					VHCC Actual controls
				Leukemia (340/493)	1.61 (0.99-2.63) Ideal controls 1.31 (0.81-2.11)

Abbreviations: VLCC = very low current code; OLCC = ordinary low current code; OHCC = ordinary high current code VHCC = very high current code; MF= magnetic field measurement; RDD = Random Digit Dialing

Table 2. Studies on Electric and Magnetic Fields and Childhood leukemia, 1979-2009

Author, Location, Year	Study population	Residence	Study design	Cancer Cases/controls	Magnetic field measurement odds ratio (95% CI)
Tomenius, Stockholm, Sweden, 1988 (95)	Cases: Swedish Cancer Registry, 1958-1973, Controls: birth certificates. < 19 years	birth and diagnosis residence	Case control	 All cancers (1,033/890) Leukemia (243/212) Brain tumors (294/253)	<0.3μT: reference ≥0.3 μT 1.85 (0.97-3.51) 0.35 (0.11-1.13) 3.73 (1.05-13.23)
Savitz, Denver, USA, 1988 (34)	Cases: The Colorado Central Cancer Registry. death 1976-1983. Controls: RDD. < 15 years	Residence at time of diagnosis	Case control	 All cancers (128/207) Leukemia (36/207) Brain tumors (25/207)	<0.25μT: reference ≥0.25 μT 1.35 (0.63-2.90) 1.93 (0.67-5.56) 1.04 (0.22-4.82)
London, Los Angeles, USA, 1991 (32)	Cases: Los angeles County Cancer Surveillance Program 1980-1987, Controls: friends and RDD. < 10 years	Residence at time of diagnosis	Case control	 Leukemia (162/143)	<0.31μT: reference ≥0.125 μT 1.22 (0.52-2.82)
Feychting, Sweden, 1993 (96)	Cases: Swedish Cancer Registry, Controls: matched cohort. < 15 years	Historically calculated fields, residence within 300m	Nested CC	 All cancers (141/554) Leukemia (38/554) Brain tumors (33/554)	<0.09μT: reference ≥0.3 μT 1.3 (0.6-2.7) 3.8 (1.4-9.3) 1.0 (0.2-3.9)
Linet, 9 mid-Athlantic and Midwestern States, USA ,1997 (31)	Cases: Children's Cancer Group, 1989-1993. Controls: RDD. < 15 years	Residence > 5 years before diagnosis	Case control	 Leukemia (624/615)	<0.065μT: reference ≥0.5 μT 1.01 (0.26-3.99)
Michaelis, Germany, 1997 (97)	Cases: German Childhood Cancer Registry, 1991-1995. Controls: government office residents registry. < 15 years	24-hr bedroom MF measurement	Case control	 Leukemia (176/414)	<0.2μT: reference ≥0.2 μT 3.2 (0.7-14.9)
Dockerty, New Zealand, 1998 (58)	Cases: New Zealand cancer registry, 1990-1993. Controls: birth certificates. < 15 years	24-hr bedroom MF measurement	Case control	 Leukemia (115/117)	<0.2μT:reference ≥0.2 μT 15.5 (1.1-224)

Author, Location, Year	Study population	Residence	Study design	Cancer Cases/controls	Magnetic field measurement odds ratio (95% CI)
McBride, Canada, 1999 (33)	Cases: cancer registries, 1990-1994. Controls: province health insurance rolls. < 15 years	24 and 48hr MF measurement	Case control	48hr: Leukemia (293/339) 24hr: Leukemia (272/304)	<0.2μT: reference ≥0.2 μT 1.04 (0.69-1.57) 1.27 (0.69-2.33)
Green, Canada, 1999 (55)	Cases: Hospital for Sick Children, 1985-1993. Controls: telephone marketing lists. < 15 years	48hr MF measurement	Case control	48hr: Leukemia (88/133)	<0.03μT: reference ≥0.14 μT 4.5 (1.3-15.9)
United Kingdom Childhood Cancer Study, England, 1999 (98)	Cases: Family Health Service Authorities, 1992-1995. Controls: Family Health Services Authorities registry. < 15 years	90 min and 48hr MF measurement	Case control	All cancers (2,265/2,270) Leukemia (1,094/1,096)	<0.1μT: reference ≥0.4 μT 0.89 (0.34-2.3) 1.68 (0.40-7.10)
Schuz, Germany, 2001 (99)	Cases: nation-wide GCCR Registry, 1992-1995. Controls: same region as cases. < 15 years	24 MF measurement	Case control	Leukemia (514/1,301)	<0.2μT: reference 0.2 - 0.4 μT 1.16 (0.43-3.11) ≥0.4 μT 5.81 (0.80-44.1)
Kabuto, Japan, 2006 (100)	Cases: 5 major children's cancer study groups in Japan, 1999-2001 Controls: Japanese resident registration system. < 15 years	Bedroom MF measurements	Case control	ALL+AML (312/603) ALL (251/495)	<0.1μT: reference > 0.4 μT 2.56 (0.76-8.58) > 0.4 μT 4.67 (1.15-19.0)

Abbreviations: MF= magnetic field

Table 3. Studies on pesticides exposure and risk of childhood leukemia, 1990-2009

Author, Location, Year	Source of Subjects	Study design	Leukemia	Case /Control	Primary Results
Leiss and Savitz, USA, 1995 (101)	Cases: Colorado Central Cancer Registry, 1976-1983 Controls: random digit dialing. <15 years	Case control, interview	Leukemia	252/222	**Pest strips** 3rd trimester 3.0 (1.6, 5.7) Birth - 2 years 1.7 (1.2, 2.4) 2 years - diagnosis 2.6 (1.7, 3.9) **House extermination** 3rd trimester 0.4 (0.1, 1.2) Birth - 2 years 0.3 (0.1, 0.8) 2 years - diagnosis 0.9 (0.5, 1.4) **Yard pesticide treatment** 3rd trimester 1.1 (0.6,1.9) Birth - 2 years 0.9 (0.5, 1.8) 2 years - diagnosis 1.1 (0.8, 1.5)
Meinert, Germany, 1996 (49)	Cases: German Childhood Cancer Registry 1988–1992. Controls: Population-weighted sampling scheme, local and state controls. < 15 years	Case control: Structured telephone questionnaire	ALL, Leukemia	173/220	Pesticide use in garden 2 years before birth till diagnosis: 2.5 (1.0-6.1)
Infante-Rivard, Canada, 1999 (46)	Cases: Tertiary care centers in Quebec 1980-1993. Controls: Family allowance files. < 10 years	Case control: Interview	ALL	491/491	**During pregnancy:** Herbicides 1.84 (1.32-2.57) Insecticides 1.97 (1.32-2.94) Pesticides 1.70 (1.12-2.59) Repellants 0.70 (0.45-1.09) Product for slug 1.57 (0.43-5.62) **During childhood:** Herbicides 1.41 (1.06-1.86) Insecticides 1.82 (1.31-2.52) Pesticides 1.41 (1.011.97) Repellants 0.65 (0.42-0.94)

Author, Location, Year	Source of Subjects	Study design	Leukemia	Case /Control	Primary Results
Meinert, Germany, 2000 (48)	Cases: German Childhood Cancer Registry 1992-1994, Controls: Lists of local resident registration offices. <15 years	Case control: Interview	ALL, Leukemia	1,184/ 2,588	**Maternal occupational exposure:** During pregnancy 3.6 (1.5-8.8) After pregnancy 2.5 (1.0-6.4) Ever 2.5 (1.3-4.7) **Paternal occupational exposure:** During pregnancy 1.6 (1.1-2.2) After pregnancy 1.3 (0.0-1.9) Ever 1.6 (1.1-2.3) **Garden pesticides from birth to diagnosis:** 1.0 (0.8-1.2)
Schreinmachers, USA, 2000 (102)	Cases: National Center for Health Statistics mortality during 1980–1989. < 15 years	Ecological study	Leukemia	59	Mortality among boys 1.40 (0.75,2.62) Mortality among girls 1.43 (0.49,4.18)
Alexander, several countries, 2001 (103)	Cases: Hospitals in several countries. Controls: inpatients and outpatients at hospitals. < 18 months	Case control, interview	ALL, AML	136/266	Maternal exposure to pesticides during pregnancy. ALL 2.53 (0.71-8.97) AML 5.08 (1.84-14.0)
Feychting, Sweden, 2001 (104)	Cases: Swedish Cancer Registry. Controls: cohort. Age: 54% <15 years, 23% <13, 23% <12 years	Cohort study	Leukemia	235,635	Father's occupational exposure tp pesticides. before conception: 0.90 (0.37–2.19)
Ma, California, USA, 2002 (44)	Cases: major clinical centers in Californa, 1995-1999. Controls: statewide birth certificate files. < 15 years	Case control: Interview	ALL, Leukemia	162/162	**Professional pest control at home:** 3-mo before pregnancy 1.9 (0.7-4.7) During pregnancy 2.3 (0.9-5.4) 3 mo before pregnancy to 3 years 2.6 (1.2-5.4) **Insecticides at home:** 3 mo before pregnancy 1.7 (1.0-3.1) During pregnancy 2.3 (1.3-4.0) 3 mo before pregnancy - 3 years 2.2 (1.0–4.6) **Flea control products used at home** 3 mo before pregnancy 0.8 (0.4-1.6) During pregnancy 0.7 (0.4-1.4) 3 mo before pregnancy - 3 years 1.0 (0.5-1.8) **Herbicides used at home:** 3 mo before pregnancy 1.6 (0.8-3.3) During pregnancy 1.8 (0.9-3.5) 3 mo before pregnancy - 3 years 1.0 (0.6-1.8)

Author, Location Year	Source of Subjects	Study design	Leukemia	Case /Control	Primary Results
McKinney, England and Wales, 2003 (105)	Cases and Controls: Family Health Services Authority. < 14 years	Case control, interview	Leukemia , ALL	1737	Agrochemical exposure at preconception **Maternal** Leukemia 0.81 (0.31 - 2.12) ALL 0.97 (0.37 - 2.52) **Paternal** Leukemia 0.83 (0.58 - 1.19) ALL 0.85 (0.58 - 1.24)
Flower, USA, 2004 (106)	Cases: Iowa Cancer Registry, 1975-1998. Controls: Iowa pesticide applicators. <19 years	Cohort study	Leukemia	17,357	Paternal occupation as a pesticide applicator, before birth: 0.91 (0.47-1.75)
Alderton, USA, 2006 (50)	Cases: Children's Oncology Group, 1997-2002, Controls; from same primary care clinic as cases. <19 years	Case control, interview	ALL, AML	158/173	ALL, maternal exposure during pregnancy. **Insecticides** Low 1.56 (0.85,2.87) High 1.82 (0.94,3.52) **Flea or tick control** Low 1.83 (0.89,3.76) High 1.25 (0.59,2.65) **Professional pest exterminations** Low 3.44 (1.41,8.39) High 1.28 (0.46,3.55)
Rudant, France, 2007 (47)	Cases: pediatric oncology centers and national registry of childhood blood Malignancies 2003-2004. Controls: National telephone directory. < 15 years	Case control: structured telephone questionnaire	ALL, AML	764/1681	Residential exposure during pregnancy: **Maternal:** Pesticides 2.2 (1.8-2.6) Insecticides 2.1 (1.7-2.5) Herbicides 1.5 (1.0-2.2) **Paternal:** Pesticides 1.5 (1.2-1.8) Insecticides 1.4 (1.2-1.8) Herbicides 1.2 (1.0-1.4)
Menegaux,, France, 2006 (45)	Cases: hospitals of Lille, Lyon, 1995-1999 Controls; from same hosital as cases. <15 years	Case control, interview	Leukemia	280/288	During pregnancies **Insecticides** Ever use 1.8 (1.2-2.8) **Pesticides** Ever use 2.5 (0.8-7.2) During childhood **Insecticides** Ever use 1.7 (1.1-2.4) **Pesticides** Ever use 1.7 (1.1-2.7)

Author, Location Year,	Source of Subjects	Study design	Leukemia	Case /Control	Primary Results
Rull, California, USA, 2009 (107)	Cases: major clinical centers in California, 1990-2002. Controls: statewide birth certificate files. < 15 years	Case control: Interview	ALL, Leukemia	213/268	Lifetime exposure; agricultural pesticides applied within 1/2-mi of residences **Insecticides (bl/mi^2)** 1-72 1.5 (0.9-2.4) 72-3218 0.8 (0.5-1.4) **Herbicides (bl/mi^2)** 1-57 1.2 (0.8-1.9) 57-2186 0.9 (0.5-1.5)
Ward, California, USA, 2009 (108)	Cases: major clinical centers in California, 1995-1999. Controls: statewide birth certificate files. < 7 years	Case control: Interview	ALL	184/212	concentrations and loadings of α-Chlordane pesticides in carpet dust **Chemical concentration** 3.5 to < 8.3 1.18 (0.60-2.09) 8.3 to < 22.9 1.32 (0.71-2.43) 22.9-1,916 1.27 (0.69-2.35) **Chemical loadings** 3.3 to < 10.8 0.67 (0.37-1.21) 10.8 to < 30.4 0.34 (0.18-0.66) ≥ 30.4 0.78 (0.42-1.42)

CHAPTER TWO

Racial Differences in the Incidence of Childhood Cancer by Source of Data

Racial Differences in the Incidence of Childhood Cancer by Source of Data

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ABSTRACT

This study compares racial differences in childhood cancer incidence estimated by case-control studies with incidence data from population-based registries.
Methods Peer-reviewed publications on childhood leukemia and brain tumors from North America, published between 1980 and 2007, were reviewed. Incidence data by race/ethnicity were compiled from research publications, federal cancer statistics, and cancer registries. Meta-analysis was conducted to assess racial/ethnic differences by study characteristics. Racial distributions of cases from published case-control studies were compared to those of a presumably noncensored case distribution (i.e. include both participating and non-participating cases in a case-control study) or cases recorded by cancer registries.
Results In interview-based case-control studies of childhood cancer, the proportion of Whites compared to non-Whites tended to be higher among controls than among cases; however, the opposite was true for record-based case-control studies. Additionally, the proportion of Whites tended to be higher among the participating cases in the published case-control studies compared to the proportion of Whites among the non-participating cases or in cancer registries.
Conclusions Investigators need to consider differential participation by racial group as a potential source of bias in the interpretation of case-control study results.

INTRODUCTION

Because malignant neoplasms in children are relatively rare, most epidemiologic studies have been case-control in design. Nevertheless, malignant neoplasms are the second leading cause of death in children 1–19 years of age in the United States, accounting for 2197 deaths in 2004 (1). Case-control studies are prone to a number of well known biases, notably those due to differences between cases and controls in the recall of exposure information and selection of study subjects. Selection bias typically occurs when case and control selection or participation is differential based on their exposure status or based on other characteristics related to exposure (2).

The association between socioeconomic status (SES) and participation in epidemiologic studies, especially case-control studies, is well documented, with individuals of higher SES more likely to participate than individuals of lower SES (3-7). Participation may also differ by race or ethnic status; for example, Hispanics may be less likely to participate than non-Hispanic Whites (8-13). A recent review of SES and childhood leukemia by Poole et al. (2006) observed that while case-control studies with interviews or self-administered questionnaires reported an inverse association between individual level measures of SES (family income, mother's education) with childhood leukemia, record-based case-control and ecologic studies tended to show a positive association between childhood leukemia and father's occupational class or average occupational class (14). The authors indicated that it is not clear whether the observed differences were due to inherent differences in the SES measures or due to differences in study design.

Although selection bias most frequently refers to the selection of controls, case selection may also be a source of bias if non-participation occurs among cases. The current analysis compares race and ethnic status differences in childhood cancer rates as estimated by case-control epidemiologic studies with various design features. It also compares estimates of race and ethnic status distribution among cases as reported by case-control studies to those observed for an ideal case series with complete ascertainment of cases for these studies or in population-based cancer registries in corresponding geographic regions and calendar periods.

MATERIALS AND METHODS

Literature search and inclusion criteria

PubMed was searched from January 1st 1980 through February 28, 2007 for original research in English, using the keywords 'childhood', 'leukemia', 'leukaemia', 'cancer', 'brain tumor', 'astrocytoma', 'central nervous system', 'glioma', and 'miscellaneous'. Case reports, case series, articles on diagnostic or prognostic characteristics or treatment outcomes, letters, editorials, and news briefs were excluded. To be included, a study had to present incidence data for leukemia or brain tumors for children or young adults (ages 0-24) in North America and had to provide incidence by race and/or ethnic status, classified at a minimum by White and non-White status. Only

full-text articles were included since abstracts did not always provide sufficient information on race or ethnic status. For studies with multiple reports, we selected as the primary source of information the most recent report or the report with the highest number of race and ethnic status categories. In the instance of multiple reports we referred to the other reports for supplemental information.

Data collection

Information was abstracted from the selected case-control studies onto a standard form that included geographic area, dates of diagnosis, cancer subtype, inclusion criteria and ascertainment, primary exposure(s) of interest, participation rate(s), categories of race and ethnic status, number of cases and controls, source of cases (hospital, registry etc.), source of controls (Random Digit Dialing, registry etc.), and source of race and ethnic status classification (interview, questionnaires, or record based). The race/ethnic status categories included White, Black, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Hispanic or other.

For selected case-control studies with well-defined geographic areas, the cancer incidence data in corresponding geographic regions and calendar periods were collected from the SEER*Stat program (15) or from the corresponding cancer registries. The Surveillance, Epidemiology and End Results (SEER) program collects cancer incidence data from 14 population-based cancer registries and three supplemental registries. Childhood cancer incidence rates for areas not included in the SEER, were collected from the corresponding cancer registries in the US or from the population-based provincial cancer registries in Canada. For studies with ill-defined geographic areas (mostly hospital-based) or for studies conducted in populations lacking cancer registry data, the authors were asked to provide the race/ethnic status distribution of the non-participating cases. In three studies (16-18) the race/ethnic status distribution of cases as reported by the case-control studies (Table 3) differed from that reported in the cancer registry (Table 4). In these studies, the published data for race/ethnic status were derived from birth certificates; however birth certificate data were not available for non-participating cases. In order to use the same data source for race/ethnic status of both participating cases and non-participating cases, the publication authors provided race/ethnic status data from the appropriate cancer registries for the participating and non-participating cases. For the purpose of assessing racial differences, the racial distribution reported by SEER, cancer registries, or the authors of the hospital based studies were recorded for the same strata of race, age, and geographic area as published by the selected case-control studies, to provide a suitable comparison with the latter. Eight studies were excluded because data from SEER or the appropriate cancer registry were not available for the requested time period and the first author could not provide the requested data for the non-participating cases. The data for race/ethnic status of the participating cases as reported by five of the leukemia studies and six of the brain tumor studies were compared to the data for race/ethnic status from the cancer registries and SEER*Stat. Distributions of cases by race/ethnic status for the remaining studies were compared to the race/ethnic status distribution among the ideal cases (i.e. participating and non-participating) of these studies, as reported by the authors.

Analytic methods

The first analysis utilized data for race/ethnic status from the published case-control studies, after excluding eight studies that matched on race (19-26). Odds ratios (OR) with 95% confidence interval (CI) were calculated to assess the relationship between race, i.e., White and five other race/ethnic status classifications (Black, Asian, Hispanic, non-Whites, other), and case/control status separately for interview/questionnaire-based studies or record based studies (Table 3, Figure 1 and 2).

In addition, meta-analyses using the Random-effect models were conducted to provide overall ORs that compare the distribution of Whites and five other racial/ethnical categories among cases and controls, by study design and cancer type (leukemia or brain cancer). The between-study heterogeneity was assessed using the Q-statistic to test the null hypothesis that the estimated effect is the same for all studies. The second analysis compared distributions of race and ethnic status among participating cases as reported by case-control studies to those found for either the ideal cases of those studies or in the population-based cancer registries for the corresponding geographic regions and calendar periods. Only studies for which corresponding registry-based data or data for the non-participating cases were available were included in this analysis.

RESULTS

The PubMed search yielded 3760 citations. After exclusion of ineligible studies (not case-control studies, n= 1478; age above 24 years old, n=193; survival studies, n= 188; conducted outside North America, n= 1636), 135 manuscripts were reviewed in further detail. The second exclusions (no racial information, n=18; cancer registry with complete case ascertainment, n=17; no racial information from authors or cancer registry, n=8) provided a final set of 92 eligible reports representing 27 independent studies. These studies are summarized in Tables 1 and 2.

The results of the first comparison of race/ethnic status derived from published childhood leukemia and brain tumor case-control studies indicated that the proportion of non-Whites (Hispanics, Asians, others) among cases in the interview-based childhood leukemia studies was higher than that among controls (overall ORs for Hispanics, Asians, and others were =3.17, 2.78, and 1.42, respectively, $P<0.05$). In contrast, in the record-based studies, proportion of Whites among cases was higher than that among controls (overall ORs for Blacks, Asians, and others were 0.45, 0.92, and 0.91, respectively) as shown in Table 3 and Figures 1 and 2. Not in line with this trend is the overall OR for Blacks vs. Whites in the childhood leukemia interview-based studies (OR=0.43; 95% CI:0.21-0.91), which is similar to that from record-based studies (OR=0.45; 95% CI:0.35-0.57). Although, based on only two studies (27, 28), these results support the general observation that black children experience a lower incidence of childhood leukemia than white children (29).

A similar trend was observed for the relationship between race and case-control status in the brain tumor studies. The proportion of non-Whites (Blacks, Asians, Hispanics) among cases in the interview-based studies was higher than that among

controls (overall ORs=1.59, 1.27, and 1.09, respectively). But this pattern was not observed in the record based studies where the proportion of Whites among cases was higher than that among controls (overall ORs for Blacks, Asians and Hispanics were 0.82, 0.63, 0.62, and 0.55, respectively, $P<0.05$).

Meta-analyses for White vs. non-White comparisons are summarized graphically in Figures 1 and 2. All but one (30) of the interview based case-control studies suggested that cases, compared to controls, were more likely to be non-White than White with an overall OR of 1.37 (95% CI 1.13, 1.67). Three studies that were included in the meta-analysis indicated a statistically significant difference by race/ethnic status with cases more likely to be non-White than White compared to controls 1.67 (95% CI 1.07, 2.61) (31); 1.47 (95% CI 1.01, 2.15) (32); 1.44 (95% CI 1.15, 1.80) (33). In this analysis, three large studies contributed a disproportionate amount of the weight in the meta-analysis with 15.3%, 24.2%, and 17.6% (30, 32, 33), respectively. Nevertheless, the combined OR when each of these studies was excluded one at a time remained significant, indicating that no one large study completely explains the observed trend (data not shown).

In contrast to the results of the interview-based studies, all but three of the record-based case-controls studies (34-36) indicated that cases, compared to controls, are less likely to be non-White than White, with an overall OR of 0.81 (95% CI 0.72,0.91) (Figure 2).

The comparison of racial distributions among participating cases as reported by case-control studies to those found in either the ideal cases of those studies or in the population-based cancer registries in corresponding geographic regions and calendar periods is presented in Table 4. In this analysis, with one exception (31), the percentage of White cases was higher in all published childhood leukemia case-control studies compared to that using cancer registry data or data from ideal cases of the same studies. However, the observed difference in distribution of race and ethnic status was consistent with statistical significance in only two studies (22, 23). This trend was less consistent for the comparisons of the brain tumor studies, where six of the nine studies indicated a higher percent of White cases in the published case-control studies.

An example of selection bias in a hypothetical case-control study when the selection of controls varies by ethnicity (Hispanics vs. non-Hispanics Whites) and prevalence of exposure is shown in Figure 3. A similar analysis was conducted by Mezei et al. for socioeconomic status (37). For this example, it is assumed that confounding and random variability are absent, that all incident cases during the study period are included, and that there is no association between exposure and disease (i.e. true OR=1.0). An incidence rate of 40 per million (0.00004), similar to the childhood leukemia incidence rate in the US is used (29). Although Hispanics have a higher incidence rate than non-Hispanic Whites (48.5 per million vs. 41.6 per million, respectively) (29), for simplicity similar incidence rates are assumed for both groups, 0.00004 or 40 per million. Two controls are selected for each case with no matching on race or ethnic status and the exposure prevalence remained constant among the non-Hispanic Whites (0.05) but changed among the Hispanics (ranged from 0.05 to 0.15). For this example, Figure 3 shows how changes in the exposure prevalence and in the ratio of Hispanic to non-Hispanic White controls will result in an estimated measure of association that is biased away from the null. For example, if the prevalence of exposure is 0.05 among non-

Hispanic Whites and 0.15 among Hispanics and the ratio of Hispanic to non-Hispanic White controls is 2:4, then the biased OR is 1.22.

DISCUSSION

Results from the current analyses indicate differences in race and ethnic status distributions of cases and controls by method of data collection (interview-based vs. record-based). In North American interview-based childhood cancer case-control studies with no matching on race or ethnicity, the proportion of non-Whites among cases is higher than that among controls. In contrast, in record-based case-control studies, cases are less likely to be non-White than controls. These results suggest that interview-based case-control studies of childhood cancer, which do not match on race/ethnic status, may suffer from over-representation of Whites among cases and under-representation of non-Whites among participating controls. In addition, the proportion of Whites tended to be higher among participating cases compared to the proportion of Whites among non-participating cases or to the proportion of Whites among cases recorded in the cancer registries.

The distribution of race and ethnic status of cases reported in the published case-control studies may differ from the race and ethnic distribution of cases in the population-based cancer registries or among the non-participating cases for several reasons. Most case-control studies in North America require that the respondent speak either English or Spanish. Such inclusion criteria may eliminate certain minorities from participating in interview-based case-control studies, when these cases would be included in studies using population-based cancer registry data. Another source of bias in case-control studies could be the exclusion of deceased children, since certain groups, including Black and Hispanic children, may have poorer outcomes compared with that of White children. Kadan-Lottick and colleagues (38) found that Black, Hispanic, and American Indian/Alaskan Native children have a significantly poorer prognosis of childhood leukemia compared with White and Asian children. Hence, if survival is associated with race/ethnic status, then Black and Hispanic cases may be underrepresented in case-control studies which include only surviving cases.

Selection bias in case-control studies may also develop through differential selection and/or participation of cases based on their SES or due to some other cultural reasons. Previous studies have shown that individuals of higher SES are more likely to participate than individuals of lower SES (3-7) Since SES is associated with race/ethnic status, certain minorities may be underrepresented in case-control studies. Few studies have examined the sociocultural characteristics that influence research participation among Hispanics (39) which are observed to have low participation rates (8-13). Hispanics are more likely than non-Hispanic Whites in the United States to have low income and low educational levels (40), factors which are recognized to be associated with non-participation in epidemiological studies. The Northern California Childhood Leukemia Study has conducted analyses to assess differences in recruitment patterns by race and ethnic status, particularly for Hispanics, and factors that impact non-participation across race and ethnic groups (41). Participation rates for both cases and

controls were considerably lower among Hispanic families (approximately 40% of study population) than non-Hispanics. Several factors influenced the decision of Hispanic families to participate in this interview-based case control study, including language and ethnic characteristics of study personnel, cultural factors of the respondents (machismo and fatalism), level of staff training, and methods of contact (mailed information, telephone calls, in-person).

The observed differential participation bias in the interview-based case-control studies, where cases are less likely to be White than controls, may result in biased effect estimates for various potential risk factors, including SES, that are associated with race or ethnicity. This source of bias, which can result in spurious associations between disease and the wide range of exposures linked to ethnic status and SES, challenges the interpretation of data from many case-control studies. For example, selection bias is a major concern in studies looking at the association of childhood leukemia with exposures to extremely low frequency-magnetic fields (ELF-MF) (37, 42). Owing to low participation among cases and controls in some past ELF-MF studies, the potential for selection bias is large in most studies of ELF-MF exposure and childhood leukemia, except for the ones that were based on existing records and thus did not require subject participation (37, 43).

The comparison of differences by race/ethnic status between the record-based studies and the interview-based studies was limited as the majority of the record-based studies reported multiple ethnic groups while only a few interview-based studies reported data on more than one ethnic group in addition to Whites and others.

A further limitation of these analyses is that four record-based studies (16-18, 44) reported the race/ethnic status distribution as found in birth certificates, while the available race/ethnic status data from the corresponding cancer registry were coded into non-comparable categories developed by the registry. Such a difference in the source of the race/ethnic status data could contribute to misclassification. However, for three of the four studies (16-18) the data for race/ethnic status distribution as recorded in the cancer registry for both the participating cases and non-participating cases were available (Table 4). The distribution of race/ethnic status derived from the cancer registry codes were slightly different than the race/ethnic status distribution published in the three case-control studies, with the published distribution having a lower proportion of Whites.

Another limitation of these analyses is that although considerable efforts were made to obtain corresponding cancer registry data or data regarding non-participating cases, these data were not available for eight studies (28, 32, 34, 45-49). Three of the studies without reference data reported case participation rates of 43%-69% (28, 34, 49) which may represent a wide range of differential selection. Hence, it is unlikely that the absence of these studies would substantially alter the observed results.

In conclusion, investigators may need to consider differential participation by race and ethnic status as a potential source of bias in the interpretation of results from case-control studies of childhood cancer. It is important to develop strategies to improve study participation of subjects from minority groups and to evaluate the potential effects of differential participation on the study results.

Funding

This work was supported by the Electrical Power Research Institute (EP-P20634/C10044) and the National Institute of Environmental Health Sciences (PS42 ES04705, R01 ES09137).

Acknowledgements

The authors grateful for Dr. Colleen McLaughlin at the New York State Cancer Registry, Dr. Roberta McKean-Cowdin at Keck School of Medicine University of Southern California, Dr. Paula Rosenbaum at the Center for Outcomes Research & Evaluation at SUNY Upstate Medical University, Bruna DiMonte at the Pediatric Oncology Group of Ontario, Dr. David R. Risser at Texas Department of State Health Services, and Dr. Greta R. Bunin at Children's Hospital of Philadelphia for providing cancer registry data and data of non-participating cases. We also thank Dr. Jeffrey Chang for his helpful comments.

REFERENCES

1. Anderson RN SB. Deaths: leading causes for 2002. Natl Vital Stat Rep 2005;53:1-89.

2. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol 1996;25:1107-16.

3. Freudenstein U, Arthur AJ, Matthews RJ, Jagger C. Community surveys of late-life depression: who are the non-responders? Age Ageing 2001;30:517-21.

4. Goldberg M, Chastang JF, Leclerc A, Zins M, Bonenfant S, Bugel I et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: a prospective study of the French GAZEL cohort and its target population. Am J Epidemiol 2001;154:373-84.

5. Hoeymans N, Feskens EJ, Van Den Bos GA, Kromhout D. Non-response bias in a study of cardiovascular diseases, functional status and self-rated health among elderly men. Age Ageing 1998;27:35-40.

6. Purdie DM, Dunne MP, Boyle FM, Cook MD, Najman JM. Health and demographic characteristics of respondents in an Australian national sexuality survey: comparison with population norms. J Epidemiol Community Health 2002;56:748-53.

7. van den Akker M, Buntinx F, Metsemakers JF, Knottnerus JA. Morbidity in responders and non-responders in a register-based population survey. Fam Pract 1998;15:261-3.

8. Ashing-Giwa KT, Padilla GV, Tejero JS, Kim J. Breast cancer survivorship in a multiethnic sample: challenges in recruitment and measurement. Cancer 2004;101:450-65.

9. Des Jarlais G, Kaplan CP, Haas JS, Gregorich SE, Perez-Stable EJ, Kerlikowske K. Factors affecting participation in a breast cancer risk reduction telephone survey among women from four racial/ethnic groups. Prev Med 2005;41:720-7.

10. Howard CA, Samet JM, Buechley RW, Schrag SD, Key CR. Survey research in New Mexico Hispanics: some methodological issues. Am J Epidemiol 1983;117:27-34.

11. Vernon SW, Roberts RE, Lee ES. Ethnic status and participation in longitudinal health surveys. Am J Epidemiol 1984;119:99-113.

12. Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research participants. Annu Rev Public Health 2006;27:1-28.

13. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346-57.

14. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol 2006;35:370-84.

15. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER). Finding Cancer Statistics. National Cancer Institute; Bethesda, MD. 2003. (http://seer.cancer.gov/). (Accessed December 3, 2008).

16. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Birth weight, maternal weight and childhood leukaemia. Br J Cancer 2006;94:1738-44.

17. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol 2002;155:603-13.

18. Von Behren J, Reynolds P. Birth characteristics and brain cancers in young children. Int J Epidemiol 2003;32:248-56.

19. Bunin GR, Robison LL, Biegel JA, Pollack IF, Rorke-Adams LB. Parental heat exposure and risk of childhood brain tumor: a Children's Oncology Group study. Am J Epidemiol 2006;164:222-31.

20. Choi HS, Shim YK, Kaye WE, Ryan PB. Potential residential exposure to toxics release inventory chemicals during pregnancy and childhood brain cancer. Environ Health Perspect 2006;114:1113-8.

21. Gold EB, Leviton A, Lopez R, Gilles FH, Hedley-Whyte ET, Kolonel LN et al. Parental smoking and risk of childhood brain tumors. Am J Epidemiol 1993;137:620-8.

22. Kwan ML, Metayer C, Crouse V, Buffler PA. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. Am J Epidemiol 2007;165:27-35.

23. London SJ, Thomas DC, Bowman JD, Sobel E, Cheng TC, Peters JM. Exposure to residential electric and magnetic fields and risk of childhood leukemia. Am J Epidemiol 1991;134:923-37.

24. Preston-Martin S, Yu MC, Benton B, Henderson BE. N-Nitroso compounds and childhood brain tumors: a case-control study. Cancer Res 1982;42:5240-5.

25. Rosenbaum PF, Buck GM, Brecher ML. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. Paediatr Perinat Epidemiol 2005;19:152-64.

26. Wilkins JR, 3rd, Sinks T. Parental occupation and intracranial neoplasms of childhood: results of a case-control interview study. Am J Epidemiol 1990;132:275-92.

27. Infante-Rivard C, Olson E, Jacques L, Ayotte P. Drinking water contaminants and childhood leukemia. Epidemiology 2001;12:13-9.

28. Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B et al. Maternal diet and infant leukemia: the DNA topoisomerase II inhibitor hypothesis: a report from the children's oncology group. Cancer Epidemiol Biomarkers Prev 2005;14:651-5.

29. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER Program. NIH Pub. No. 99-4649 1999.

30. Preston-Martin S, Navidi W, Thomas D, Lee PJ, Bowman J, Pogoda J. Los Angeles study of residential magnetic fields and childhood brain tumors. Am J Epidemiol 1996;143:105-19.

31. Green LM, Miller AB, Villeneuve PJ, Agnew DA, Greenberg ML, Li J et al. A case-control study of childhood leukemia in southern Ontario, Canada, and exposure to magnetic fields in residences. Int J Cancer 1999;82:161-70.

32. McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli JJ et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol 1999;149:831-42.

33. Norman MA, Holly EA, Ahn DK, Preston-Martin S, Mueller BA, Bracci PM. Prenatal exposure to tobacco smoke and childhood brain tumors: results from the United States West Coast childhood brain tumor study. Cancer Epidemiol Biomarkers Prev 1996;5:127-33.

34. Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991;68:1351-5.

35. Shaw G, Lavey R, Jackson R, Austin D. Association of childhood leukemia with maternal age, birth order, and paternal occupation. A case-control study. Am J Epidemiol 1984;119:788-95.

36. Spector L, Groves F, DeStefano F, Liff J, Klein M, Mullooly J et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. Eur J Cancer 2004;40:579-84.

37. Mezei G, Kheifets L. Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. Int J Epidemiol 2006;35:397-406.

38. Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. Jama 2003;290:2008-14.

39. Frack SA, Woodruff SI, Candelaria J, Elder JP. Correlates of compliance with measurement protocols in a Latino nutrition-intervention study. Am J Prev Med 1997;13:131-6.

40. Ramirez RR DlCG. The Hispanic in the Unites States: March 2002. Current population report 2003:20-545.

41. Stroup AM. Cultural Competency in a Case-Control Study of Childhood Leukemia: Recruitment of Latinos in the Northern California Childhood Leukemia study [dissertation]. Berkeley, CA: University of California Berkeley; 2004.

42. Gurney JG, Davis S, Schwartz SM, Mueller BA, Kaune WT, Stevens RG. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. Epidemiology 1995;6:31-5.

43. Mezei G, Spinelli JJ, Wong P, Borugian M, McBride ML. Assessment of selection bias in the Canadian case-control study of residential magnetic field exposure and childhood leukemia. Am J Epidemiol 2008;167:1504-10.

44. Okcu MF, Goodman KJ, Carozza SE, Weiss NS, Burau KD, Bleyer WA et al. Birth weight, ethnicity, and occurrence of cancer in children: a population-based, incident case-control study in the State of Texas, USA. Cancer Causes Control 2002;13:595-602.

45. Neglia JP, Smithson WA, Gunderson P, King FL, Singher LJ, Robison LL. Prenatal and perinatal risk factors for neuroblastoma. A case-control study. Cancer 1988;61:2202-6.

46. Podvin D, Kuehn CM, Mueller BA, Williams M. Maternal and birth characteristics in relation to childhood leukaemia. Paediatr Perinat Epidemiol 2006;20:312-22.

47. Shu XO, Potter JD, Linet MS, Severson RK, Han D, Kersey JH et al. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. Cancer Epidemiol Biomarkers Prev 2002;11:177-85.

48. Hatch EE, Linet MS, Kleinerman RA, Tarone RE, Severson RK, Hartsock CT et al. Association between childhood acute lymphoblastic leukemia and use of electrical appliances during pregnancy and childhood. Epidemiology 1998;9:234-45.

49. Gold E, Gordis L, Tonascia J, Szklo M. Risk factors for brain tumors in children. Am J Epidemiol 1979;109:309-19.

50. Walker KM, Carozza S, Cooper S, Elgethun K. Childhood cancer in Texas counties with moderate to intense agricultural activity. J Agric Saf Health 2007;13:9-24.

51. Emerson JC, Malone KE, Daling JR, Starzyk P. Childhood brain tumor risk in relation to birth characteristics. J Clin Epidemiol 1991;44:1159-66.

52. Gurney JG, Mueller BA, Davis S, Schwartz SM, Stevens RG, Kopecky KJ. Childhood brain tumor occurrence in relation to residential power line configurations, electric heating sources, and electric appliance use. Am J Epidemiol 1996;143:120-8.

53. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). Cancer Causes Control 2006;17:1267-74.

Table 1. Characteristics of Selected Childhood Leukemia Case-Control Studies

First author	Area	Period, outcome	No. cases	Primary exposure of interest	Race/ethnicity categories*	Design	Individually Match on race
Shaw, 1984 [35]	California	1975-1980	255	Several characteristics	W, B, H, O	Records	-
Kaye, 1991 [34]	Minnesota	1969-1988	337	Birth characteristics	W, NW	Records	-
London, 1991 [23]	Los Angeles, California	1980-1987	232	Magnetic fields	NHW, B, A, H	Interview	+
Green, 1999 [31]	Ontario, Canada	1985-1993	201	Magnetic fields	W, A, O	Interview	+
McBride, 1999 [32]	Quebec, Canada	1990-1994	399	Magnetic fields	W, A, O	Interview	-
Infante-Rivard, 2001 [27]	Quebec, Canada	1980-1993	491	Drinking water	W, B, O	Interview	-
Reynolds, 2002 [17]	California	1988-1997	1407	Birth characteristics	NHW, B, A, H, NA/O	Records	-
Okcu, 2002 [44]	Texas	1995	104	Birth characteristics	W, B, H, O	Records	-
Spector, 2004 [36]	California, Washington	1985-1999	180	Allergies	W, B, O	Records	-
Rosenbaum, 2005 [25]	New York state	1980-1991	255	Allergies, infections	W, NW	Records, mailed questionnaires	+
Spector, 2005 [28]	United States	1996-2002	240	Maternal diet	W, B, H, O	Interview	-
Podvin, 2006 [46]	Washington	1981-2003	595	Birth characteristics	W, B, A, NA, H, O	Records	-
McLaughlin, 2006 [16]	New York state	1985-2001	1070	Birth weight	NHW, B, H, O	Records	-
Walker, 2007 [50]	Texas	1990-1998	1207	Agricultural activity	W, B, H, O	Records	-
Kwan, 2007 [22]	California	1995-2002	365	Maternal illnesses	NHW, NHB, H, O	Interview	+

*W-White, B-Black, A-Asian, NW- non-White, NHW- non-Hispanic White, NHB- non-Hispanic Black, NA-Native American, H-Hispanic, O-other

Table 2. Characteristics of Selected Childhood Brain Tumor Case-Control Studies

First author	Area	Period, outcome	No. cases	Primary exposure of interest	Race/ethnicity categories*	Design	Individually Match on race
Preston-Martin, 1982 [24]	Los Angeles, California	1972-1977	209	N-Nitroso Compounds	W, B	Interview	+
Wilkins, 1990 [26]	Columbus, Ohio	1975-1982	110	Parental occupation	W, NW	Interview	+
Emerson, 1991 [51]	Washington	1974-1986	157	Birth characteristics	W, NW	Records	-
Gold, 1993 [21]	Eight SEER registries	1977-1981	361	Parental smoking	NHW, B, A, H, O	Interview	+
Gurney, 1996 [52]	Washington	1984-1990	133	Magnetic fields	W, NW	Interview	-
Norman, 1996 [33]	California, Washington	1984-1991	540	Parental smoking	W, B, A, H, O	Interview	-
Preston-Martin, 1996 [30]	Los Angeles, California	1984-1991	298	Magnetic fields	NHW, NHB, A, H, O	Interview	-
Von Behren, 2003 [18]	California	1988-1997	746	Birth characteristics	NHW, NHB, A/NA/O, H, U	Records	-
Shaw, 2006 [53]	British Colombia, Quebec, Manitoba, Saskatchewan, & Alberta, Canada	1980-1999	272	Early infections	W, NW	Interview	-
Bunin, 2006 [19]	Midwestern & mid-Atlantic states	1991-1997	318	Electromagnetic fields	H, NHW, NHB, O	Interview	+
Choi, 2006 [20]	Florida, New Jersey, New York, Pennsylvania	1993-1997	382	Residential toxics	W, B, O	Interview	+
Walker, 2007 [50]	Texas	1990-1998	766	Agricultural activity	W, B, H, O	Records	-

* W-White, B-Black, A-Asian, NW- non-White, NHW- non-Hispanic White, NHB- non-Hispanic Black, NA-Native American, H-Hispanic, O-other, U-unknown

Table 3. Racial Distribution in Cases and Controls by Case-Control Study Design

	Cases %					Controls %				
	White/ NH White	Black/NH Black	Asian	Hispanic	Other	White/ NH White	Black/NH Black	Asian	Hispanic	Other
Leukemia: Interview-based studies										
Green, 1999	79.6		7.5		12.9	86.7		3.2		10.1
McBride, 1999	79.0		4.1		16.9	84.7		1.3		13.9
Infante-Rivard, 2001	94.9	1.0			4.1	96.5	2.2			1.3
Spector, 2005	79.5	2.1		10.5	7.9	85.5	5.5		3.5	5.5
Overall OR 95%CI										
Leukemia: Record-based studies										
Shaw, 1984	64.3	5.1		26.7	3.9	64.3	8.8		19.8	7.1
Kaye, 1991	97.3				2.7	98.5				1.5
Okcu, 2002	50.9	2.9		45.2	1.0	45.1	12.5		39.8	2.6
Reynolds, 2002	38.5	2.7	10.9	47.2	0.6	35.7	8.4	10.8	44.6	0.6
Spector, 2004	52.0	6.8			41.2	51.9	12.4			35.7
McLaughlin, 2006	81.1	4.3		10.4	4.2	75.9	6.6		13.3	4.2
Podvin, 2006	81.4	2.7	5.1	8.4	2.3	79.0	5.3	5.6	7.3	2.8
Walker, 2007	49.8	5.9		42.6	1.7	47.3	13.4		36.8	2.5
Overall OR 95%CI										
Brain Tumor: Interview-based studies										
Gurney, 1996	89.5	10.5				94.8	5.2			
Norman, 1996	58.0	7.8	5.4	27.2	1.7	66.5	5.1	3.6	22.9	1.9
Preston-Martin, 1996	39.6	8.7	5.0	45.6	1.0	35.9	8.1	5.4	49.3	1.3
Shaw, 2006	93.8	6.3				96.7	3.3			
Overall OR 95%CI										
Brain Tumor: Record-based studies										
Emerson, 1991	95.5				4.5	91.0				9.0
Von Behren, 2003	46.7	8.9	8.8[†]	35.6		34.6	9.5	10.3	45.6	
Walker, 2007	56.0	14.4		28.6	1.0	47.3	13.4		36.8	2.5

[*] NH - non-Hispanic. [†]Asian & Other.

Table 3. Continued

	Black/NH* Black vs.White/ NH White		Asian vs. White/ NH White		Hispanic vs. White/ NH White		Other vs. White/ NH White	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Leukemia: Interview-based studies								
Green, 1999			2.54	1.18,5.46			1.40	0.82,2.36
McBride, 1999			3.27	1.17,9.11			1.30	0.87,1.94
Infante-Rivard, 2001	0.46	0.16,1.34					1.85	0.88,3.90
Spector, 2005	0.41	0.14,1.15			3.17	1.44,6.96	1.55	0.76,3.17
Overall OR 95%CI	0.43	0.21,0.91	2.78	1.50,5.13	3.17	1.44,6.96	1.42	1.08,1.87
Leukemia: Record-based studies								
Shaw, 1984	0.58	0.30,1.10			1.35	0.94,1.93	0.56	0.27,1.15
Kaye, 1991							1.81	0.81,4.00
Okcu, 2002	0.20	0.06,0.66			1.00	0.67,1.50	0.33	0.04,2.41
Reynolds, 2002	0.30	0.21,0.43	0.94	0.75,1.17	0.98	0.85,1.13	0.98	0.43,2.21
Spector, 2004	0.55	0.28,1.05					1.15	0.81,1.64
McLaughlin, 2006	0.61	0.45,0.83			0.73	0.60,0.90	0.95	0.69,1.30
Podvin, 2006	0.50	0.30,0.84	0.88	0.60,1.30	1.12	0.82,1.52	0.83	0.47,1.44
Walker, 2007	0.42	0.32,0.55			1.10	0.96,1.27	0.64	0.39,1.05
Overall OR 95%CI	0.45	0.35,0.57	0.92	0.76,1.12	1.01	0.86,1.17	0.91	0.72,1.14
Brain Tumor: Interview-based studies								
Gurney, 1996	2.15	0.99,4.66						
Norman, 1996	1.74	1.11,2.74	1.70	1.00,2.90	1.37	1.05,1.77	1.02	0.44,2.36
Preston-Martin, 1996	0.98	0.53,1.81	0.85	0.40,1.80	0.84	0.59,1.19	0.68	0.15,3.11
Shaw, 2006	1.95	0.85,4.45						
Overall OR 95%CI	1.59	1.14,2.20	1.27	0.65,2.48	1.09	0.67,1.75	0.93	0.45,1.93
Brain Tumor: Record-based studies								
Emerson, 1991							0.47	0.21,1.05
Von Behren, 2003	0.70	0.51,0.97	0.63	0.46,0.87	0.58	0.47,0.70	0.63	0.46,0.87
Walker, 2007	0.91	0.72,1.15			0.66	0.55,0.79	0.35	0.17,0.74
Overall OR 95%CI	0.82	0.64,1.05	0.63	0.46,0.87	0.62	0.54,0.71	0.55	0.40,0.75

Table 4. Cases by Race as Derived From Published Case-Control Studies and Cancer Registries

	Case-control studies (cases only) n(%)					Cancer registries, ideal cases n(%)				
Author, year	**White/ NH[a] White**	**Black / NH Black**	**Asian**	**Hispanic**	**Other / NH Other**	**White/ NH White**	**Black / NH Black**	**Asian**	**Hispanic**	**Other / NH Other**
Leukemia: Interview-based studies										
London, 1999*, †	117 (50.4)	13 (5.6)	17 (7.3)	85 (36.6)		205 (41.2)	40 (8.0)	22 (4.4)	216 (43.5)	14 (2.8)
Green, 1999†	160 (79.6)		15 (7.5)		26 (12.9)	778 (83.0)	19 (6.9)	65 (2.0)		76 (8.1)
Kwan, 2007*, †	188 (51.5)	13 (3.6)		130 (35.6)	34 (9.3)	433 (41.8)	49 (4.7)		405 (39.0)	150 (14.5)
Leukemia: Record-based studies										
Okcu, 2002†	53 (50.9)	3 (2.9)		47 (45.2)	1 (1.0)	65 (47.1)	9 (6.5)		61 (44.2)	3 (2.2)
Reynolds, 2002†	702 (42.5)	55 (3.3)	173 (10.5)	693 (42.0)	28 (1.7)	820 (41.7)	67 (3.4)	197 (10.0)	863 (43.9)	18 (0.9)
Rosenbaum, 2005‡	245 (96.1)				10 (3.9)	369 (92.2)				31 (7.8)
McLaughlin, 2006‡	945 (88.3)	55 (5.1)		44 (4.1)	26 (2.4)	1091 (86.8)	68 (5.4)		59 (4.7)	39 (3.1)
Brain Tumor: Interview-based										
Preston-Martin, 1982†	192 (91.9)	19 (8.2)				315 (89.2)	38 (10.8)			
Wilkins, 1990‡	106 (96.4)				4 (3.6)	142 (94.0)				9 (6.0)
Gold, 1993†	276 (76.5)	32 (8.8)	31 (8.6)	19 (5.3)	3 (0.8)	463 (75.4)	75 (12.2)	41 (6.7)	30 (4.9)	5 (0.8)
Gurney, 1996†	119 (89.5)				14 (10.5)	185 (90.7)				19 (9.3)
Norman, 1996†	313 (58.0)	42 (7.8)	29 (5.4)	147 (27.2)	9 (1.7)	555 (62.5)	83 (9.3)	34 (3.8)	210 (23.6)	7 (0.8)
Preston-Martin, 1996†	118 (39.6)	26 (8.7)	15 (5.0)	136 (45.6)	3 (1.0)	196 (43.2)	48 (10.6)	21 (4.6)	172 (37.9)	17 (3.7)
Bunin, 2006‡	260 (81.8)	16 (5.0)		31 (9.7)	11 (3.5)	403 (72.2)	43 (7.7)		72 (12.9)	40 (7.2)
Choi, 2006*, ‡	335 (87.7)	41 (10.7)			6 (1.6)	455 (86.5)	60 (11.4)			11 (2.1)
Brain Tumor: Record-based studies										
Von-Behren, 2003†	377 (50.5)	59 (7.9)	46 (6.2)	248 (33.2)	16 (2.1)	456 (50.3)	74 (8.2)	57 (6.3)	307 (33.9)	13 (1.4)

* Statistically significant difference in the percentage of white cases ($P<0.05$).
† Cancer Registry/SEER data.
‡ Ideal cases data provided by author.

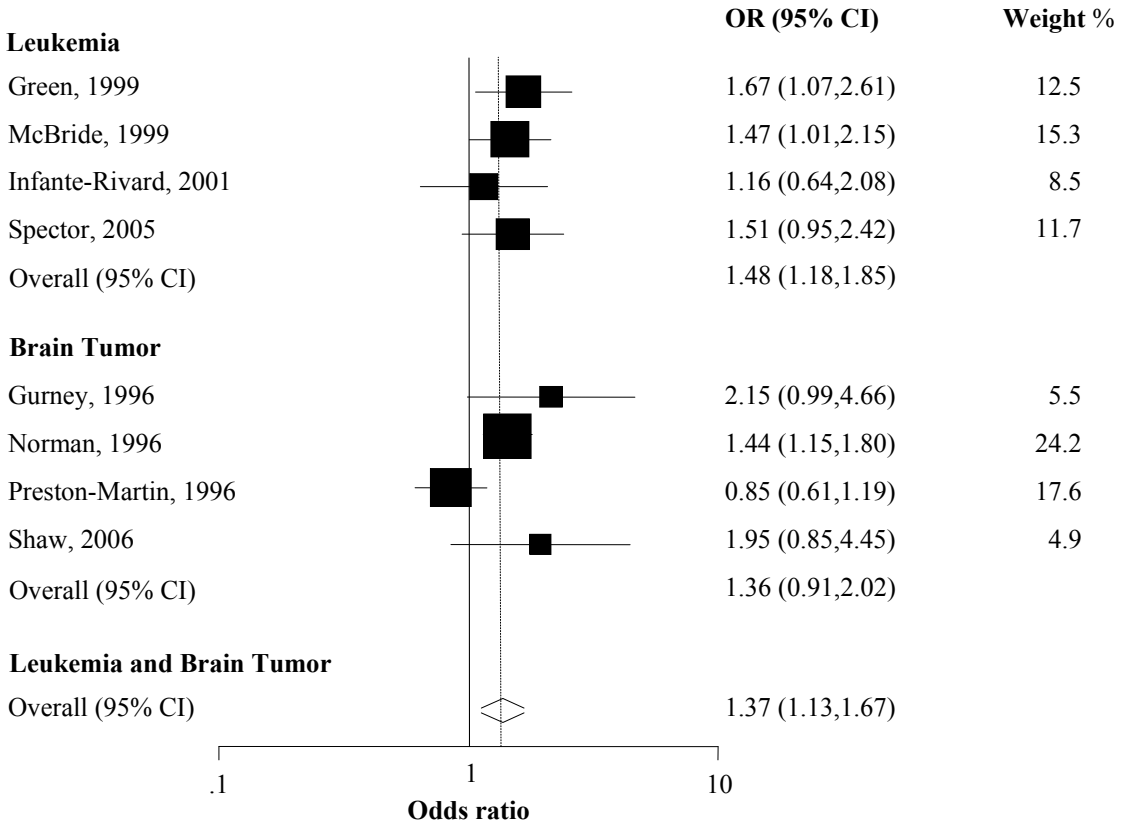


Figure 1. Forest plot displaying odds ratios and 95% confidence intervals in interview-based studies, comparing White and non-White (Black, Asian, Hispanic, other) by case-control status, random effect model

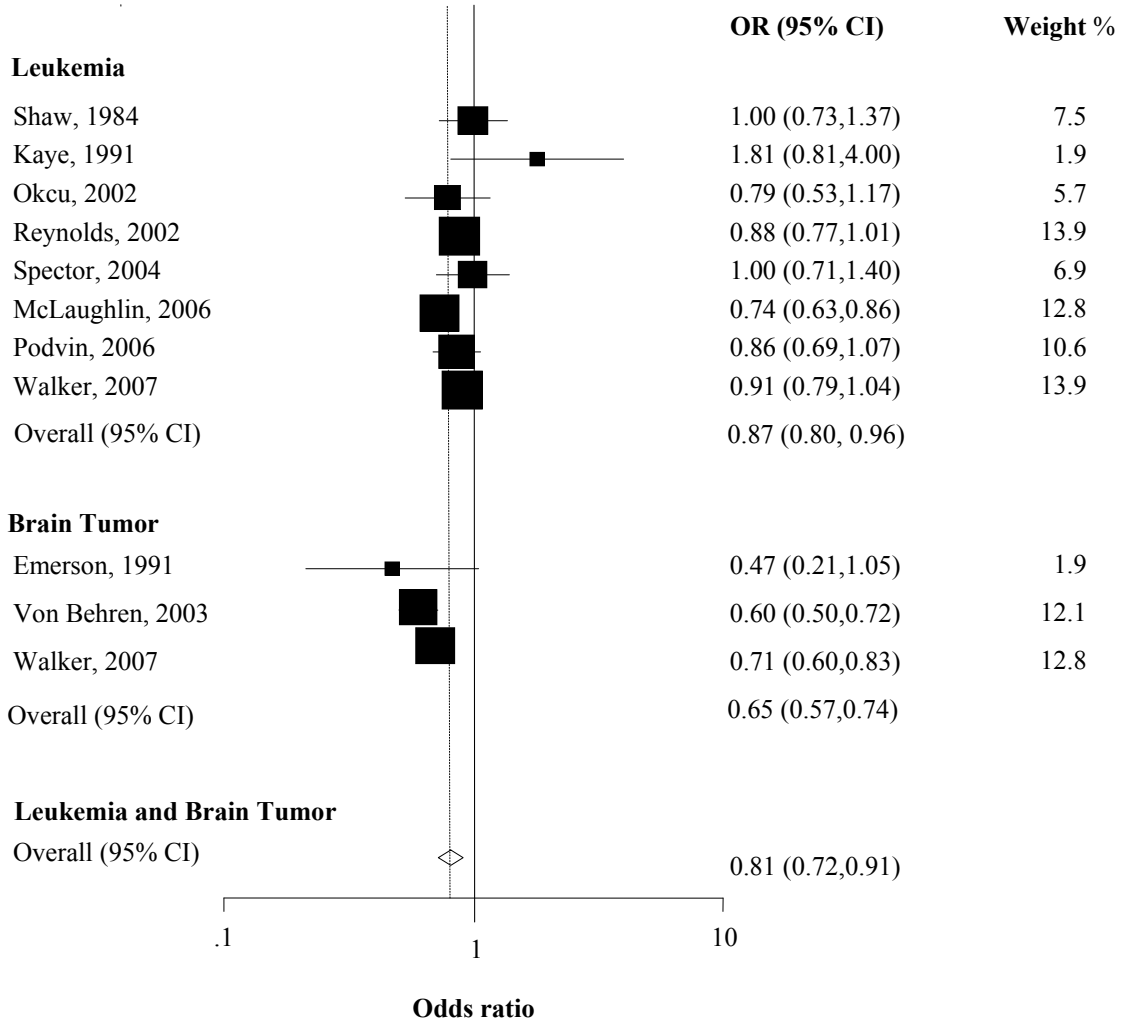


Figure 2. Forest plot displaying odds ratios and 95% confidence intervals in record-based studies, comparing White and non-White (Black, Asian, Hispanic, other) by case-control status, random effect model

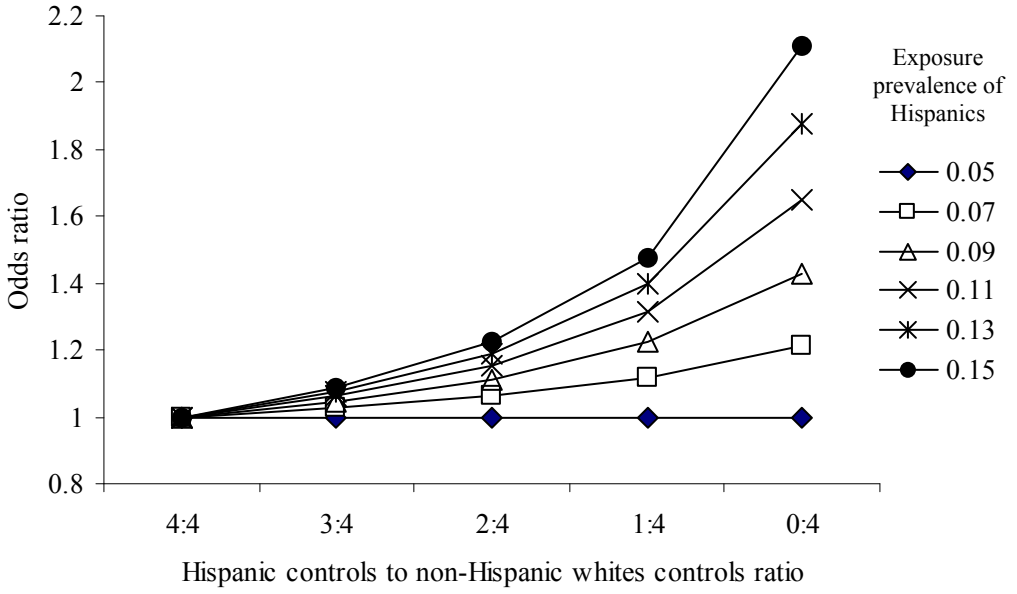


Figure 3. Example of selection bias in a hypothetical case-control study representing changes in odds ratios by control selection ratio and exposure prevalence. Exposure prevalence of non-Hispanic Whites is constant at 0.05.

CHAPTER THREE

Childhood Leukemia and Socioeconomic Status:

Direction of Association Potentially Depends on Study Design

ABSTRACT

Numerous epidemiological studies have examined the association between socioeconomic status (SES) and childhood leukemia, providing inconsistent results. Interview or questionnaire-based studies tend to show inverse associations and registry-based studies generally produced positive associations. In this paper, we compare the association between SES and childhood leukemia using data from three sources: face-to-face interview, birth certificates, and California 1990 and 2000 censuses. The study population is a subset of the Northern California Childhood Leukemia Study, an ongoing case-control study. Results indicate that the direction of association between childhood leukemia and SES depends on the study design, with interview-based-case control study design indicating inverse association but ecologic level design indicating a positive association. The results of the analysis using interview-based case-control study indicate an inverse association, with cases having lower SES levels. Participating controls had statistically significant ($P<0.05$) higher levels of household income, maternal education and maternal age at child's birth than the participating cases. In contrast, a positive association between SES and childhood leukemia was observed while using individual data from birth certificates or from the California 1990 and 2000 censuses with a study design that resembles an ecological study (comparison of ideal cases and ideal controls). The difference in the direction is probably due to differential participation between cases and controls, with participant controls of higher SES than participant cases or of non-participant controls. This source of bias, which can result in spurious associations between disease and the wide range of exposures linked to SES, challenges the interpretation of data from many case-control studies.

BACKGROUND

Numerous epidemiological studies have examined the association between socioeconomic status (SES) and childhood leukemia, providing inconsistent results. In a 1985 review of the epidemiology of childhood cancers, Greenberg and Shuster indicated a remarkable consistency of results across various study locations and periods of time, indicating a positive association between SES and risk of leukemia among children (1). More than a dozen years later, in 1999, the National Cancer Institute (NCI) classified high SES as a 'known risk factor' for acute lymphoblastic leukemia (ALL) (2). However, the report by the NCI did not include several studies published after 1982 that reported associations in the inverse direction, with lower rates of leukemia associated with higher levels of SES. These studies were included in a later review by Poole et al. (2005) on the associations between childhood leukemia and SES (3). Poole et al. concluded that the noted association depends on study design with individual level data (interview-based) tending to show inverse associations while ecologic level data (mostly census-based) tending to show positive association.

Individual-level measures of family income (4-11), mother's education (4, 6, 8-16) and parental education (4, 6, 8-11, 16-20) have been found to be consistently associated with childhood leukemia in the inverse direction, with higher rates associated with lower SES levels. However, the results of studies on childhood leukemia and ecologic or population-level measures of SES indicate that almost all of the studies of SES and childhood leukemia shows a positive association (21-27), few reported mixed results (28-30), and only two indicated an inverse association (31, 32).

The difference in the direction of association between the individual-level data and the ecologic-level (population based) data could be explained by a potential effect of selection bias. Selection bias related to SES might be a major cause underlying the heterogeneous results, with interview-based case-control studies including most cases, but only a selected subset of all relevant controls. This results in an overrepresentation of high-SES controls owing to a lower response rate in controls of lower SES. Ecologic-level studies collect data for all subjects and are less prone to selection bias.

Although there are numerous reviews of this literature, to our knowledge, this is the first study on the association between SES and childhood leukemia to use both interview-based and registry-based study design using the same study population.

METHODS

Study population

The Northern California Childhood Leukemia Study (NCCLS) is an ongoing case-control study, commenced in 1995. Phase I of the study (1995–1999) included 17 counties in the San Francisco Bay Area, and phases II and III (1999–today) included 18 additional counties in the California Central Valley. Incident cases of childhood leukemia were rapidly ascertained from nine pediatric clinical centers, usually within 72 hours after diagnosis. For each case, one or two control subjects were randomly selected from birth

certificates through the California Office of Vital Records, matched on age, sex, Hispanic ethnicity, and maternal race. The eligibility criteria for all subjects were (1) being a resident of the study area, (2) aged below 15 years at case diagnosis date (reference date for controls), (3) having at least one English- or Spanish-speaking parent or guardian, and (4) without previous cancer.

A detailed description of control selection in the parent NCCLS study has been published previously (33, 34). In short, for each control, a set of four birth certificates meeting the matching criteria was randomly generated. One of the four birth certificates was randomly chosen as a potential control to be recruited (first choice control). If the recruitment with the first-choice control was not successful, another birth certificate from those remaining was randomly selected. Additional sets of four birth certificates were requested if recruitment was not successful with the first set of birth certificates. Figure 1 presents the selection of cases and controls in the NCCLS, August 1995 - December 2004.

The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the Institutional Review Boards of all the participant hospitals.

Data collection

Individual-level data of SES measures (family income, parental education, etc.) were collected by an in-home interview with the biological mother for all of the participating subjects. In addition, data were collected from birth certificates for all subjects, regardless of their participation status. Birth certificate information included date of birth, residence at time of birth, gender, race/ethnicity, parental age, education, and occupation.

Ecologic-level data were collected using the mother's residential address at the time of child's birth. Residences were assigned address-level latitude and longitude coordinates using a geographic information system. Each address was assigned to a 1990 or 2000 US Census block group, depending on the child's date of birth. When possible, the addresses that could not be matched automatically were manually located. The geocoding was carried out using ArcView GIS software (35). Data from the U.S. Census Bureau were used to derive neighborhood measures of urbanization and SES. The methods for creating these variables have been previously described (36, 37). In short, urbanization included four levels: metropolitan urban (population greater one million; highest quartile of population density within an urbanized area), metropolitan suburb (population greater one million; the rest of the population within an urbanized area), city (population >= 50,000, outside of urbanized area), and rural/town (population < 50,000, outside of urbanized area). To create the SES neighborhood variables, the California block groups were ranked separately by education level (percentage of adults ≥ 25 years of age completing a college degree or higher), income (median family income), and occupation (percentage of adults employed in managerial/professional occupations) according to quartiles, based on the statewide adult population (38, 39). This resulted in a score of 1–4 for each of these SES attributes. A summary SES metric was created by summing the scores across each of the four SES attributes and categorizing them into four groups (high to low), based on the quartiles of this score.

Statistical analysis

Descriptive analyses were conducted to compare distributions of socio-demographic characteristics by study design and between several case and control groups (interview based case-control and record based case-control). The first analysis, using interview-based design, was done to compare individual level data (using interview data) between actual (participating) cases (n=685) and actual controls (first-choice participating and non-first choice participating controls) controls (n=877).

The second analysis was performed to compare individual-level data (using birth certificate data) between actual cases and actual controls (interview based design). It also compared ideal cases (participating and non-participating; n=791) and ideal controls (first choice participating and non-first choice participating controls; n=877). The latter comparison may use individual level data from birth certificates, but the study design resembles a record based case-control study.

The third analysis was performed to compare ecologic-level data (California 1990 and 2000 censuses) between actual cases and actual controls as well as between ideal cases and ideal controls. The results of the three analyses will be compared to assess change in the direction of the association change while using different sources of data (individual-level data versus ecologic-level data) and by study design (interview-based versus record-based). Additional analysis was done to compare SES measures between participating controls to non-participating controls.

RESULTS

The sociodemographic characteristics from the in-person interview of the actual cases (n=685) and controls (n=838) are shown in Table 1. Actual cases and controls were comparable with respect to the matching variables (age, gender, race, and Hispanic status) as well as parental occupation. Actual controls had statistically significant ($P<0.05$) higher levels of household income, maternal education and maternal age at child's birth than the actual cases. These results remained significant after adjusting for the matching variables. Overall, although not all comparisons of the interview-based data yielded significant results, all comparisons indicated an inverse association between childhood leukemia and SES, with cases more likely to have lower level of SES than controls (Table 1).

A similar trend was observed while comparing individual-level data from birth certificates between actual cases and actual controls. This comparison, also using interview-based design with individual level data, indicated an inverse association between childhood leukemia and SES characteristics in all studies characteristics. This analysis indicated that actual controls had statistically significant ($P<0.05$) higher levels maternal education and maternal age at child's birth than the actual cases. In contrast, while using the same birth certificate data with record-based design to compare ideal cases (n=791) and ideal controls (n=877) all comparisons indicated a positive association between childhood leukemia and SES characteristics. This analysis aimed to use individual-level data with a subject selection that resembles record based study design. Ideal controls had statistically significant ($P<0.05$) lower levels of paternal education

(P=0.006) and were less likely to be in the professional occupation category (p=0.021) (Table 2).

Table 3 presents the characteristics of cases and controls using population-level data from the California 1990 and 2000 censuses. Similar to the trend above, the comparison between the actual cases and the actual controls showed inverse association between SES measures and childhood leukemia, while the comparison of ideal cases to ideal controls indicate a positive association. Our results are consistent with those of previous population studies, observing an association between SES and increased risk of childhood leukemia.

Participating controls (both first choice and non-first choice) had a significantly ($P < 0.001$) higher SES than the non-participating controls in all SES categories, both birth certificates and from census (Table 4).

DISCUSSION

To our knowledge, this is the first study on the association between SES and childhood leukemia to use both interview-based and registry-based study designs, as well as three different sources of data, using the same study population. Results indicate that the direction of association between childhood leukemia and SES depends on the study design, with interview-based case- control study design indicating an inverse association, but record-based designs indicating a positive association.

The results of the analysis using data from an interview-based case-control study indicate an inverse association between childhood leukemia and SES, with cases having lower SES levels. Actual controls had statistically significant ($P<0.05$) higher levels of household income, maternal education and maternal age at child's birth than the actual cases. These results were in line with previous studies reporting an inverse association between childhood leukemia and individual level SES characteristics, such as mother education (4, 6, 8-16), and household income (4-11).

A similar trend of an inverse association was observed while comparing individual level data from birth certificates while using the same sample of actual cases and controls. In contrast, a positive association was observed while using individual level data from birth certificates (Table 2) or from the censuses (Table 3) with a study design that resembles a population study by comparing ideal cases to ideal controls. These results are consistent with those of previous population studies, reporting an association between increased risk of childhood leukemia and SES characteristics: higher paternal education, professional class, census income, and poverty (21-27).

Our conclusions are in line with Poole et al. who conducted a review of SES and childhood leukemia (2006), observing that while case-control studies with interviews or self-administered questionnaires reported an inverse association between individual level measures of SES (family income, father's education, and mother's education) and childhood leukemia, record-based case-control and ecologic studies tend to show a positive association between childhood leukemia and father's occupational class or average occupational class (3). Poole et al. indicated that it is not clear whether the observed differences were due to inherent differences in the SES measures or due to

differences in study designs. However, our second and third analysis, using comparable SES measures, indicates that the observed differences are more likely to be the result of study design than inherent differences in the SES measures.

Furthermore, our comparison between participating controls (both first choice and non-first choice) to non-participating controls indicated that participating controls had a significantly ($P < 0.001$) higher SES in all categories, of both birth certificates and census. A similar trend was observed when comparing participating cases to non-participating cases, though significance ($P<0.05$) was observed only for percent professionals, income, and college degree (data not shown). These results may indicate that the differences in the direction of association depend on study design: with interview-based case-control studies suffering from lower participation rate than record-based studies.

The low participation rates in case-control studies may allow for a wider range of differential selection but it does not necessarily indicate the presence of selection bias, and a study may be completely unbiased in spite of poor participation (40). Even if selection and/or response rates are different for cases and controls and/or for exposed and unexposed subjects, it does not necessarily indicate selection bias. Selection bias develops only if the selection/inclusion probabilities are differential for cases and controls based on their exposure status (40). The observed differential participation rates in the interview-based case-control studies, where cases are less likely to be of higher SES than controls, may result in biased effect estimates for various potential risk factors that are associated with SES. This source of bias, which can result in spurious associations between disease and the wide range of exposures linked to SES, challenges the interpretation of data from many case-control studies.

The association between participation in epidemiologic studies and SES, especially case-control studies, is well documented, with individuals of higher SES more likely to participate than individuals of lower SES (41-43). It has been shown that more educated persons are more likely to participate in studies (44), regardless of type of study or methods of data collection (45), and employed are more likely to participate than unemployed (45, 46). Participation may also differ by race/ethnicity; for example, Hispanics are less likely to participate than non-Hispanic Whites (47-52). In addition, women are more likely to participate than men (53, 54) and older persons are more likely to participate than young persons (53, 54).

Participation rates for epidemiologic studies have been declining over the past 30 years (55, 56), with even steeper declines seen in recent years. Morton et al. (2006) have conducted a retrospective review of reporting participation in epidemiologic studies to assess changes in participation over time. The authors concluded that participation rates have declined during 1970–2003 for all study designs (55), with population-based, case-control studies having the most steep decline, particularly for controls (-1.86% per year, 95% CI: -3.03,-0.69). During the past 3 decades, proportionally more studies have collected biologic specimens, but fewer than 3 in 10 reported participation for the specimen component (57).

Various studies have pointed out the increasingly challenging task of achieving high levels of participation in epidemiologic studies (55-59). Several factors have been found to affect participation. The salience of the topic exerts the strongest effect on willingness (57, 60): various family and medical history or exposure factors, especially

those involved with the topic under study (44) and including disease status (61, 62). For example, participation rates among cases in case-control studies are consistently higher than those among controls (61, 62). In addition, the methods of recruitment can contribute (44, 63), with face-to-face or other in-person approaches eliciting higher response than initial telephone contacts, but they are more expensive and harder to monitor for quality assurance (57). The personality, training, and experience of the recruiter have major effects (57). The use of incentives (64, 65) was found to enhance response, especially incentives given early in the recruitment process (57). Reducing the burden of interview is important. Clear questionnaire structure (65, 66) that reduce the time or burden of the interview; shorter instruments, and as well as method and number of contacts (65, 67). Studies requiring substantial time commitments or involving invasive procedures have lower participation rates than studies with lower participant burdens. Lastly, it is important to show respect to participants by offering them the results of the measurements done on them, as well as the option of receiving a summary of the study findings. There are many different methods for increasing participation rates, yet the constant decline in participation rate in epidemiological studies over the past three decades shows that improving participation rates has become more and more challenging for investigators.

The comparison of differences by SES between the studies using population-based data and the interview-based data was limited because of the matching on race done in the NCCLS. Although our analysis used a sample of the NCCLS study population and therefore wasn't a matched file, our cases and controls did come from the matched NCCLS and therefore had some racial similarity which prevented us from comparing racial and Hispanic status between cases and controls. In addition, with race being associated with many SES characteristics it also had potential to reduce the observed differences between the actual cases and controls, as well as between the ideal cases and controls.

Results indicate that the direction of association between childhood leukemia and SES depends on the study design, with interview-based case-control study design indicating an inverse association but studies using record-based designs indicating a positive association. The difference in the direction is probably due to differential participation between cases and controls in the interview-based study, with participant controls of higher SES than participant cases or of non-participant controls. The observed differential participation bias may result in biased effect estimates for various potential risk factors that are associated with SES. This source of bias, which can result in spurious associations between disease and the wide range of exposures linked to SES, challenges the interpretation of data from many case-control studies. With the constant decrease over the last three decades in subject participation, it is important to develop strategies to improve study participation and collection of data from non-participants in order to adjust for potential bias introduced by study nonparticipation.

REFERENCES

1. Greenberg RS, Shuster JL, Jr. Epidemiology of cancer in children. Epidemiol Rev 1985;7:22-48.

2. Ries LG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al. Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995. Bethesda, MD: National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. 1999.

3. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol 2006;35:370-84.

4. Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. J Natl Cancer Inst 1996;88:24-31.

5. Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J et al. Diagnostic X-ray and ultrasound exposure and risk of childhood cancer. Br J Cancer 1994;70:531-6.

6. Groves FD, Gridley G, Wacholder S, Shu XO, Robison LL, Neglia JP et al. Infant vaccinations and risk of childhood acute lymphoblastic leukaemia in the USA. Br J Cancer 1999;81:175-8.

7. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol 2002;155:603-13.

8. McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli JJ et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol 1999;149:831-42.

9. Green LM, Miller AB, Agnew DA, Greenberg ML, Li J, Villeneuve PJ et al. Childhood leukemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. Cancer Causes Control 1999;10:233-43.

10. Brondum J, Shu XO, Steinbuch M, Severson RK, Potter JD, Robison LL. Parental cigarette smoking and the risk of acute leukemia in children. Cancer 1999;85:1380-8.

11. Ma X, Buffler PA, Selvin S, Matthay KK, Wiencke JK, Wiemels JL et al. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2002;86:1419-24.

12. Dockerty JD, Elwood JM, Skegg DC, Herbison GP. Electromagnetic field exposures and childhood cancers in New Zealand. Cancer Causes Control 1998;9:299-309.

13. Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). Cancer Causes Control 2000;11:547-53.

14. Petridou E, Kassimos D, Kalmanti M, Kosmidis H, Haidas S, Flytzani V et al. Age of exposure to infections and risk of childhood leukaemia. Bmj 1993;307:774.

15. Rosenbaum PF, Buck GM, Brecher ML. Early child-care and preschool experiences and the risk of childhood acute lymphoblastic leukemia. Am J Epidemiol 2000;152:1136-44.

16. Thompson JR, Gerald PF, Willoughby ML, Armstrong BK. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: a case-control study. Lancet 2001;358:1935-40.

17. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res 1989;49:4030-7.

18. Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W et al. A population-based case-control study of childhood leukemia in Shanghai. Cancer 1988;62:635-44.

19. Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991;68:1351-5.

20. Perrillat F, Clavel J, Auclerc MF, Baruchel A, Leverger G, Nelken B et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. Br J Cancer 2002;86:1064-9.

21. Dickinson HO, Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: the Seascale cluster. Br J Cancer 1999;81:144-51.

22. Browning D, Gross S. Epidemiological studies of acute childhood leukemia. A survey of Cuyahoga county, Ohio. Am J Dis Child 1968;116:576-85.

23. Githens JH, Elliot FE, Saunders LH. The Relation of Socioeconomic Factors to Incidence of Childhood Leukemia. Public Health Rep 1965;80:573-8.

24. Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. Bmj 1993;306:743-8.

25. McWhirter WR. The relationship of incidence of childhood lymphoblastic leukaemia to social class. Br J Cancer 1982;46:640-5.

26. Pinkel D, Nefzger D. Some epidemiological features of childhood leukemia in the Buffalo, N. Y., area. Cancer 1959;12:351-8.

27. Richardson S, Monfort C, Green M, Draper G, Muirhead C. Spatial variation of natural radiation and childhood leukaemia incidence in Great Britain. Stat Med 1995;14:2487-501.

28. Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Community lifestyle characteristics and risk of acute lymphoblastic leukaemia in children. Lancet 1990;336:1461-5.

29. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;30:1428-37.

30. Muirhead CR. Childhood leukemia in metropolitan regions in the United States: a possible relation to population density? Cancer Causes Control 1995;6:383-8.

31. McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. Br J Cancer 1999;80:1844-51.

32. Reynolds P, Elkin E, Scalf R, Von Behren J, Neutra RR. A case-control pilot study of traffic exposures and early childhood leukemia using a geographic information system. Bioelectromagnetics 2001;Suppl 5:S58-68.

33. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915-21.

34. Chang JS, Metayer C, Fear NT, Reinier K, Yin X, Urayama K et al. Parental social contact in the work place and the risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2007;97:1315-21.

35. Environmental Systems Research Institute I. ArcView, version 3.3. Redlands (CA): ESRI. 2000.

36. Reynolds P, Hurley SE, Gunier RB, Yerabati S, Quach T, Hertz A. Residential proximity to agricultural pesticide use and incidence of breast cancer in California, 1988-1997. Environ Health Perspect 2005;113:993-1000.

37. Reynolds P, Hurley SE, Quach AT, Rosen H, Von Behren J, Hertz A et al. Regional variations in breast cancer incidence among California women, 1988-1997. Cancer Causes Control 2005;16:139-50.

38. Armstrong R, Chettle DR, Scott MC, Somervaille LJ, Pendlington M. Repeated measurements of tibia lead concentrations by in vivo x ray fluorescence in occupational exposure. Br J Ind Med 1992;49:14-6.

39. United States Bureau of the Census. Tiger2000 [data file]. Washington DC: US Census Bureau 2002.

40. Mezei G, Kheifets L. Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. Int J Epidemiol 2006;35:397-406.

41. Purdie DM, Dunne MP, Boyle FM, Cook MD, Najman JM. Health and demographic characteristics of respondents in an Australian national sexuality survey: comparison with population norms. J Epidemiol Community Health 2002;56:748-53.

42. Goldberg M, Chastang JF, Leclerc A, Zins M, Bonenfant S, Bugel I et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: a prospective study of the French GAZEL cohort and its target population. Am J Epidemiol 2001;154:373-84.

43. Hoeymans N, Feskens EJ, Van Den Bos GA, Kromhout D. Non-response bias in a study of cardiovascular diseases, functional status and self-rated health among elderly men. Age Ageing 1998;27:35-40.

44. Corbie-Smith G, Viscoli CM, Kernan WN, Brass LM, Sarrel P, Horwitz RI. Influence of race, clinical, and other socio-demographic features on trial participation. J Clin Epidemiol 2003;56:304-9.

45. Partin MR, Malone M, Winnett M, Slater J, Bar-Cohen A, Caplan L. The impact of survey nonresponse bias on conclusions drawn from a mammography intervention trial. J Clin Epidemiol 2003;56:867-73.

46. Shahar E, Folsom AR, Jackson R. The effect of nonresponse on prevalence estimates for a referent population: insights from a population-based cohort study. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Ann Epidemiol 1996;6:498-506.

47. Howard CA, Samet JM, Buechley RW, Schrag SD, Key CR. Survey research in New Mexico Hispanics: some methodological issues. Am J Epidemiol 1983;117:27-34.

48. Des Jarlais G, Kaplan CP, Haas JS, Gregorich SE, Perez-Stable EJ, Kerlikowske K. Factors affecting participation in a breast cancer risk reduction telephone survey among women from four racial/ethnic groups. Prev Med 2005;41:720-7.

49. Vernon SW, Roberts RE, Lee ES. Ethnic status and participation in longitudinal health surveys. Am J Epidemiol 1984;119:99-113.

50. Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research participants. Annu Rev Public Health 2006;27:1-28.

51. Ashing-Giwa KT, Padilla GV, Tejero JS, Kim J. Breast cancer survivorship in a multiethnic sample: challenges in recruitment and measurement. Cancer 2004;101:450-65.

52. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346-57.

53. Dunn KM, Jordan K, Lacey RJ, Shapley M, Jinks C. Patterns of consent in epidemiologic research: evidence from over 25,000 responders. Am J Epidemiol 2004;159:1087-94.

54. Burg JA, Allred SL, Sapp JH, 2nd. The potential for bias due to attrition in the National Exposure Registry: an examination of reasons for nonresponse, nonrespondent characteristics, and the response rate. Toxicol Ind Health 1997;13:1-13.

55. Morton LM, Cahill J, Hartge P. Reporting participation in epidemiologic studies: a survey of practice. Am J Epidemiol 2006;163:197-203.

56. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17:643-53.

57. Hartge P. Participation in population studies. Epidemiology 2006;17:252-4.

58. Hartge P. Raising response rates: getting to yes. Epidemiology 1999;10:105-7.

59. Rogers A, Murtaugh MA, Edwards S, Slattery ML. Contacting controls: are we working harder for similar response rates, and does it make a difference? Am J Epidemiol 2004;160:85-90.

60. Wilkins JR, 3rd, Hueston WD, Crawford JM, Steele LL, Gerken DF. Mixed-mode survey of female veterinarians yields high response rate. Occup Med (Lond) 1997;47:458-62.

61. Olson SH. Reported participation in case-control studies: changes over time. Am J Epidemiol 2001;154:574-81.

62. Moorman PG, Newman B, Millikan RC, Tse CK, Sandler DP. Participation rates in a case-control study: the impact of age, race, and race of interviewer. Ann Epidemiol 1999;9:188-95.

63. Slattery ML, Edwards SL, Caan BJ, Kerber RA, Potter JD. Response rates among control subjects in case-control studies. Ann Epidemiol 1995;5:245-9.

64. Rosoff PM, Werner C, Clipp EC, Guill AB, Bonner M, Demark-Wahnefried W. Response rates to a mailed survey targeting childhood cancer survivors: a comparison of conditional versus unconditional incentives. Cancer Epidemiol Biomarkers Prev 2005;14:1330-2.

65. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R et al. Increasing response rates to postal questionnaires: systematic review. Bmj 2002;324:1183.

66. Dunn KM, Jordan K, Croft PR. Does questionnaire structure influence response in postal surveys? J Clin Epidemiol 2003;56:10-6.

67. Stang A, Ahrens W, Jockel KH. Control response proportions in population-based case-control studies in Germany. Epidemiology 1999;10:181-3.

Figure 1. Selection of cases and controls for the Northern California Childhood Leukemia Study, August 1995 - December 2004

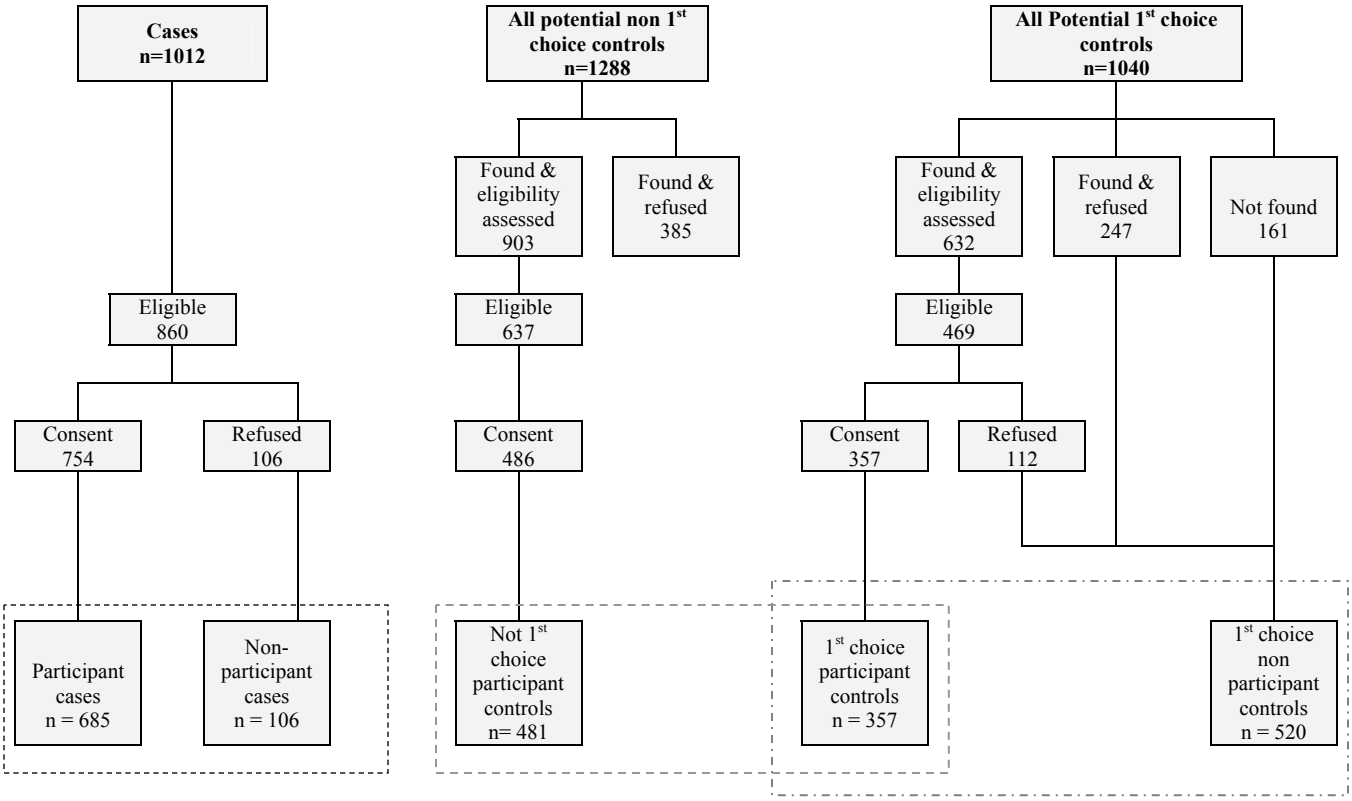


Table 1. Characteristics of actual cases and actual controls using individual-level data from in-person interview, the Northern California Childhood Leukemia Study, August 1995 - December 2004

	Actual Cases n=685	Actual controls n=838	Direction of association	p value[1]	OR (95% CI)[2]
	No. (%)	No. (%)			
Child's age, years					
Mean (SE)	5.52 (0.14)	5.43 (0.13)		0.619	-
Child's Sex					
Male	382 (55.77)	471 (56.2)		0.863	-
Female	303 (44.23)	367 (43.8)			
Race/ethnicity					
Non-Hispanic White	268 (39.3)	355 (42.4)		0.633	-
Non-Hispanic Black	22 (3.2)	23 (2.7)			
Non-Hispanic other	102 (14.9)	116 (13.8)			
Hispanic	291 (42.6)	344 (41.1)			
Hispanic status					
Non-Hispanic	392 (57.4)	494 (58.9)		0.541	-
Hispanic	291 (42.6)	344 (41.1)			
Maternal age at child's birth					
Mean (SE)	28.2 (0.24)	29.1 (0.21)	-	0.004	-0.01 (-0.00; -0.01)
Maternal Education, years					
High school or less	289 (42.4)	298 (35.6)		0.025	
Some college	198 (29.0)	268 (32.0)			0.73 (0.56-0.95)
College or postgraduate	195 (28.6)	271 (32.4)	-		0.70 (0.53-0.93)
Paternal Education, years					
High school or less	222 (45.2)	264 (41.1)		0.267	
Some college	109 (22.2)	166 (25.9)			0.80 (0.58-1.09)
College or postgraduate	160 (32.6)	212 (33.0)	-		0.93 (0.67-1.28)
Household income, $					
< 15,000	115 (16.8)	80 (9.6)		< 0.001	
15,000-44,999	226 (33.1)	216 (25.8)			0.71 (0.50-1.00)
45,000-74,999	162 (23.7)	214 (25.5)			0.46 (0.32-0.67)
≥75,000	180 (26.4)	328 (39.1)	-		0.31 (0.21-0.45)
Parental occupation					
Factory, agriculture	164 (34.3)	167 (33.6)			
Clerical, sales, services	153 (31.9)	151 (30.4)			
Professional, technical, managers	162 (33.8)	179 (36.0)	-	0.757	
Residence type					
Trailer & other	9 (2.6)	4 (1.8)		0.272	
Apartment	67 (19.7)	56 (14.9)			
Multiple family homes	35 (10.3)	36 (9.6)			
Single family homes	230 (67.4)	277 (73.7)	-		

[1] Direction of association – between cases and controls comparing last category. [2] p values derived from chi-squared tests for categorical variables and t-tests for continuous variables. [3] Odds ratio and 95% confidence intervals (CI) using logistic regressions for categorical variables and Linear regression for continuous variables adjusting for: Child's age at dx, sex, Hispanic status, and race.

Table 2. Characteristics of cases and controls using population-level data from birth certificates, the Northern California Childhood Leukemia Study, August 1995 - December 2004

	Actual cases n=685	Actual controls n=838	Direction of association [1]	Actual cases vs. Actual controls p value[2]	OR (95% CI)[3]	Ideal cases n=791	Ideal controls n=877	Direction of association [1]	Ideal cases vs. Ideal controls p value[2]	OR (95% CI)[3]
	No. (%)	No. (%)				No. (%)	No. (%)			
Race/ethnicity										
Non-Hispanic White	281 (41.0)	368 (43.9)		0.535		298 (39.0)	339 (38.8)		0.720	
Non-Hispanic Black	28 (4.1)	26 (3.1)				36 (4.7)	36 (4.1)			
Non-Hispanic other	77 (11.2)	86 (10.3)				86 (11.3)	87 (10.0)			
Hispanic	299 (43.6)	358 (42.7)	-			344 (45.0)	411 (47.1)	+		
Hispanic status										
Non-Hispanic	386 (56.3)	480 (57.3)		0.716		420 (55.0)	462 (52.9)		0.406	
Hispanic	299 (43.7)	358 (42.7)	-			344 (45.0)	411 (47.1)	+		
Maternal age, years										
Mean (SE)	28.2 (0.24)	29.1 (0.21)	-	0.004	-0.01 (-0.00; -0.00)	28.1 (0.23)	27.7 (0.22)	+	0.259	0.01 (-0.01 – 0.00)
Maternal Education, years										
≤ 12	295 (52.9)	338 (45.1)		0.016		345 (55.3)	483 (59.8)		0.118	
13-15	104 (18.7)	173 (23.1)			0.66 (0.49-0.90)	108 (17.3)	140 (17.4)			0.89 (0.60-1.31)
≥ 16	158 (28.4)	238 (31.8)	-		0.72 (0.54-0.97)	171 (27.4)	184 (22.8)	+		0.77 (0.54-1.12)
Mean (SE)	12.6 (0.16)	13.2 (0.12)	-	0.004		12.5 (0.15)	12.2 (0.13)	+	0.148	
Paternal Education, years										
≤ 12	256 (48.4)	342 (46.9)		0.856		306 (51.6)	446 (58.2)		0.037	
13-15	103 (19.5)	143 (19.6)			0.99 (0.72-1.34)	105 (17.7)	127 (16.6)			1.09 (0.74-1.61)
≥ 16	170 (32.1)	244 (33.5)	-		0.98 (0.73-1.31)	182 (30.7)	193 (25.2)	+		1.07 (0.74-1.54)
Mean (SE)	13.1 (0.16)	13.2 (0.14)	-	0.856		13.0 (0.16)	12.4 (0.14)	+	0.006	
Parental occupation										
Factory, agricultural	210 (36.8)	280 (35.4)		0.868		239 (37.4)	336 (41.3)		0.021	
Clerical, sales, services	193 (33.9)	274 (34.7)			0.96 (0.73-1.25)	220 (34.4)	300 (36.8)			1.14 (0.82-1.60)
Professional, technical, managers	167 (29.3)	236 (29.9)	-		0.96 (0.72-1.29)	180 (28.2)	178 (21.9)	+		1.07 (0.74-1.55)

[1] Direction of association – between cases and controls comparing last category. [2] p values derived from chi-squared tests for categorical variables and t tests for continuous variables. [3] Odds ratio and 95% confidence intervals (CI) using logistic regressions for categorical variables and Linear regression for continuous variables adjusting for: Child's age at dx, sex, Hispanic status, and race.

Table 3. Characteristics of cases and controls using ecological-level data from California 1990 and 2000 census, the Northern California Childhood Leukemia Study, August 1995 - December 2004

	Actual cases n=685 No. (%)	Actual controls n=838 No. (%)	Direction of association [1]	Actual cases vs. Actual controls p value[2]	OR (95% CI)[3]	Ideal cases n=791 No. (%)	Ideal controls n=877 No. (%)	Direction of association [1]	Ideal cases vs. Ideal controls p value[2]	OR (95% CI)[3]
SES										
Low	160 (24.5)	153 (19.7)		0.191	0.82 (0.60-1.12)	178 (25.4)	251 (29.0)		0.195	
Medium - Low	156 (24.0)	178 (23.0)			0.68 (0.49-0.95)	168 (24.0)	218 (25.2)			0.94 (0.64-1.39)
Medium - High	160 (24.5)	215 (27.7)			0.69 (0.49-0.97)	169 (24.1)	202 (23.4)			0.86 (0.57-1.29)
High	176 (27.0)	229 (29.6)	-			185 (26.4)	194 (22.4)	+		0.85 (0.56-1.30)
Percent Income ($)										
< 35,000	154 (23.6)	147 (19.0)		0.818		167 (23.8)	237 (27.4)		0.114	
35,000 – 49,999	143 (21.9)	171 (22.1)			0.79 (0.60-1.09)	158 (22.5)	213 (24.6)			0.89 (0.60-1.31)
50,000 – 74,999	169 (25.9)	211 (27.2)			0.75 (0.54-1.03)	177 (25.3)	209 (24.2)			0.98 (0.66-1.46)
≥ 75,000	187 (28.6)	246 (31.7)	-		0.70 (0.50-0.98)	199 (28.4)	206 (23.8)	+		0.86 (0.57-1.29)
Mean (SE)	42,831 (682)	43,065 (749)	-			43,881 (714)	40,069 (583)	+	< 0.001	
Percent college degree										
< 10.0	161 (24.7)	162 (20.9)		0.188		178 (25.4)	256 (29.6)		0.078	
10.0 – 19.9	152 (23.3)	166 (21.4)			0.91 (0.66-1.24)	161 (23.0)	219 (25.3)			1.05 (0.71-1.55)
20.0 – 39.9	167 (25.5)	219 (28.3)			0.74 (0.54-1.02)	181 (25.8)	194 (22.4)			0.89 (0.60-1.31)
≥ 40.0	173 (26.5)	228 (29.4)	-		0.73 (0.53-1.02)	181 (25.8)	196 (22.7)	+		0.91 (0.60-1.37)
Mean (SE)	26.4 (0.8)	27.5 (0.7)	-	0.305		26.0 (0.8)	23.3 (0.6)	+	0.007	
Percent professionals										
< 2.0	170 (26.1)	169 (21.8)		0.125		187 (26.7)	249 (28.8)		0.731	
2.0 – 2.9	156 (23.9)	174 (22.5)			0.87 (0.64-1.19)	168 (24.0)	213 (24.6)			0.98 (0.66-1.44)
3.0 – 3.9	173 (26.5)	218 (28.1)			0.76 (0.56-1.04)	185 (26.4)	213 (24.6)			0.85 (0.57-1.25)
≥ 4.0	153 (23.5)	214 (27.6)	-		0.67 (0.48-0.94)	160 (22.9)	190 (22.0)	+		0.75 (0.49-1.14)
Mean (SE)	25.9 (0.6)	29.9 (0.5)	-	0.194		25.6 (0.5)	24.2 (0.4)	+	0.054	
Percent below poverty										
< 4.0	193 (29.6)	235 (30.3)		0.056		202 (28.8)	206 (23.8)		0.127	
4.0 – 7.9	148 (22.7)	217 (28.0)			0.84 (0.63-1.12)	160 (22.8)	197 (22.8)			0.88 (0.61-1.25)
8.0 – 19.9	153 (23.4)	168 (21.7)			1.13 (0.84-1.52)	165 (23.5)	221 (25.5)			1.08 (0.74-1.57)
≥ 20.0	159 (24.3)	155 (20.0)	-		1.28 (0.93-1.80)	174 (24.8)	241 (27.9)	+		1.07 (0.71-1.59)
Mean (SE)	12.1 (0.4)	12.9 (0.4)	-	0.328		12.2 (0.4)	13.7 (0.4)	+	0.004	

[1] Direction of association – between cases and controls comparing last category. [2] p values derived from chi-squared tests for categorical variables and t tests for continuous variables. [3] Odds Ratios (OR) and 95% confidence intervals (CI) using logistic regressions adjusting for: child's age at dx, sex, Hispanic status, and race.

Table 4. Characteristics of participant and non-participant controls, data from birth certificates and California 1990 and 2000 census, the Northern California Childhood Leukemia Study, August 1995 - December 2004

	Participant controls n= 838	Non-participant controls n= 520	
	No. (%)	No. (%)	p value[1]
Race/ethnicity			
Non-Hispanic White	368 (43.9)	165 (32.0)	< 0.001
Non-Hispanic Black	26 (3.1)	25 (4.8)	
Non-Hispanic other	86 (10.3)	61 (11.8)	
Hispanic	358 (42.7)	265 (51.4)	
Maternal age at child's birth			
Mean (SE)	29.1 (0.21)	26.9 (0.28)	< 0.001
Maternal Education, years			
≤ 12	338 (45.1)	324 (67.9)	< 0.001
13-15	173 (23.1)	76 (15.9)	
≥ 16	238 (31.8)	77 (16.2)	
Mean (SE)	13.2 (0.12)	11.5 (0.12)	< 0.001
Paternal Education, years			
≤ 12	342 (46.9)	292 (65.3)	< 0.001
13-15	143 (19.6)	67 (15.0)	
≥ 16	244 (33.5)	88 (19.7)	
Mean (SE)	13.2 (0.14)	11.8 (0.19)	< 0.001
Parental occupation			
Factory, agricultural	280 (35.4)	206 (43.4)	< 0.001
Clerical, sales, services	274 (34.7)	191 (40.3)	
Professional, technical, managers	236 (29.9)	77 (16.2)	
SES			
Low	153 (19.7)	173 (34.0)	< 0.001
Medium - Low	178 (23.0)	135 (26.5)	
Medium - High	215 (27.7)	109 (21.4)	
High	229 (29.6)	92 (18.1)	

[1] p values derived from chi-squared tests for categorical variables and t tests for continuous variables.
[2] Odds Ratios (OR) and 95% confidence intervals (CI) using logistic regressions adjusting for: Child's age at dx, sex, Hispanic status, and race.

CHAPTER FOUR

Evaluation of Selection Bias in the Association between Childhood Leukemia and Residential Magnetic Fields Exposure

ABSTRACT

Data from the Northern California Childhood Leukemia Study were used to assess whether control selection bias may explain the association between electromagnetic fields and childhood leukemia as previously observed in case-control studies. Information on residential address at the time of child's birth and parental socio-demographic characteristics were available from the birth certificate for all subjects, regardless of their participation. Five control groups were defined: first selected [choice] participant (A); non-first choice participant (B); first choice non-participant (C); actual controls (A & B); ideal controls (A & C). Wiring configuration codes were determined for birth residences of control groups A (n=174), B (n=220), C (n=252), as well as of participating cases (n=310) and non-participant cases (n=66). Analyses indicated that actual controls tended to be of higher socioeconomic status than the first choice non-participant controls, and that lower socioeconomic status was related to higher configuration codes categories. The odds ratios (OR) for developing childhood leukemia in the high-current configurations category were 1.43 (95% confidence interval (CI): 0.91, 2.26) compared to control A, while no associations were observed when compared to controls B (OR=1.06, 95% CI: 0.71-1.60) or C (OR=1.06, 95% CI:0.71-1.57). Participant cases assigned to high-current configurations experience a non-significant increased risk of childhood leukemia, when compared to the actual controls (OR=1.21, 95% CI: 0.85-1.72). The comparison between ideal cases to the ideal controls indicated a similar result (OR=1.18, 95% CI: 0.85-1.64). Our results show that the observed risk estimates depend on the selected control group. In addition, our results indicate no association between wire configuration codes and childhood leukemia in the NCCLS and that selection bias is not likely to play a role in this study.

BACKGROUND

The association between extremely low-frequency (ELF) magnetic fields (MF) and childhood leukemia has been extensively studied since the first publication in 1979 by Wertheimer and Leeper (1). Since then, more than 25 epidemiological studies have been conducted on this topic, with major improvements in exposure assessment over time. Most of these studies were included in two pooled analyses published in 2000 by Greenland et al. (2) and Ahlbom et al. (3), including original data from 15 and nine studies, respectively. Greenland et al. indicated no association between childhood leukemia and MF levels less than 0.3 μT, but reported a statistically significant 1.7 fold increased risk for MF levels over 0.3 μT, compared to reference of less than 0.1 μT. Based on four studies with both wire configuration codes (used as a surrogate for EMF exposure) and MF measurement data (4-7), the summary effect estimate for VHCC (very high current configurations) vs. LCC (low current configurations) was elevated after adjusting for MF levels (OR=1.6; 95% CI: 1.2–2.3)(2). The second pooled analysis, by Ahlbom et al., used more restrictive inclusion criteria and similar to the results by Greenland et al., indicated no apparent association between MFs and childhood leukemia below MF level of 0.4 μT. However, the summary odds ratio for exposure >0.4 μT as compared with exposure <0.1 μT was 2.1 (95% CI: 1.3 -3.3) (3).

Following these two pooled analysis in 2002, the International Agency for Research on Cancer (IARC) classified power-frequency magnetic field as a possible human carcinogen (group 2B) (8). In addition, the International Commission for Non-Ionizing Radiation Protection (ICNIRP) Standing Committee on Epidemiology concluded that among all the health outcomes evaluated in epidemiological studies of ELF-MF, the strongest evidence for an association exists between childhood leukemia and post-natal exposure to MFs greater than 0.4 μT (9).

In spite of the suggestive epidemiological findings, and IARC classification, there is no supporting biological evidence in either cellular or animal experimental studies to support the epidemiological observation. Hence, it remains uncertain whether the association between childhood leukemia and MF is causal. Among alternative explanations are the role of confounding factors, measurement errors, and selection bias. Confounding effects of socioeconomic status (SES), residential mobility, residence type, viral contacts, and traffic density have been raised as possible explanations for the observed associations (10-13). Despite the extensive research, no single confounder or set of confounders has been identified that could explain the observed association (11, 14). Selection bias has been suggested as a potential explanation in several studies. However, the assessment of selection bias requires considerable resources as well as early planning and therefore it is difficult to be assessed. To our knowledge, only three studies to date have assessed the role of selection bias in the association between childhood leukemia and MF. Hatch et al. estimated the risk of acute lymphoblastic leukemia (ALL) for four levels of wire configuration codes, and compared analyses with and without partial participant controls (controls for whom no indoor-measurement were available) (11). The OR associated with living in homes with VHCC increased by 23% when partial participants were excluded from the model. The authors conclude that while confounding alone is unlikely to be an important source of bias, selection bias may be

more of a concern, particularly in light of the generally low response rates among controls in case-control studies (11). Gurney et al. assessed the relationship between family income and wire configuration codes and noted that lower family income tended to be associated with higher wire configuration codes (12). The authors estimated that differential participation of cases and controls by their income status could result in an upward bias of the high wire configuration codes and childhood leukemia association in a case-control study; the odds ratio would be inflated by 1.03 to 1.24-fold. A recent publication by Mezei et al. evaluated the role of selection bias in the 1999 Canadian case-control study of childhood leukemia and residential magnetic field exposure (5, 15). This study included 340 cases and 493 controls. The authors reported that the risk estimates for childhood leukemia in the highest exposure category were 1.6 (95% CI: 1.0, 2.6) when the actual participant controls (first choice and non-first choice) were used and 1.3 (95% CI: 0.8, 2.1) when the first-choice controls (participant and non-participant) were used (15).

The aim of our study is to assess whether selection bias may explain the observed epidemiological association between electromagnetic fields and childhood leukemia, using birth certificates information for a large number of non-participant and participant leukemia cases and controls.

MATERIALS AND METHODS

Study population

The study population is a subset of the Northern California Childhood Leukemia Study (NCCLS), an ongoing case-control study that began in 1995. The NCCLS has been recruiting children with leukemia from nine hospitals in the 35 counties located in the Northern California region. Incident cases of childhood leukemia were identified on the basis of the International Classification of Diseases for Oncology criteria (WHO 2000) using rapid case ascertainment procedures, usually within 72 hours after diagnosis.

The NCCLS eligibility criteria for cases and controls were: 1) being a resident of the study area; 2) being less than 15 years of age at the time of case diagnosis (reference date for controls); 3) having no previous diagnosis of cancer; and 4) having at least one English or Spanish-speaking parent or guardian. The latter were included in the study of wire configuration codes if they were eligible. The present wire configuration codes study (2002 – 2006) includes all NCCLS eligible subjects (regardless of their participation to the study) who met three additional eligibility criteria; 1) being less than 8 years of age at the time of case diagnosis (reference date for controls); 2) living in the same residence since diagnosis for cases (reference date for controls); and 3) interviewed before October 2006.

A detailed description of control selection in the parent NCCLS study has been published previously (16, 17). For each case four potential control subjects were randomly selected from birth certificates through the California Office of Vital Records, matched on age, sex, Hispanic ethnicity, and maternal race. The birth certificates for the four potential birth certificate controls and the case (if born in California) were obtained from the Center for Health Statistics (17). One of the four birth certificate controls was

randomly selected as the first potential control to be recruited for the study (referred to as ideal controls). Professional interviewers contacted each family using standardized searching protocols. If the first-choice control could not be located, was ineligible, or declined to participate (first-choice non-participant controls), the next randomly selected potential control was pursued. This procedure was repeated until an eligible and consenting control was enrolled in the study (non-first choice participant control). If no control was enrolled by using the first set of four birth certificates, additional certificates were requested from the Center for Health Statistics and the process described above was repeated. A detailed figure presenting the process of selection of cases and controls is presented in Figure 1. The controls were divided into two groups: actual controls (n=394) and ideal controls (n=426). Actual controls include first choice participant controls (group A, n=174) combined with non-first choice participant controls (group B, n=220). Ideal controls consist of first-choice participant controls (A, n=174) and first-choice non-participant controls (group C, n=252). Ideal cases include participating cases (n=310) and non participant cases (n=66).

The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the Institutional Review Boards of all the participant hospitals.

Data collection

Socio-demographic and residency information was collected from birth certificates for all cases and controls, regardless of their participation status, including child's age, gender, race, Hispanic status, parental education (years) and occupation, and residency at birth. Residences were assigned address-level latitude and longitude coordinates using a geographic information system. Each address was assigned to a 1990 or 2000 US Census block group, depending on the child's date of birth. When possible, the addresses that could not automatically be matched were manually located. The geocoding was carried out using ArcView GIS software (18). Data from the U.S. Census Bureau were used to derive neighborhood measures of urbanization and SES. The methods for creating these variables have been previously described (19, 20). In short, urbanization included three levels: large metro (population greater than or equal to one million), city (population less than one million), and rural/town (population < 50,000). To create the SES neighborhood variables, the California block groups were ranked separately by education level (percentage of adults ≥ 25 years of age completing a college degree or higher), income (median family income), and occupation (percentage of adults employed in managerial/professional occupations) according to quartiles, based on the statewide adult population (21, 22). This resulted in a score of 1–4 for each of these SES attributes. A summary SES metric was created by summing the scores across each of the four SES attributes and categorizing them into four groups (high to low), based on the quartiles of this score.

Trained engineering technicians (blinded to the subjects' case or control status) recorded on a diagram the distance from the home of any overhead power lines within 150 ft of the residence, including transmission lines, thick and thin three-phase primary-distribution lines, any open (with separated wires) or spun (with wires bound together)

secondary distribution lines, and first-span secondary distribution lines. On the basis of the diagrams, a computer algorithm assigned a wire configuration codes to each residence according to the five-category Wertheimer–Leeper classification (1) including underground (UG), very-low-current configuration (VLCC), ordinary low-current configuration (OLCC), ordinary high-current configuration (OHCC), and very-high-current configuration (VHCC), as well as the Kaune and Savitz three categories (low, medium, and high) (23). We used the wire configuration codes method, despite its known limitations as a surrogate for magnetic fields, because it is the only method that can be used to classify EMF exposure for residencies of non-participants as it required no subject participation or in-home access.

Statistical Analysis

Descriptive analyses were conducted to compare distribution of socio-demographic characteristics between several case and control groups. Additional analysis was done to assess whether there is a correlation between wire code categories and socio-demographic characteristics. Unconditional logistic regression analyses were performed using wiring configuration codes as the predictor variable and case-control status as the outcome, adjusting for child's age at diagnosis (reference date for controls), gender, Hispanic status, and maternal race. The wire code categories used in the analyses include the five Wertheimer–Leeper categories, as well as the three Kaune and Savitz.

RESULTS

The demographic characteristics of the study subjects are shown in Table 1. Participant cases (n=310) had statistically significant ($P<0.05$) higher maternal education than the first choice non-participant controls but statistically significant lower education than the participant (Actual) controls. Similar results were observed for paternal education (data not shown). Compared to non-participant controls, participant controls (both the first choice and the non-first choice) had statistically significant higher maternal education, older maternal age at child's birth, and were more likely to live in a single-family home or had a higher neighborhood SES (Table 1). However, although both the first choice and the non-first choice participant controls had a high SES, the first-choice participant controls appear to have higher (non-significant) SES than the non-first choice participant controls.

The wire configuration codes were associated with socio-demographic and residential characteristics. Wire configuration codes levels were strongly related to child's race, Hispanic status, parental education, and neighborhood SES. Non-Hispanic whites and those with higher level of education were more likely to live in a residence with an underground level of wire configuration codes ($P < 0.005$). In addition, residences located in urban areas had higher wire configuration codes levels than residences in rural areas (Table 2). Overall, the participant controls (first-choice and non-first choice) tended to be of higher socioeconomic status than the first choice non-

participant controls, and lower socioeconomic status was related to higher wire configuration codes categories.

Cases had a non significant increased odds of living near VHCC & OHCC compared to first-choice participant controls (OR=1.43, 95% CI: 0.91-2.26), when adjusting for age, gender, Hispanic status and maternal race (Table 3). However, no such increased risk was observed while comparing the cases to the non-first choice participant controls (OR=1.06, 95% CI: 0.71-1.60), or to the first-choice non-participant controls (OR=1.06, 95% CI: 0.71-1.57) (Table 3). The first-choice non-participant controls had a non-significant increased odds of living near OHCC and VHCC (OR=1.48, 95% CI: 0.91-2.40) compared to the first-choice participant controls (UG and VLCC as a reference). In addition, the logistic regression indicated that the first-choice non-participant controls had a non-significant increased odds of living near OHCC/VHCC (OR=1.48, 95% CI: 0.91-2.40) compared to the first-choice participant controls.

When the five categories of the Wertheimer-Leeper wire configuration codes were used, with underground as the reference, slightly different results were observed due to the low number of cases in the VHCC category (n=13). These results indicated that participant cases had an increased odds for living near OHCC compared to the higher SES first-choice participant controls (OR=1.70, 95% CI: 1.00-2.88), non first-choice participant controls (OR=1.38, 95% CI: 0.86-2.20), and first-choice nonparticipant controls (OR=1.38, 95% CI: 0.88-2.18) (Table 3). In contrast, cases assigned to VHCC (N=13) experienced statistically non-significant decreased risks of childhood leukemia, when compared to the first-choice participant controls (OR=0.74, 95% CI: 0.33-1.65), non-first choice participant controls (OR=0.59, 95% CI: 0.29-1.20), and first-choice non-participant controls (OR=0.54, 95% CI: 0.27-1.07). For the Kaune-Savitz classification, we observed a similar pattern to the five-category Wertheimer-Leeper classification, although the increase in the odds for the medium category was smaller.

Similar comparisons using the Wertheimer-Leeper and the Kaune-Savitz classifications while comparing actual participant cases to the actual controls and ideal cases to the ideal controls is presented in Table 4. Actual participant cases had a non-significant increase odd for OHCC & VHCC compared to the actual controls (OR=1.21, 95% CI: 0.85-1.72). Results were similar when ideal cases were compared to the ideal controls (OR=1.18, 95% CI: 0.85-1.64).

DISCUSSION

This is the first study to use complete case and control ascertainment in order to investigate the association between electromagnetic fields (assessed by wire configuration codes) and childhood leukemia, therefore providing a unique opportunity to evaluate the association without the effect of selection bias. The unbiased analyses using ideal case and ideal control comparison groups indicate that there is no association between childhood leukemia and OHCC/VHCC wire configurations, using UG/VLCC as the referent (OR=1.18, 95% CI: 0.85-1.64). In addition, adjustment for socioeconomic or other potentially confounding variables had no effect on the observed risk estimate. When the Wertheimer-Leeper five wire configuration codes categories were used, living

near OHCC alone was associated with an elevated odds ratio (of borderline significance) while a non-significant decreased OR was observed with living near VHCC. These results are probably due to random variability because of low number of cases in the VHCC category.

Our results indicating no associations between childhood leukemia and magnetic field were in line with some previous studies (5, 7) but in contrast to others (1, 4, 6, 24). Most of the previous studies indicating a positive association have argued that the observed association could also be a result of uncontrolled confounding or selection bias. The use of birth certificate controls allowed us to assess the role of selection bias on the association between childhood leukemia and magnetic fields. Our results indicate that participation status is related to both socioeconomic status and wire configuration codes, which may indicate the potential for selection bias. In our study, the first-choice participant controls tended to be of higher SES than the first-choice non-participant controls, with higher parental education, maternal age at child's birth, neighborhood SES, proportion of non-Hispanic whites, and more likely to live in a single-family home. Similar results, yet not as statistically significant, were observed while comparing the first choice non-participant controls and the non-first choice participant controls (the replacement group).

Mezei et al., were the first to directly examined the effect of control nonparticipation in a previously published Canadian case-control study of residential magnetic field exposure and childhood leukemia (5, 15). Similar to our study, the authors indicated that the first-choice nonparticipant controls tended to be of lower SES than the non-first-choice participant controls, and lower socioeconomic status was related to higher wire configuration codes categories (15). In line with these results are the results of Hatch et al. indicating that "partial participants" were more likely to have a lower level of education and income and were less likely to live in single family homes than subjects who participated fully (11). The author defined "partial participants" as study subjects who didn't participate in all phases of the study and for whom exposure was assessed using magnetic field measurements at the front door or by wire configuration codes, but for whom no indoor magnetic field measurements were available.

With wire configuration codes associated both with participation status and SES one may assume that the observed risk estimate of the association between childhood leukemia and magnetic field is likely to be biased. Indeed, our results indicate that the value of the OR for the observed association depends on the control group. In our study, the participant cases had a non significant increased odds of being in the OHCC/VHCC category when compared to the first-choice participant controls (OR=1.43, 95% CI: 0.91-2.26). However, no such increased risk was observed when comparing the cases to the non-first choice participant controls (OR=1.06, 95% CI: 0.71-1.60), or to the first-choice non-participant controls (OR=1.06, 95% CI: 0.71-1.57). Results were similar when matched-pair conditional regressions were used (data not shown). These findings illustrate that the association between childhood leukemia and wire configuration codes is influenced by the characteristics of the control group and therefore is prone to selection bias.

Specifically in our study, first choice participant control were likely to differ from other control groups. However, the distribution of wire configuration codes was similar

between the first-choice non-participant controls and their replacement group (the non-first choice participant controls) (OR=1.00, 95% CI: 0.66-1.55), suggesting that there was probably no additional source of control selection bias in our study. In order to fully assess whether selection bias may affect the association with wire configuration codes, we also considered case participation. The results of the analyses using the complete set of ideal cases and controls (OR=1.18, 95% CI: 0.85-1.64) were similar to the results while using only actual participating cases and controls (OR=1.21, 95% CI: 0.85-1.72), indicating that the selection bias in our study is probably minor and that if it does exist; it is likely to be non-differential.

The results above indicate that in the NCCLS the observed OR for the association between childhood leukemia and wire coding is not likely to be highly affected by selection bias. This is probably due to the careful control recruitment process conducted by the NCCLS, providing representative replacement control group. Despite the substantial burden on families, the NCCLS made a major effort to achieve high participation rates in the study. For these wire configuration codes analyses the overall participation rates among eligible cases and controls were 80.9 and 70.0, respectively. In addition, it may be that our non-first choice controls are of slightly higher SES status than the non-participant first-choice controls, however, our results (not shown) indicate that the participant cases are also of slightly higher SES than the non-participant cases which is probably a source for a non-differential misclassification.

In the Canadian study, Mezei et al. noted that the odds ratios for childhood leukemia in the VHCC category (underground, VLCC, and OLCC as referent) were 1.6 (95% CI: 1.0, 2.6) when the actual participant controls were used and 1.3 (95% CI: 0.8, 2.1) when the first-choice ideal controls were used (15). Overall, Mezei et al. conclude that, although there is some evidence for control selection or participation bias in their study, it is unlikely to explain entirely the observed association between wire configuration codes and childhood leukemia (15). The study by Mezei et al. did not collect data for complete case and control ascertainment (it lacked data on non-participating cases) and therefore could not fully evaluate the association without the effect of selection bias. Hatch et al. also reported that the odds ratio for ALL among those living in homes with VHCC were 1.00 (95% CI: 0.62, 1.61) when all subjects were included in the model and 1.23 (95% CI: 0.74, 2.04) when the partial participants were excluded from the model (11). The study of Hatch et al. lacked information on cases and controls who were found to be eligible but never participated in any phase of the study (4% of cases and 25% of controls), and therefore the full effect of selection bias could not be assessed.

A limitation of all these studies is the use of wire configuration codes as surrogate for magnetic fields exposure as they are known to have limited ability to measure magnetic field exposure (25). Wire configuration codes were used because our aim was to assess the role of selection bias and this method is the only method that could be applied to any known address and required no subject participation or property access. Another limitation, which is also related to our aim, is the use of only residence at time of birth, since it is the only available residence information for the non-participant cases and controls. To reduce a potential effect of misclassification, two eligibility criteria were added to this study (being less than 8 years of age at the time of case diagnosis and living in the same residence since diagnosis).

Our results indicate a lack of an association between wire configuration codes and childhood leukemia and that selection bias is not likely to play a role in an analysis specifically designed to use complete case and control ascertainment. However, our results show that the observed risk estimates do depend on the selected control group. This may indicate that the elevated risk estimate observed in early studies may have been subject to bias due to less careful control selection, especially those using Random-Digit Dialing method for control selection (4, 6). The improvement in study subject selection in the past three decades may explain the reduction in the observed risk estimates over time. Since supportive laboratory evidence is lacking and biophysical plausibility of carcinogenicity of MFs is questionable, the epidemiologic literature deserves careful consideration because it is essentially on this evidence alone that suggestions about long-term effects on human health relay.

REFERENCES

1. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979;109:273-84.

2. 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;11:624-34.

3. 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;83:692-8.

4. Savitz DA, Wachtel H, Barnes FA, John EM, Tvrdik JG. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol 1988;128:21-38.

5. McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli JJ et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol 1999;149:831-42.

6. London SJ, Thomas DC, Bowman JD, Sobel E, Cheng TC, Peters JM. Exposure to residential electric and magnetic fields and risk of childhood leukemia. Am J Epidemiol 1991;134:923-37.

7. Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune WT, Friedman DR et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. N Engl J Med 1997;337:1-7.

8. Humans IWGotEoCRt. Non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monogr Eval Carcinog Risks Hum 2002;80:1-395.

9. Ahlbom IC, 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 6:911-33.

10. Jones TL, Shih CH, Thurston DH, Ware BJ, Cole P. Selection bias from differential residential mobility as an explanation for associations of wire codes with childhood cancer. J Clin Epidemiol 1993;46:545-8.

11. Hatch EE, Kleinerman RA, Linet MS, Tarone RE, Kaune WT, Auvinen A et al. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? Epidemiology 2000;11:189-98.

12. Gurney JG, Davis S, Schwartz SM, Mueller BA, Kaune WT, Stevens RG. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. Epidemiology 1995;6:31-5.

13. Feychting M, Svensson D, Ahlbom A. Exposure to motor vehicle exhaust and childhood cancer. Scand J Work Environ Health 1998;24:8-11.

14. Kheifets L, Mezei G, Greenland S. Comment concerning "Childhood leukemia and residential magnetic fields: are pooled analyses more valid than the original studies?" (Bioelectromagnetics 27:1-7 [2006]). Bioelectromagnetics 2006;27:674-5; discussion 675-6.

15. Mezei G, Spinelli JJ, Wong P, Borugian M, McBride ML. Assessment of selection bias in the Canadian case-control study of residential magnetic field exposure and childhood leukemia. Am J Epidemiol 2008;167:1504-10.

16. Chang JS, Metayer C, Fear NT, Reinier K, Yin X, Urayama K et al. Parental social contact in the work place and the risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2007;97:1315-21.

17. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915-21.

18. Environmental Systems Research Institute I. ArcView, version 3.3. Redlands (CA): ESRI; 2000.

19. Reynolds P, Hurley SE, Gunier RB, Yerabati S, Quach T, Hertz A. Residential proximity to agricultural pesticide use and incidence of breast cancer in California, 1988-1997. Environ Health Perspect 2005;113:993-1000.

20. Reynolds P, Hurley SE, Quach AT, Rosen H, Von Behren J, Hertz A et al. Regional variations in breast cancer incidence among California women, 1988-1997. Cancer Causes Control 2005;16:139-50.

21. United States Bureau of the Census. Tiger2000 [data file]. Washington DC: US Census Bureau 2002.

22. United States Bureau of the Census. Census of population and housing. Modified age/race, sex and Hispanic origin (MARS) state and county file [data file]. Washington DC: US Bureau of the Census 1992.

23. Kaune WT, Savitz DA. Simplification of the Wertheimer-Leeper wire code. Bioelectromagnetics 1994;15:275-82.

24. Schuz J, Grigat JP, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukaemia: results from a German population-based case-control study. Int J Cancer 2001;91:728-35.

25. Tworoger SS, Davis S, Schwartz SM, Mirick DK. Stability of Wertheimer-Leeper wire codes as a measure of exposure to residential magnetic fields over a 9- to 11-year interval. J Expo Anal Environ Epidemiol 2002;12:448-54.

Table 1. Characteristics of Cases and Controls in the Wire Code Study, NCCLS, 2001–2004

	Participant cases n=310	1st choice participant controls n=174 [1]		Non 1st choice participant controls n=220 [2]		1st choice non participant controls n=252 [3]		[1]vs. [3]	[2] vs. [3]
	No. (%)	No. (%)	*P* Value[1]	No. (%)	*P* Value[1]	No. (%)	*P* Value[1]	*P* Value[2]	*P* Value[2]
Gender									
Male	169 (54.5)	93 (53.4)	0.821	118 (53.6)	0.841	136 (54.0)	0.897	0.916	0.943
Female	141 (45.5)	81 (46.6)		102 (46.4)		116 (46.0)			
Age at diagnosis, years									
Mean (SE)	3.7 (0.1)	3.3 (0.1)	0.469	3.9 (0.1)	0.330	3.7 (0.1)	0.118	0.040	0.589
Race									
Non-Hispanic White	131 (42.2)	86 (49.4)	0.405	87 (39.6)	0.861	79 (31.4)	0.067	0.002	0.248
Hispanic	127 (41.0)	66 (37.9)		94 (42.7)		121 (48.0)			
Non-Hispanic Black	12 (3.9)	6 (3.5)		7 (3.2)		13 (5.1)			
Other	40 (12.9)	16 (9.2)		32 (14.5)		39 (15.5)			
Maternal age at child's birth, years									
Mean (SE)	28.2 (0.4)	29.3 (0.5)	0.070	28.7 (0.4)	0.308	26.2 (0.4)	0.026	< 0.001	< 0.003
Maternal education, years									
Mean (SE)	12.2 (0.2)	12.9 (0.3)	0.023	13.4 (0.2)	0.016	11.1 (0.2)	0.001	< 0.001	< 0.001
Birth residence type									
Single family homes	207 (66.7)	135 (77.6)	0.098	152 (69.1)	0.926	147 (58.3)	0.181	< 0.001	0.093
Apartment	62 (20.0)	24 (13.8)		39 (17.7)		64 (25.4)			
Multiple family home	33 (10.7)	12 (6.9)		23 (10.5)		30 (11.9)			
Trailer & other	8 (2.6)	3 (1.7)		6 (2.7)		11 (4.4)			
Neighborhood type									
Single family homes	210 (67.7)	134 (77.0)	0.187	150 (68.2)	0.505	146 (57.9)	0.085	< 0.001	0.015
Apartment	42 (13.6)	18 (10.3)		32 (14.6)		43 (17.0)			
Multiple family home	36 (11.6)	13 (7.5)		29 (13.2)		34 (13.5)			
Trailer & other	22 (7.1)	9 (5.2)		9 (4.0)		29 (11.5)			
Neighborhood SES									
Low	62 (20.1)	31 (17.9)	0.605	33 (15.0)	0.401	89 (35.3)	< 0.001	< 0.001	< 0.001
Med low	80 (25.9)	39 (22.5)		58 (26.4)		64 (25.4)			
Med high	85 (27.5)	48 (27.8)		27 (27.3)		45 (17.9)			
High	82 (26.5)	55 (31.8)		69 (31.4)		54 (21.4)			
Urbanization level									
Large metro	167 (53.9)	91 (52.6)	0.037	137 (62.3)	0.154	141 (56.0)	0.760	0.117	0.361
City	81 (26.1)	32 (18.5)		46 (20.9)		59 (23.4)			
Rural/town	62 (20.0)	50 (28.9)		37 (16.8)		52 (20.6)			

[1] *P* Values comparing controls to cases derived from chi-square tests for categorical variables and from Student's *t*-test for continuous variables

[2] *P* Value comparing 1st choice participant controls to 1st choice non-participant controls

Table 2. Distribution of Wire Code Categories in 1,022 Homes by Socio-demographic and Residential Characteristics

	Underground No. (%)	VLCC No. (%)	OLCC No. (%)	OHCC & VHCC No. (%)	*P* Value[1]
Race					
Non-Hispanic White	175 (43.4)	47 (50.5)	82 (36.3)	93 (31.0)	< 0.001
Hispanic	148 (36.7)	32 (34.4)	112 (49.6)	149 (49.7)	
Non-Hispanic Black	10 (2.5)	3 (3.2)	10 (4.4)	18 (6.0)	
Other	70 (17.4)	11 (11.8)	22 (9.7)	40 (13.3)	
Maternal age at child's birth, years					
< 20	113 (28.0)	29 (31.2)	79 (35.0)	102 (34.0)	0.311
20-24	125 (31.0)	24 (23.6)	55 (24.3)	80 (26.7)	
25-29	115 (28.5)	28 (30.1)	54 (23.9)	73 (24.3)	
30-34	50 (12.4)	14 (15.1)	38 (16.8)	45 (15.0)	
Maternal education, years					
≤ 12	182 (46.0)	49 (52.7)	139 (62.1)	172 (58.3)	0.004
13-15	92 (23.2)	21 (22.6)	35 (15.6)	56 (19.0)	
≥ 16	122 (30.8)	23 (24.7)	50 (22.3)	67 (22.7)	
Residence type					
Single family homes	263 (65.3)	58 (62.4)	161 (71.2)	199 (66.3)	0.163
Apartment	93 (23.1)	23 (24.7)	38 (16.8)	54 (18.0)	
Multiple family homes	34 (8.4)	7 (7.5)	23 (10.2)	39 (13.0)	
Trailer & other	13 (3.2)	5 (5.4)	4 (1.8)	8 (2.7)	
Neighborhood type					
Single family homes	264 (65.5)	55 (59.1)	163 (72.1)	200 (66.7)	< 0.001
Apartment	77 (19.1)	21 (22.6)	22 (9.8)	26 (8.6)	
Multiple family homes	37 (9.2)	9 (9.7)	24 (10.6)	44 (14.7)	
Trailer & other	25 (6.2)	8 (8.6)	17 (7.5)	30 (10.0)	
Neighborhood SES					
High	58 (14.4)	22 (23.9)	80 (35.6)	77 (25.7)	< 0.001
Med high	94 (23.4)	23 (25.0)	52 (23.1)	87 (29.0)	
Med low	114 (28.4)	22 (23.9)	50 (22.2)	66 (22.0)	
Low	136 (33.8)	25 (27.2)	43 (19.1)	70 (23.3)	
Urbanization level					
Large metro	189 (63.0)	128 (56.6)	49 (53.3)1	204 (50.8)	0.015
City	57 (19.0)	49 (21.7)	18 (19.6)	115 (28.6)	
Rural/town	54 (18.0)	49 (21.7)	25 (27.1)	83 (20.6)	

VLCC = very low current code; OLCC = ordinary low current code; OHCC = ordinary high current code VHCC = very high current code

[1] *P* Values derived from chi-square tests for categorical variables and from Student's *t*-test for continuous variables

Table 3. Odds Ratio and 95% Confidence Intervals for Childhood Leukemia by Wertheimer-Leeper and Kaune-Savitz Wire Code Classifications, NCCLS, 2002-2007

	Participant Cases [1] n=310	1st choice participant controls [2] vs. [1] n=174		Non 1st choice participant controls [3] vs [1] n=220		1st choice non participant controls [4] vs.[1] n=252		Controls [2] vs. [4]	Controls [3] vs. [4]
	No. (%)	No. (%)	OR (95%CI)[1]	No. (%)	OR (95%CI)[1]	No. (%)	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]
Wertheimer-Leeper wire code with three categories									
UG/VLCC	145 (46.8)	95 (54.6)	Ref.	105 (47.7)	*Ref.*	121(48.0)	*Ref.*	*Ref.*	*Ref.*
OLCC	72 (23.2)	38 (21.8)	1.22 (0.76-1.97)	50 (22.7)	1.07 (0.69-1.68)	51 (20.2)	1.28 (0.82-1.99)	0.93 (0.56-1.56)	0.83 (0.52-1.35)
OHCC/VHCC	93 (30.0)	41 (23.6)	1.43 (0.91-2.26)	65 (29.6)	1.06 (0.71-1.60)	80 (31.8)	1.06 (0.71-1.57)	1.48 (0.91-2.40)	1.00 (0.66-1.55)
Wertheimer-Leeper wire code with five categories									
UG	116 (47.4)	74 (42.5)	*Ref.*	88 (40.0)	*Ref.*	99 (39.3)	*Ref.*	*Ref.*	*Ref.*
VLCC	29 (9.4)	21 (12.1)	0.88(0.47-1.67)	17 (7.7)	1.33 (0.69-2.58)	22 (8.7)	1.16 (0.62-2.18)	0.86 (0.43-1.73)	1.11 (0.55-2.24)
OLCC	72 (23.2)	38 (21.8)	1.19 (0.73-1.96)	50 (22.7)	1.15 (0.72-1.83)	51 (20.2)	1.32 (0.83-2.10)	0.90 (0.53-1.54)	0.95 (0.52-1.40)
OHCC	77 (24.8)	28 (16.1)	1.70 (1.00-2.88)	44 (20.0)	1.38 (0.86-2.20)	53 (21.0)	1.38 (0.88-2.18)	1.35 (0.76-2.38)	0.99 (0.60-1.65)
VHCC	16 (5.2)	13 (7.5)	0.74 (0.33-1.65)	21 (9.6)	0.59 (0.29-1.20)	27 (10.7)	0.54 (0.27-1.07)	1.63 (0.77-3.46)	1.09 (0.57-2.08)
Kaune-Savitz wire code with three categories									
Low	144 (46.5)	96 (55.2)	*Ref.*	114 (51.8)	*Ref.*	118 (46.8)	*Ref.*	*Ref.*	*Ref.*
Medium	119 (38.4)	52 (29.9)	1.48 (0.97-2.26)	67 (30.5)	1.47 (0.99-2.18)	83 (32.9)	1.29 (0.88-1.90)	1.15 (0.73-1.82)	1.14 (0.75-1.73)
High	47 (15.1)	26 (14.9)	1.15 (0.66-2.00)	39 (17.7)	0.99 (0.60-1.63)	51 (20.3)	0.81 (0.50-1.31)	1.63 (0.93-2.87)	1.20 (0.73-1.98)

VLCC = very low current code; OLCC = ordinary low current code; OHCC = ordinary high current code VHCC = very high current code

[1] Odds Ratios (OR) and 95% confidence intervals (CI) comparing controls to cases estimated using multiple logistic regressions adjusting for: Child's age at diagnosis (reference date for controls), sex, Hispanic status, and maternal race

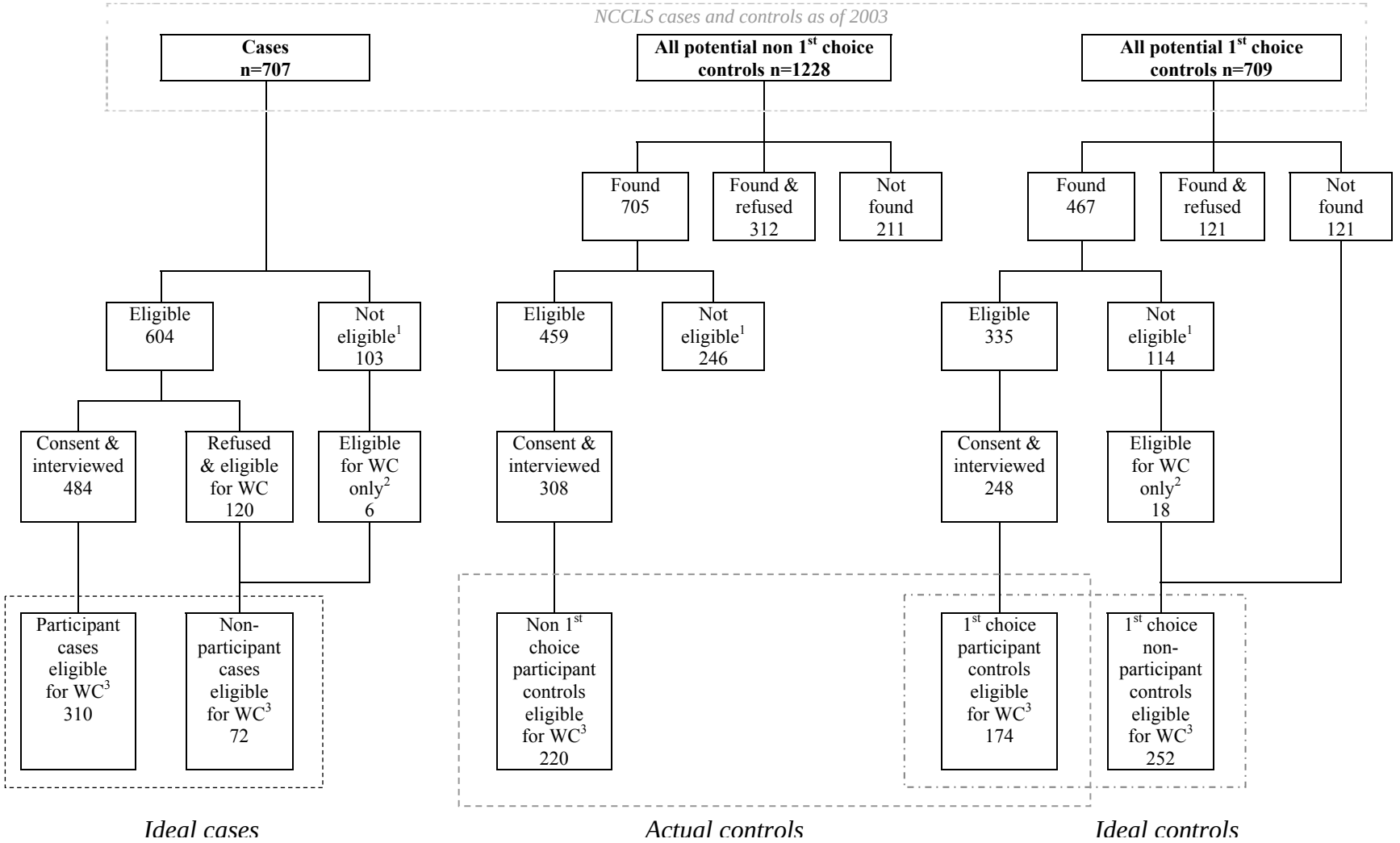
Table 4. Odds Ratio and 95% Confidence Intervals for Childhood Leukemia by Wertheimer-Leeper and Kaune-Savitz Wire Code Classifications, NCCLS, 2002-2006

	Participant cases n=310	Actual controls n=394		All cases n=376	Ideal controls n=426	
	No. (%)	No. (%)	OR (95%CI) vs. participant cases[1]	No. (%)	No. (%)	OR (95%CI) vs. all cases[1]
Wertheimer-Leeper wire code with three categories						
UG/VLCC	145 (46.8)	200 (50.8)	*Ref.*	175 (46.6)	216 (50.7)	*Ref.*
OLCC	72 (23.2)	88 (22.3)	1.14 (0.77-1.67)	87 (23.1)	89 (20.9)	1.25 (0.87-1.79)
OHCC/VHCC	93 (30.0)	106 (26.9)	1.21 (0.85-1.72)	114 (30.3)	121 (28.4)	1.18 (0.85-1.64)
Wertheimer-Leeper wire code with five categories						
UG	116 (47.4)	162 (41.1)	*Ref.*	142 (37.7)	173 (40.6)	*Ref.*
VLCC	29 (9.4)	38 (9.7)	1.08 (0.63-1.85)	33 (8.8)	43 (10.1)	0.96 (0.58-1.60)
OLCC	72 (23.2)	88 (22.3)	1.16 (0.78-1.73)	87 (23.1)	89 (20.9)	1.24 (0.85-1.81)
OHCC	77 (24.8)	72 (18.3)	1.50 (1.00-2.24)	93 (24.7)	81 (19.0)	1.45 (0.99-2.11)
VHCC	16 (5.2)	34 (8.6)	0.65(0.34-1.23)	21 (5.6)	40 (9.4)	0.64 (0.36-1.13)
Kaune-Savitz wire code with three categories						
Low	144 (46.5)	210 (53.3)	*Ref.*	171 (45.5)	214 (50.2)	*Ref.*
Medium	119 (38.4)	119 (30.2)	1.47 (1.05-2.06)	148 (39.4)	135 (31.7)	1.42 (1.04-1.94)
High	47 (15.1)	65 (16.5)	1.05 (0.68-1.63)	57 (15.1)	77 (18.1)	0.93 (0.62-1.40)

VLCC = very low current code; OLCC = ordinary low current code; OHCC = ordinary high current code VHCC = very high current code

[1] Odds Ratios (OR) and 95% confidence intervals (CI) comparing controls to cases estimated using multiple logistic regressions adjusting for: Child's age at diagnosis (reference date for controls), sex, Hispanic status, and maternal race

Figure 1. Selection of Cases and Controls for the Northern California Childhood Leukemia Study Wire Configuration Codes Analysis



WC = wire configuration codes

[1] Not eligible; previous treatment or diagnosis for cancer, not residence of the study area, no guardian who speaks English or Spanish; [2] Eligible for WC only; no guardian who speaks English or Spanish; [3] Not eligible for WC study includes; born outside of the study area, age >7, missing BC address

CHAPTER FIVE

Reliability of Maternal-Reports Regarding the Use of Household Pesticides?: Experience from a case-control study of childhood leukemia

Acknowledgements: We thank the children and their families for their participation in the Northern California Childhood Leukemia Study, and participating hospitals and clinical collaborators including: University of California Davis Medical Center (Dr Jonathan Ducore), University of California San Francisco (Dr Mignon Loh and Dr Katherine Matthay), Children's Hospital of Central California (Dr Vonda Crouse), Lucile Packard Children's Hospital (Dr Gary Dahl and Dr Carolyn Russo), Children's Hospital Oakland (Dr James Feusner), Kaiser Permanente Sacramento (Dr Vincent Kiley), Kaiser Permanente Santa Clara (Dr Alan Wong), Kaiser Permanente San Francisco (Dr Daniel Kronish), and Kaiser Permanente Oakland (Dr Stacy Month). We also acknowledge our collaborating study group headed by Dr Peggy Reynolds at the Northern California Cancer Center and the entire Northern California Childhood Leukemia Study staff and the University of California Berkeley Survey Research Center for their effort and dedication.

Grant support: This study was supported by grant from the National Institute of Environmental Health Sciences (PS42 ES04705 and R01 ES09137).

ABSTRACT

BACKGROUND: Household pesticide use has been associated with higher risk of childhood leukemia in a number of case-control studies. However, an overestimation of risk due to differential recall of use of pesticide products by case control status is of concern.
OBJECTIVE: To assesses the reliability of maternal reports of household use of pesticides and potential differences in reliability by case-control status, and by socio-demographic characteristics.
METHODS: A subset of the Northern California Childhood Leukemia Study population were interviewed twice about household pesticide. Eligible households included those with case or control children less than 8 years old, who lived in the same residence since diagnosis. Kappa, percent positive and negative agreements were used to assess reliability of responses to ever/never use of six pesticide types.
RESULTS: Kappa statistics ranged from 0.31 to 0.61 (fair to substantial agreement), with 9 out of the 12 tests indicating moderate agreement. The percent positive agreement ranged from 46%-80% and the percent negative agreement from 54%-95%. Reliability for all pesticide types as assessed by the three reliability measures did not differ significantly for cases and controls as confirmed by bootstrap analysis. For most pesticide types, Kappa and percent positive agreement were higher for non-Hispanics than Hispanics and for households with higher income versus lower income.
CONCLUSIONS: Reproducibility of maternal-reported pesticide use was moderate to high and was similar among cases and controls suggesting that differential recall is not likely to be a major source of bias.

INTRODUCTION

Household pesticide use has been associated with increased risk of childhood leukemia in most case-control studies that relied on self-reported exposure data (1). Although specific biochemical mechanisms relating pesticide exposures to childhood cancer have yet to be established (2), insecticides and herbicides induce oxidative stress and have been shown to have direct genotoxic effects in both occupational (3) and residential (4) exposure settings. Exposure effects from household pesticide use could occur before conception through germline mutations that can be passed on to the child, during pregnancy through transplacental crossover, and postnatally through direct exposure to the child.

Most epidemiological studies conducted over the past two decades have indicated positive associations between self-reported home pesticides use and childhood leukemia. A study previously published by the Northern California Childhood Leukemia Study (NCCLS) reported a positive association between childhood leukemia and maternal reports of household use of pesticides (5). In that study, Ma et al. reported that cases were exposed indoors to more pesticides than were the controls and that the highest odds ratio (OR) was seen for these exposures during pregnancy (OR = 2.2; 95% confidence interval (CI): 1.3–3.6) (5). The authors also reported that more frequent indoor exposure to insecticides (but not herbicides) was associated with a higher risk, consistent with a dose response relationship. Similarly, eight other studies reported positive and significant results for the association between childhood leukemia and household pesticide use during pregnancy (6-12) and five studies reported significant results for exposure in early childhood (7-11). In addition, five studies showed significant associations with garden products used during pregnancy (8, 10, 12) and early childhood (8, 10, 11, 13).

Previous studies on the association between pesticides and childhood cancer have been case-control in design and have relied on self-reported retrospective exposure assessment, for which there are concerns about recall bias. Recall bias, also called reporting bias or differential recall, can be defined as a measurement error characterized by differences in the accuracy of subject recall or report between compared groups (14). Recall bias can distort the measure of association between exposure and disease by any magnitude and direction, and this distortion is frequently difficult to predict (15). For example, it is recognized that parents of cases might be more motivated to search for causes or specific events that occurred in the past and either over report an experience or recall trivial events, whereas a parent of a healthy child may simply not remember or may not report an exposure they believe to be unimportant. It is difficult to evaluate the direction of the resulting bias, if it exists, because cases could over or under report the exposure depending on whether recognition of past exposure or guilt about that exposure took precedence (12).

To our knowledge, no prior studies of childhood leukemia have measured the reliability of maternal-reported household pesticide. Previous reliability and validity studies of chemical exposures include studies of occupational epidemiology studies that compared the self-reported exposure with expert-assessed or exposure biomarkers (16-18) and evaluated the reliability by comparing information from repeated interviews (19,

20). In the absence of an objective reference, i.e., a "gold standard" to evaluate validity, we assessed the reproducibility of maternal-reported household pesticide use between cases and controls in a subset of the NCCLS.

MATERIALS AND METHODS

Study population

The study population included in this reliability study is a subset of the parent NCCLS case-control study conducted from 1995 to 2008. A detailed description of the NCCLS design has been published elsewhere (21, 22). In brief, the parent study recruited children with leukemia from hospitals in 35 counties in Northern and Central California, using rapid case ascertainment procedures to report cases usually within 72 hours after diagnosis. For each case, one or two control subjects were randomly selected from birth certificates through the California Office of Vital Records, matched on date of birth, sex, Hispanic ethnicity, and maternal race. Participating controls in the NCCLS were determined to be representative of the sampled population by parental age, parental education, and mother's reproductive history; characteristics which indicate a reduced potential for selection bias (21). Eligibility criteria for cases and controls participating in the parent NCCLS include: 1) residence in the 35-county study area; 2) less than 15 years of age at the time of case diagnosis (referent date for controls); 3) availability of an English or Spanish-speaking biological parent; and 4) no previous diagnosis of cancer. The reliability study was conducted for a subset of this study population between October 2001 - December 2006 and included subjects who met the following eligibility criteria: 1) less than 8 years of age at the time of case diagnosis (reference date for controls), and 2) residing at the same address since diagnosis for cases and corresponding date for matched controls. Approximately 55% of households enrolled in the parent NCCLS from 2001 to 2006 were eligible for the reliability study. Of those, 86% consented to participate providing 209 case and 235 control families for the present analysis.

The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the Institutional Review Boards of all the participating hospitals and institutions. A written informed consent was obtained from the parents or legal guardian of all participating subjects.

Data collection

Pesticide data were collected during two separate in-person interviews conducted by trained staff in English or Spanish. The initial interview (referred to as Tier 1) was scheduled as soon as consent was obtained and the follow-up interview (referred to as Tier 2) was conducted within 3–12 months following the Tier 1 interview. In both interviews, respondents (usually the biologic mother) were asked questions about household use of pesticide products targeting fleas and ticks; ants, flies, and cockroaches; and outdoor weeds and insects. Respondents were also queried about the use of indoor foggers and use of professional services for pest control and lawn and garden

maintenance. Information collected included the name of the products (household use only), timing of use (preconception, pregnancy, postnatal), and frequency of use. A detailed description of the NCCLS Tier 1 interview process has been published previously (1). Standardized questionnaires were used at the time of both interviews including show cards and calendars to elicit responses regarding exposure to a wide range of chemicals used at home and at work, for critical periods of the child's development (before conception, three trimesters of the pregnancy, and early years of life up to age three years).

Both the Tier 1 and 2 interviews asked questions regarding the same types of pest treatments; however, the methods of data collection differed slightly due to different study objectives. The main objective of the Tier 2 interview was to link EPA registration numbers obtained from pesticide products stored in the homes to publicly available EPA databases, thus allowing for identification of active ingredients, chemical composition, intended target pest, and potential toxicity for each product. Consistent with this objective, the Tier 2 interview began with an inventory of pesticide products found in and around the home using a standard questionnaire to record the name, EPA registration number, the purpose of product use (i.e., type of pest treated), and the period and locations the product was used. Once this information was recorded, a standardized questionnaire was used to collect information about additional pest treatments that were not ascertained during the home product inventory. The questions about “flea and ticks” and “weed and plant/tree insects/diseases” differed slightly between the interviews. Specifically, the Tier 1 questionnaire included three separate questions about “flea and tick” products while the Tier 2 included one multi-part question. Questions in the Tier 1 questionnaire were: 1) Did you use flea or tick soaps or shampoos?, 2) Did you use sprays, dusts, powders or skin applications (such as Frontline or Advantage) for fleas or ticks?, and 3) Did you use flea or tick collars? The Tier 2 question was “Did you have a pet that was treated for fleas or ticks using shampoos, soaps, collars, sprays, dusts, powders, or skin applications?” Both questionnaires obtained time-period specific use for each product reported.

Statistical Analysis

Kappa statistics, percent positive and negative agreement (with 95% CI) were used to assess reliability of responses in Tier 1 to Tier 2 for ever or never pesticide use. Pesticide use was defined as pesticide use anytime from three months prior to conception until three years of age. Percent positive, percent negative, and Kappa statistics, were used to assess reliability of six categories of pesticide applications or services: 1) fleas or ticks, 2) ants, flies, or cockroaches, 3) indoor foggers, 4) weeds and plant/tree insects/diseases, 5) professional pesticide services, and 6) professional lawn services. An overall measure of agreement was calculated for the three reliability measures using data from the six categories together. In order to assess the potential for differential recall between cases and controls these analyses were conducted by case-control status. To determine whether the reliability of self-reported household pesticide use was consistent across subgroups, tests of agreement were also calculated by Hispanic ethnicity, household income and parental education. Kappa statistics ranging from 0.21 to 0.40 were interpreted as "fair"

agreement, from 0.41 to 0.60 as "moderate" agreement, 0.61 to 0.80 as "substantial" agreement, and those of ≥ 0.81 have been interpreted to indicate "almost perfect" agreement as suggested by Landis and Koch (23). In addition, a bootstrap analysis (24) based on 2000 replicate samples was used to estimate the mean reliability differences by case/control status, Hispanic ethnicity, and other socio-economic characteristics. The 95% CIs and p-values of the bootstrap were computed based on the distribution of replications.

RESULTS

Cases and controls in this analysis were comparable for all demographic characteristics evaluated (Table 1). In addition, the mean number of days between the two interviews was similar between cases (218.6 days) and controls (212.9 days) (p-value = 0.521). Table 2 presents the frequencies of self-reported pesticide use at Tier 1 and Tier 2. The category with the highest frequency of use was ants, flies, or cockroaches with reported use in 65.1% and 70.3% of Tier 1 and Tier 2 interviews, respectively. The category with the lowest frequency of self-reported use was indoor foggers with 8.8% and 10.6% in Tier 1 and Tier 2, respectively.

Table 3 presents the results of the reliability assessment of self-reported pesticide use among cases and controls. Kappa statistics ranged from 0.35 to 0.61 among cases and from 0.31 to 0.58 among controls, indicating fair to substantial agreement. Among cases, the highest agreement was for self-reported use of professional lawn services. Among controls, the agreement was highest for both professional pest services and treatment of fleas and ticks. The lowest agreement was observed for self-reported use of products for ants, flies, or cockroaches among both cases and controls. The percent positive agreement ranged from 47%-80% among cases and 46-77% among controls with and self-reported use of products for ants and flies showed the highest agreement. Percent negative agreement ranged from 55-95% among cases and 54-94% among controls; indoor foggers showed the highest agreement for both cases and controls.

Reproducibility of responses for all pesticide categories using the three reliability measures was similar between cases and controls. Moreover, the overall reliability measures (using data from the six categories together) produced similar results, with an overall Kappa for cases and controls of 0.58 (95% CI: 0.52-0.62), and 0.56 (95% CI: 0.51-0.61), respectively. Importantly, there were no differences in reproducibility of responses between cases and controls for the overall percent positive agreement [72% (95% CI: 69-76%) and 72% (95% CI: 68-75%), respectively], and for the overall percent negative agreement [85% (95% CI: 83-87%) and 85% (95% CI: 83-86%), respectively]. Bootstrapping of the mean differences and their variances of the three measures also showed no apparent difference in the recall between the cases and controls.

Table 4 presents results of the reliability assessment of self-reported pesticide use by Hispanic ethnicity (n=173 Hispanic, n=271 non-Hispanic) for cases and controls combined. Similar results were obtained for household income (data not shown) and therefore these results are summarized together. Reproducibility of responses for the majority of the pesticide categories using Kappa and percent positive agreement were

higher among non-Hispanics participants and participants with higher household incomes than among Hispanics and those with lower household incomes. Significant differences for both Kappa and percent positive agreement were observed only in the professional pest service category: Kappa (0.66 for non-Hispanic vs. 0.37 for Hispanic; and 0.37 for low income vs. 0.70 for high income) and percent positive agreement (79% for non-Hispanic vs. 57% for Hispanic; 52% for low income vs. 82% for high income). In addition, the overall percent positive agreement as well as the bootstrap estimates of the mean difference of percent positive agreement, revealed that both non-Hispanic participants and those with higher income had higher percent positive agreement than Hispanic participants (p-value = 0.009) and those with lower household income (p-value = 0.020).

Table 5 shows the results of the reliability assessment by two levels of maternal education, 12 or less years of education (n=134), and more than 12 years of education (n=310). Reproducibility of responses by educational status were similar for all comparisons except for the overall percent negative agreement. Overall results of the percent negative agreement indicate a high concordance of negative responses among mothers with 12 or less years of education (88%; 95% CI: 85-89%) compared to those mothers with more than 12 years of education (84%; 95% CI: 82-85%). The reliability assessment by the same levels of paternal education produced similar results to those of maternal education (data not shown). In addition, no difference in reproducibility of responses was found when similar comparisons were done between urban and rural subgroups (data not shown).

DISCUSSION

These analyses, conducted using data from an ongoing case-control study of childhood leukemia, are the first to assess reliability of self-reported home pesticide use. Based on the Kappa statistics, the overall agreement was fair to substantial depending on the type of pest treatment. Using all three reliability measures (Kappa, percent positive and negative) as well as the bootstrap analysis, we found no difference in reproducibility of responses between Tier 1 and Tier 2 interviews for cases and controls. These results suggest that perhaps differential recall bias may not explain the observed associations between childhood leukemia and residential use of pesticides as previously reported in the parent NCCLS (5) and possibly other case-control studies with similar reliance on self-reported exposures and retrospective exposure assessment (1). However, with the observation of fair and moderate agreement in both cases and controls, potential non-differential recall of exposure that attenuates the ability to detect exposure–outcome associations and results in an estimated measure of association that is biased toward the null can not be ruled out.

Concordance of positive responses was somewhat lower among Hispanic families and those with lower socio-economic status especially for reporting of professional pesticide and lawn services. This difference in recall is difficult to explain as families might be expected to accurately report the use of professional services, which are memorable events. A possible explanation for this difference may be related the fact that

more of the Hispanic parents engaged in lawn care as an occupation, and concepts related to interpretation of use of professional services for lawn care may have been commingled. Alternatively, the definition of professional pest control services and lawn services may have been unclear in the Spanish version of the questionnaire at the time of the initial and follow-up interview.

The estimated Kappa statistics generally ranged from 0.31 to 0.61 while the percent positive and negative agreements were much higher and generally ranged from 46 to 80% and from 55 to 95%, respectively. Although perfect agreement would generate a Kappa value of 1.0, values much lower still represent good agreement as the Kappa statistic is highly dependent on prevalence of the characteristic in the population. Thompson and Walter have shown that for factors with a true prevalence of 0.2 to 0.8 and with a high sensitivity and specificity (70–90%), Kappa statistics fall into a range 0.3–0.6 (25). Thus, Kappa statistics can be low, and percent positive and/or negative agreements high for situations in which the factor is highly prevalent or extremely rare. This could have been the situation when we observed low Kappa statistics and high percent negative agreement for indoor flea foggers (used by only 8.8% of cases and controls) and high percent positive for ants, flies, and cockroach use (highly used in about 65.1 % of cases and controls).

Previous studies that compared the magnitude of the associations between pesticides and different types of malignancies have also indicated that differential recall cannot explain pesticide associations. These studies indicated that the magnitude of the associations with pesticide use varies by histological type of leukemia and other hematopoietic malignancies (6, 12, 26, 27), suggesting that differential recall bias may not explain the observed associations between childhood leukemia and residential use of pesticides. Indeed, if systematic over-reporting by case mothers may have explained the results, over reporting would not be expected to depend on the disease type.

One study (28) that commented on the potential effect of differential recall bias examined the association of self-reported occupational exposure to various hydrocarbons among parents and childhood ALL. The authors indicated that ALL risk associated with parental exposure to hydrocarbons varied with the time window of exposure, and the association appeared to differ by chemical. For example, maternal exposure to solvents, paints, and thinners (substances that are fat soluble, highly volatile, and likely to be able to cross the placenta) were associated with an increased risk of ALL during the perinatal period, whereas maternal exposure to the same chemicals during the postnatal period were unrelated to the risk (28). In contrast, maternal exposure to plastic materials, which are less likely to be able to cross the placenta, was not related to the risk of ALL during the perinatal period but exposure to plastic materials was associated with an elevated risk postnatally. These time-specific associations argue against a differential recall bias (28).

Previous validity studies of chemical exposures include epidemiologic studies of occupationally exposed groups that compared the self-reported exposure with expert-assessed or exposure biomarkers. A recent study found a high correlation between self-reported residential pesticide exposure and levels of pesticides in household dust samples (29). The authors also indicated that the correlations appeared to hold for different geographic areas and for differences among individuals. However, another study (30) found no significant associations between the questionnaire items and the levels of pesticides in the house. Self-reported household pesticide use data collected with either a

self-administrated questionnaire or in-depth personal interview found that 90% of respondents who did not report the use of pesticides in the questionnaire reported it during the interview (31). Conversely, those reporting pesticide use in the questionnaire were more likely to also report home and garden pesticide use in the interview. The authors concluded that pesticide use may be underreported in self-administered questionnaires, and behaviors and risk perception may affect the reporting (31). Underreporting of pesticide use leads to misclassification of exposure to pesticides within homes and gardens and results in loss of power in epidemiological studies and if differential by disease status in case-control studies, may bias the risk estimates.

A strength of this study is the use of in-person interviews that use several tools to facilitate recall of cases and controls including standardized questionnaires, show cards and calendars to elicit responses regarding exposure to a wide range of chemicals and pesticides used at home and at work, for critical periods of the child's development. However, even these methods are limited by an individual's ability to correctly recall past events. Some limitations of this study must be considered. While both interviews at Tier 1 and Tier 2 asked questions regarding the same pesticides products, the methods of data collection were slightly different due to the interviews different objectives. While these differences may have contributed to a lower level of agreement it would not effect our conclusion regarding the non-differential recall bias between cases and controls. Because pest treatment information was collected primarily from mothers, their knowledge about paternal use of pesticides may have been inaccurate. Therefore, some pesticide exposures may not have been ascertained, introducing additional misclassification.

In conclusion, our results indicate that the reliability of maternal-reported household pesticide use was similar among cases and controls suggesting that differential recall of maternal-reported household use of pesticides may not be substantial. To directly assess differential recall in studies of childhood cancer, additional efforts to evaluate the validity of self-reported pesticide exposures are needed. However, based on the Kappa statistics, the overall agreement was fair to substantial, indicating potential non-differential recall of exposure which may attenuate estimates of association. The similar in reliability between cases and controls as observed in these analyses, supports previous findings by the NCCLS suggesting that exposure to household pesticides is associated with elevated risk childhood leukemia.

SUPPLEMENTAL MATERIAL

Y_i = number of yes responses, tier i

N_i = number of no responses, tier i

Percent positive = $[2Y_1Y_2 / (2Y_1Y_2+Y_1N_2+N_1Y_2)]$

Percent negative = $[2N_1N_2 / (2N_1N_2+Y_1N_2+N_1Y_2)]$

REFERENCES

1. Metayer C, Buffler PA. Residential exposures to pesticides and childhood leukaemia. Radiat Prot Dosimetry 2008;132:212-9.

2. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev 2007;10:81-99.

3. Garaj-Vrhovac V, Zeljezic D. Evaluation of DNA damage in workers occupationally exposed to pesticides using single-cell gel electrophoresis (SCGE) assay. Pesticide genotoxicity revealed by comet assay. Mutat Res 2000;469:279-85.

4. Lieberman AD, Craven MR, Lewis HA, Nemenzo JH. Genotoxicity from domestic use of organophosphate pesticides. J Occup Environ Med 1998;40:954-7.

5. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110:955-60.

6. Alderton LE, Spector LG, Blair CK, Roesler M, Olshan AF, Robison LL et al. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: a report from the Children's Oncology Group. Am J Epidemiol 2006;164:212-21.

7. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res 1989;49:4030-7.

8. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 1999;10:481-7.

9. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health 1995;85:249-52.

10. Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S et al. Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst 1987;79:39-46.

11. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 2006;63:131-4.

12. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y et al. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environ Health Perspect 2007;115:1787-93.

13. 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:1943-8.

14. Drews CD, Kraus JF, Greenland S. Recall bias in a case-control study of sudden infant death syndrome. Int J Epidemiol 1990;19:405-11.

15. Kelsey J, Whittemore A, Evans A. Methods in observational epidemiology. New York, NY: Oxford University Press 1996.

16. Perry MJ, Marbella A, Layde PM. Nonpersistent pesticide exposure self-report versus biomonitoring in farm pesticide applicators. Ann Epidemiol 2006;16:701-7.

17. Hu YA, Smith TJ, Xu X, Wang L, Watanabe H, Christiani DC. Comparison of self-assessment of solvent exposure with measurement and professional assessment for female petrochemical workers in China. Am J Ind Med 2002;41:483-9.

18. Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H et al. Assessment of occupational exposures in a general population: comparison of different methods. Occup Environ Med 1999;56:145-51.

19. Hobson AJ, Sterling DA, Emo B, Evanoff BA, Sterling CS, Good L et al. Validity and reliability of an occupational exposure questionnaire for parkinsonism in welders. J Occup Environ Hyg 2009;6:324-31.

20. Rosenberg CR. An analysis of the reliability of self reported work histories from a cohort of workers exposed to polychlorinated biphenyls. Br J Ind Med 1993;50:822-6.

21. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915-21.

22. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 2006;163:1091-100.

23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

24. Efron BTR. An Introduction to the Bootstrap. 1993;New York.

25. Thompson WD, Walter SD. A reappraisal of the kappa coefficient. J Clin Epidemiol 1988;41:949-58.

26. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001;61:2542-6.

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;151:639-46; discussion 647-50.

28. Shu XO, Stewart P, Wen WQ, Han D, Potter JD, Buckley JD et al. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol Biomarkers Prev 1999;8:783-91.

29. Colt JS, Lubin J, Camann D, Davis S, Cerhan J, Severson RK et al. Comparison of pesticide levels in carpet dust and self-reported pest treatment practices in four US sites. J Expo Anal Environ Epidemiol 2004;14:74-83.

30. Sexton K, Adgate JL, Eberly LE, Clayton CA, Whitmore RW, Pellizzari ED et al. Predicting children's short-term exposure to pesticides: results of a questionnaire screening approach. Environ Health Perspect 2003;111:123-8.

31. Nieuwenhuijsen MJ, Grey CN, Golding J. Exposure misclassification of household pesticides and risk perception and behaviour. Ann Occup Hyg 2005;49:703-9.

Table 1. Characteristics of cases (n=209) and controls (n= 235), NCCLS, 2001–2006, included in the reliability study of self-reported pesticide use

Characteristics	Cases n (%)	Controls n (%)
Gender		
Male	125 (59.8)	139 (59.2)
Female	84 (40.2)	96 (40.8)
Age at diagnosis, years (reference date for controls)		
Mean (s.e.)	3.76 (0.13)	3.88 (0.12)
Race/ethnicity		
Non-Hispanic white	72 (34.4)	106 (45.1)
Hispanic	88 (42.1)	85 (36.2)
Non-Hispanic black	7 (3.4)	7 (3.0)
Non-Hispanic other races	42 (20.1)	37 (15.7)
Maternal age at child's birth, years		
Mean (s.e.)	30.3 (0.43)	30.5 (0.38)
Household income, $		
< 29,999	53 (25.4)	37 (15.7)
30,000-44,999	30 (14.3)	27 (11.5)
45,000-59,999	27 (12.9)	34 (14.5)
60,000-74,999	16 (7.7)	26 (11.1)
≥ 75,000	83 (39.7)	111 (47.2)
Maternal education		
High school or less	66 (31.6)	68 (28.9)
Some college	60 (28.7)	68 (28.9)
College or postgraduate	83 (39.7)	99 (42.2)
Paternal education		
High school or less	82 (40.0)	82 (35.6)
Some college	40 (19.5)	63 (27.4)
College or postgraduate	83 (40.5)	85 (37.0)
Urban/rural residence		
Rural	22 (10.5)	36 (15.3)
Suburban	32 (15.3)	24 (10.2)
Urban	155 (74.2)	175 (74.5)
Days between interviews		
Mean (s.e.)	218.6 (7.2)	212.9 (5.4)

Table 2. Comparison of self-reported pesticide use1 by cases and controls combined (n=444) at Tier 1 and Tier 2, NCCLS, 2001-2006

	Tier 1 n (%)	**Tier 2** n (%)
Fleas, ticks	159 (35.9)	169 (38.2)
Ants, flies, cockroaches	289 (65.1)	312 (70.3)
Indoor foggers	39 (8.8)	47 (10.6)
Weeds, insects, plants	191 (43.2)	195 (32.9)
Professional pest service	142 (32.2)	145 (32.9)
Professional lawn service	99 (22.5)	75 (17.1)

[1] pesticide use: from three months prior to conception until three years of age

Table 3. Comparison of reliability of self-reported pesticide use1 by case-control status (cases, n=209 and controls, n=235), NCCLS, 2001-2006

	Kappa (95% CI)		**Percent positive** (%) (95% CI)		**Percent negative** (%) (95% CI)	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Fleas, ticks	0.53 (0.41-0.65)	0.58 (0.47-0.68)	70 (61-78)	74 (66-81)	83 (78-88)	84 (79-88)
Ants, flies, cockroaches	0.35 (0.22-0.49)	0.31 (0.18-0.43)	80 (75-85)	77 (71-82)	55 (45-66)	54 (44-63)
Indoor foggers	0.42 (0.21-0.63)	0.40 (0.21-0.58)	47 (28-67)	46 (28-63)	95 (92-97)	94 (91-96)
Weeds, insects, plants	0.52 (0.40-0.64)	0.47 (0.35-0.58)	70 (62-78)	72 (66-79)	81 (76-86)	74 (68-81)
Professional pest service	0.56 (0.44-0.68)	0.58 (0.47-0.69)	70 (61-79)	72 (64-80)	86 (81-90)	86 (82-90)
Professional lawn service	0.61 (0.48-0.74)	0.51 (0.36-0.66)	71 (61-81)	58 (45-72)	90 (87-94)	92 (90-95)
Overall	0.58 (0.52-0.62)	0.56 (0.51-0.61)	72 (69-76)	72 (68-75)	85 (83-87)	85 (83-86)
Mean difference (95% CI)[2]	- 0.02 (-0.06, 0.01)		- 2.0 (-4.0, 1.0)		-1.0 (-2.0, 0.1)	
p-value[3]	0.840		0.927		0.812	

[1] pesticide use: from three months prior to conception until three years of age

[2] Bootstrap estimates for difference of means and variances between cases and controls, [3] Bootstrap estimated p-value

Table 4. Comparison of reliability of self-reported pesticide use1 by Hispanic Status (Non-Hispanic, n=271 and Hispanic n=173), NCCLS, 2001-2006

	Kappa (95% CI)		**Percent positive** (%) (95% CI)		**Percent negative** (%) (95% CI)	
	Hispanics	**Non-Hispanics**	**Hispanics**	**Non-Hispanics**	**Hispanics**	**Non-Hispanics**
Fleas, ticks	0.49 (0.36-0.63)	0.59 (0.49-0.69)	66 (56-76)	75 (69-82)	83 (78-88)	84 (80-88)
Ants, flies, cockroaches	0.25 (0.10-0.40)	0.38 (0.26-0.49)	76 (70-82)	80 (75-84)	50 (38-61)	57 (49-66)
Indoor foggers	0.41 (0.20-0.62)	0.41 (0.22-0.59)	47 (28-67)	46 (28-63)	94 (91-96)	95 (93-97)
Weeds, insects, plants	0.46 (0.32-0.60)	0.48 (0.38-0.59)	63 (52-74)	75 (69-81)	83 (78-88)	73 (67-79)
Professional pest service	0.37 (0.21-0.53)	0.66 (0.57-0.75)	57 (44-70)	79 (73-85)	85 (80-89)	87 (83-91)
Professional lawn service	0.39 (0.19-0.59)	0.63 (0.52-0.74)	47 (28-65)	72 (63-80)	92 (89-95)	91 (88-94)
Overall	0.50 (0.44-0.55)	0.60 (0.56-0.64)	65 (60-69)	76 (73-78)	85 (83-87)	85 (83-87)
Mean difference (95% CI)[2]	0.13 (0.09;0.17)		12.2 (9.0; 16.0)		1.0 (-1.0;1.0)	
p-value[3]	0.031		0.009		0.739	

[1] pesticide use: from three months prior to conception until three years of age
[2] Bootstrap estimates for difference of means and variances between Hispanics and non-Hispanics, [3]Bootstrap estimated p-value

Table 5. Comparison of reliability of self-reported pesticide use1 by years of maternal education (≤ 12 years, n=134 and > 12 years n=310), NCCLS, 2001-2006

	Kappa (95% CI)		**Percent positive** (%) (95% CI)		**Percent negative** (%) (95% CI)	
	≤ 12 yrs	**> 12 yrs**	**≤ 12 yrs**	**> 12 yrs**	**≤ 12 yrs**	**> 12 yrs**
Fleas, ticks	0.45 (0.29-0.62)	0.58 (0.49-0.67)	60 (47-74)	75 (69-81)	85 (80-90)	83 (76-87)
Ants, flies, cockroaches	0.29 (0.12-0.45)	0.34 (0.23-0.45)	74 (67-82)	80 (76-84)	54 (42-66)	54 (46-63)
Indoor foggers	0.57 (0.30-0.84)	0.36 (0.19-0.52)	60 (35-85)	42 (27-57)	97 (94-99)	93 (91-95)
Weeds, insects, plants	0.49 (0.33-0.65)	0.47 (0.37-0.57)	64 (52-77)	73 (68-79)	85 (80-91)	74 (68-79)
Professional pest service	0.51 (0.34-0.69)	0.58 (0.49-0.67)	62 (48-77)	73 (67-80)	89 (84-93)	85 (81-88)
Professional lawn service	0.44 (0.20-0.69)	0.59 (0.49-0.70)	50 (27-73)	68 (60-77)	94 (91-97)	90 (88-93)
Overall	0.54 (0.47-0.60)	0.57 (0.53-0.61)	66 (61-71)	74 (71-76)	88 (85-89)	84 (82-85)
Mean difference (95% CI)[2]	-0.03 (-0.12;0.07)		-7.0 (-11.0;-2.0)		4.0 (3.0;5.0)	
p-value[3]	0.728		0.057		0.042	

[1] pesticide use: from three months prior to conception until three years of age
[2] Bootstrap estimates for difference of means and variances between ≤ $12 years and > 12 years, [3] Bootstrap estimated p-value

CHAPTER SIX

Summary of Findings and Future Directions

SUMMARY OF FINDINGS

This dissertation examined the role of SES and racial distribution on participation of subjects in case control studies of childhood cancer, the role of selection bias on the association between EMF and childhood leukemia, as well as reproducibility of self-reports of household pesticide exposure. The research presented in this dissertation was made possible by the Northern California Childhood Leukemia Study, an ongoing population-based case-control study, supported by R01 ES09137, which commenced in 1995.

In Chapter 2 a systematic review and meta-analysis was conducted to compare race and ethnic status differences in childhood cancer rates as estimated by case-control epidemiologic studies with various design features. The results indicated that in interview-based case-control studies of childhood cancer, the proportion of Whites compared to non-Whites tended to be higher among controls than among cases. The opposite was true, however, for record-based case-control studies. The results of the Meta-analyses presented in this chapter suggest that in the interview based case-control studies, cases (compared to controls) were more likely to be non-White than White with an overall OR of 1.37 (95% CI 1.13, 1.67). In contrast, in the record-based studies, cases (compared to controls) were less likely to be non-White than White, with an overall OR of 0.81 (95% CI 0.72,0.91). Chapter 2 also compares estimates of racial distribution among cases as reported by case-control studies to those observed for an ideal case series with complete case ascertainment for these studies or in population-based cancer registries in corresponding geographic regions and calendar periods. The results indicated that the proportion of Whites tended to be higher among the participating cases in the published case-control studies compared to the proportion of Whites among the non-participating cases or in cancer registries. The observed differential participation bias in the interview-based case-control studies, where cases are less likely to be White than controls, may result in biased effect estimates for various potential risk factors, including SES, that are associated with race or ethnicity. This chapter emphasizes the importance of matching on race when the racial distribution of the source population is heterogeneous. Indeed, one of the NCCLS strengths is the use of methods that achieved approximately population-based ascertainment, which provided cases and controls that are representative of the Hispanic and White Non-Hispanic populations of California.

In Chapter 3, an analysis using a subset of the NCCLS population was performed to compare the association between SES and childhood leukemia using data from three sources: face-to-face interviews, birth certificates, and California 1990 and 2000 censuses. The results of this chapter show an inverse association between childhood leukemia and SES, when an interview-based case-control study design was used. In the interview based design, participating controls had statistically significant ($P<0.05$) higher levels of household income, maternal education and maternal age at child's birth than the participating cases. In contrast, a positive association between SES and childhood leukemia was observed while using individual level data from birth certificates or from the California 1990 and 2000 censuses with a study design that resembles an ecologic study (i.e. comparing ideal controls to ideal cases). This indicates that the difference in the direction is probably due to selection bias, with participant controls of higher SES than non-participant controls in case-controls studies. This source of bias can result in

spurious associations between disease and the wide range of exposures linked to race and SES.

Selection bias has been a major concern in studies on the association of childhood leukemia with exposures to extremely low frequency-magnetic fields (ELF-MF) (1, 2). Owing to low participation among cases and controls in some past ELF-MF studies, the potential for selection bias is large in most studies of ELF-MF exposure and childhood leukemia. This aspect was further investigated in Chapter 4, using a subset of the NCCLS, which assessed whether bias related to control selection may explain the association between ELF-MF and childhood leukemia as previously observed in case-control studies. Following the results of Chapter 2 and 3, the results of this chapter were predictable. Actual controls were found to be of higher SES than the first choice non-participant controls and lower SES was related to higher wire configuration codes categories, used as a surrogate measure for residential MF exposure. This scenario, with SES being related to both participation and EMF may lead to a biased risk estimate. Indeed, the odds ratios (OR) for developing childhood leukemia in the high wire configurations codes category were 1.43 (95% confidence interval (CI): 0.91, 2.26) compared to the first choice participant controls, while no associations were observed when compared to non-first choice participant controls (OR=1.06, 95% CI: 0.71-1.60) or first choice non-participant controls (OR=1.06, 95% CI: 0.71-1.57). These three ORs suggest that the observed risk estimates depend on the selected control group. This may also indicate that the elevated risk estimate observed in early studies may have been biased due to less careful control selection, especially those using Random-Digit Dialing method for control selection.

Of importance to the NCCLS is the fact that the comparison between actual cases to actual controls and the comparison between ideal cases and ideal controls yield similar results. Participant cases assigned to high-current configurations experience a non-significant increased risk of childhood leukemia, when compared to the actual controls (OR=1.21, 95% CI: 0.85-1.72). The comparison between ideal cases to the ideal controls indicates a similar result (OR=1.18, 95% CI: 0.85-1.64). Additional results of reassurance were that the distribution of wire configuration codes was similar between the first-choice non-participant controls and their replacement group (the non-first choice participant controls) (OR=1.00, 95% CI: 0.66-1.55), suggesting that the methods for selecting controls did not introduce an additional source of control selection bias. These results indicate that while selection bias is likely to play a role in the observed association of most EMF – childhood leukemia studies, it is not likely to play a role in the NCCLS study.

Selection bias is not the only measurement error that can cause a biased effect estimates. Recall bias can distort the measure of association between exposure and disease by any magnitude and direction, and this distortion is frequently difficult to predict (3). This type of bias has been repeatedly discussed by previous studies on childhood leukemia and self-reports of pesticides exposure.

In the absence of an objective reference, i.e., a "gold standard" to perform a validity study of self-reported home pesticide use; the reproducibility of self-reported pesticide household use and potential differential recall between cases and controls was assessed (Chapter 5). The results of Chapter 5 indicate that the Kappa statistics ranged from 0.31 to 0.61 (fair to substantial agreement), with 9 out of the 12 tests indicating

moderate agreement (0.41-0.60). The percent positive agreement ranged from 46-80% and the percent negative agreement from 54-95. Reliability of responses for most categories using Kappa and percent positive agreement were higher for non-Hispanics than Hispanics and for households with higher income versus lower income. Relevant results for the NCCLS are those indicating that the reliability of self-reported exposures for all pesticide categories using the three reliability measures did not differ markedly for cases and controls as confirmed by bootstrap analysis. These results suggest that differential recall due to self-reporting of household use of pesticides was not a major source of bias in the NCCLS. In addition, this analysis provides arguments strengthening the conclusions on associations reported not only by the NCCLS (4) but also in previous studies.

FUTURE DIRECTIONS

Several recommendations for future directions derive from this dissertation and they relate to all stages of the case-control epidemiological study: design and early planning, conducting the study, analysis and reporting of study results.

Novel methods in control selection need to be developed

This dissertation's main conclusion is that in case-control studies which require participation, control selection should be done in an extremely careful manner with adequate documentation to reduce the potential for a biased risk estimate. For studies done in the United States, population based case-control studies have been shown to provide a comparison group that is more representative of the source population for the cases.

Develop strategies to improve study participation

The need for improving study participation has been raised in previous publications because participation rates for epidemiologic studies have been declining over the past 30 years (5). Epidemiologic studies with low levels of participation may be more vulnerable to self-selection bias than those with high participation. In addition, with an ongoing change in the racial distributions of populations, it is highly important to increase study participation of subjects from minority groups. As discussed in Chapter 3, several factors have been found to affect participation, including the method of recruitment, number of contacts, the use of incentives etc. However, because there are many other factors that investigators cannot control (age, gender, subject's level of interest in the topic), investigators must consider every available method to achieve a high response. In addition, pilot studies in the months before launch can help immensely in finding the approaches that achieve an adequate response.

Recent studies have discussed the utility of studies that use hybrid data collection methods for increasing participation rates. Such hybrid data collection may increase participation by providing different methods of data collections for respondents, in order

to increase convenience for respondents with different preferences (e.g. mail, internet, telephone interviews, and face-to-face interview). These methods can also help in achieving more information, even if basic, from non-respondents.

Future strategies should evaluate the development of Web-based modes of data collection, allowing respondents to complete questionnaires at a time and in a place that is most convenient for them. In the more distant future, this may even allow internet Web-Cam "face-to-face" interview with a much lower cost than today's "face-to-face" interviews. These methods should be developed and observed, but it is premature to use them in actual studies. Nevertheless, the focus should be on developing methods to increase participation of subjects of lower SES and less on subjects of higher SES.

Develop guidelines for reporting and evaluation of study participation

Standardized reporting guidelines of non-participation for epidemiologic studies needs to be developed and eventually gain a broad consensus among researchers and journal editors. In 2002, Olson et al. (6) proposed a set of standards for the reporting of participation and recruitment in case-control studies. The adoption of standardized reporting guidelines for observational epidemiologic studies could improve the current practice of reporting epidemiologic research and will ultimately stimulate improvements in the methods of recruiting study participants and the research itself. In addition, it will contribute important information for assessing the validity of individual studies (6).

Reducing recall bias and future analysis on the association between childhood leukemia and pesticides

All case control studies should make an effort to reduce recall bias by using detailed standardized questionnaires, memory aids, and use of show cards of certain exposures. In addition, the interviews should be conducted as soon as possible after the date of diagnosis. This dissertation shows that there is probably no difference in recall due to self-reporting of household use of pesticides in the NCCLS and therefore it support previous publications of the NCCLS and others indicating a positive association between childhood leukemia and pesticides (7, 8). Future studies on this topic should examine the association between parental exposure to pesticides and distinct cytogenetic subgroups of childhood leukemia.

Analyses of Selection Bias

Investigators need to evaluate the potential effects of differential participation on the study results. It is prudent to glean information about non-response from within the study population, or elsewhere, to discern the likely direction and magnitude of the resulting biases. There is a need for better evaluation of the potential for selection bias in all case–control studies. Investigators may need to consider differential participation by race and ethnic status as a potential source of bias in the interpretation of results from case-control studies of childhood cancer. In addition, advanced statistical methods for adjustment of potential bias introduced by study nonparticipation should be developed.

Future analyses on the association of childhood leukemia with exposure to EMF
Chapter Four of this dissertation illustrated that the observed risk estimates depend on the selected control group. This dissertation also shows that there is probably no association between childhood leukemia and residential EMF (assessed by wire coding configurations). After three decades of extensive research it is unlikely that additional studies will provide new results, especially due to the lack of biological plausibility, the rarity of exposure and disease together with the high non-participation rates often encountered. Given the scarcity of resources, future studies should focus on reanalyzing existing data, but there is probably no need for new large scale case-control studies on this topic.

Biases due to Selection and recall have been a major threat to the validity of case control study results since these studies were first introduced. These days, epidemiologic research has grown increasingly complicated, involving sophisticated exposure assessment methods, collaboration across different disciplines, collection of biospecimens for gene-environment interactions, as well as international collaboration. Yet, the new tools of epidemiology cannot ignore the threat of selection bias stemming from non-response in case-control studies that require participation. These sophisticated methods are improving our knowledge of the etiology of childhood leukemia and may eventually lead to disease prevention. As illustrated here, the success of these studies will still depend on a study population that is representative of the source population, high levels of participation and high quality data.

REFERENCE

1. Mezei G, Kheifets L. Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. Int J Epidemiol 2006;35:397-406.

2. Gurney JG, Davis S, Schwartz SM, Mueller BA, Kaune WT, Stevens RG. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. Epidemiology 1995;6:31-5.

3. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol 2006;35:370-84.

4. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110:955-60.

5. Morton LM, Cahill J, Hartge P. Reporting participation in epidemiologic studies: a survey of practice. Am J Epidemiol 2006;163:197-203.

6. Olson SH, Voigt LF, Begg CB, Weiss NS. Reporting participation in case-control studies. Epidemiology 2002;13:123-6.

7. Ward MH, Colt JS, Metayer C, Gunier RB, Lubin J, Crouse V et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. Environ Health Perspect 2009;117:1007-13.

8. Ma X, Urayama K, Chang J, Wiemels JL, Buffler PA. Infection and pediatric acute lymphoblastic leukemia. Blood Cells Mol Dis 2009;42:117-20.