STATE OF CONNECTICUT

SITING COUNCIL

Re:	The Connecticut Light and Power Company and The United Illuminating Company Application for a Certificate of Environmental Compatibility and Public Need for the Construction of a New 345-kV Electric Transmission Line and Associated Facilities Between Scovill Rock Switching Station in Middletown and Norwalk Substation in Norwalk, Connecticut Including the Reconstruction of Portions of Existing 115-kV and 345-kV Electric Transmission Lines, the Construction of the Beseck Switching Station in Wallingford, East Devon Substation in Milford, and Singer Substation in Bridgeport, Modifications at Scovill Rock Switching Station and Norwalk Substation and the Reconfiguration of Certain Interconnections	)	Docket 272 October 12, 2004

SUPPLEMENTAL TESTIMONY III
OF DR. WILLIAM H. BAILEY CONCERNING MAGNETIC FIELD EXPOSURE POLICY

Protection of Public Health and Safety is Not Synonymous with Zero Risk

Q. What is the purpose of this supplemental testimony?

A. To respond to suggestions made to the Connecticut Siting Council in the course of these hearings that magnetic field exposure from electric transmission lines must be drastically reduced, even to levels that are below those produced by other common sources such as distribution lines and appliances in order to eliminate all risk of exposure.

Q. Do you agree with these suggestions?

A. No.

Q. Do such suggestions recommend mitigation that goes far beyond what any public health agency has recommended?

A. Yes.

Q. What appears to be the basis for such extreme suggestions?

A. The suggestions appear to rest on two assumptions. The first is the belief that the scientific evidence for harm from EMF is strong. The second is that the protection of public health and safety requires that no project be approved that would pose even a very small real risk, or even an unproven risk.

Q. If the Council were required to follow a policy that there be 'zero' risk or hazard, could any electrical facility be permitted?

A. No. The absurdity of such a policy can be illustrated by considering the public health and safety in a non-EMF context. Electricity is by its nature potentially dangerous to persons coming in contact with energized electrical facilities. Conformance of electrical facilities with the National Electrical Safety Code does not preclude that people may accidentally form a circuit path to ground that can result in electrical shock injuries, including burns and death. As little as 20 milliamps can be fatal if it passes through the chest.[1] For comparison, common household circuit breakers may be rated at 15, 20, or 30 amps. While work-related risks of electrical injury are obviously greater than risks for the general

[1] Worker Deaths by Electrocution: A Summary of NIOSH Surveillance and Investigative Findings. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. May 1998.

public, the latter cannot be dismissed either. Such known hazards nevertheless do not preclude the permitting of such facilities and have not been considered by the State to pose any "undue hazard" that would be inconsistent with the protection of public health and safety.

60 Hz Magnetic Field Exposure Is Not Likely To Be A Hazard

Q. Is the first assumption—that the scientific evidence against EMF is strong—supported by the weight of the scientific evidence?

A No. As Dr. Cole, Dr. Aronson, and I have testified at length, and as the multidisciplinary national scientific panels of scientists that have reviewed the research including the National Institute of Environmental Health Sciences (NIEHS), the National Academy of Sciences (NAS), the National Radiological Protection Board (NRPB), Health Council of the Netherlands (HCN), International Committee on Non-ionizing Radiation Protection (ICNIRP), and the International Agency for Research on Cancer (IARC) have found, the weight of the evidence does not support this assumption.

Dr. Martha Linet's Evaluation Is That The Relationship Between Magnetic Fields And Childhood Leukemia Does Not Meet The Criteria For Causality

Q. Has a top epidemiologist at the U.S. National Cancer Institute also discussed the criteria by which to distinguish statistical associations from causal associations in studies of childhood cancer, and applied them to the evaluation of epidemiologic studies of childhood leukemia and 60-Hz magnetic fields?

A. Yes, the publication entitled: "Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer," by Martha S. Linet M.D. and others, published in Pediatrics. Vol. 112, No. 1 (July 2003), provides a particularly clear and authoritative summary of her evaluation. This publication provides the Siting Council with guidance on the specific question whether transmission line magnetic fields are likely to cause an increased risk of childhood leukemia. I strongly recommend that the Council members read this article in full and have attached it to this testimony.

Q. Please explain to the Council who Dr. Linet is, and why she is particularly qualified to address this subject.

A. Dr. Linet is the Acting Chief and Senior Investigator of the Radiation Epidemiology Branch of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute (NCI), one of the National Institutes of Health. She is a physician, board-certified in internal medicine and general preventive medicine; and she also holds a degree in public health from Johns Hopkins University. She has published extensively on the causes of leukemia, and is the author of the internationally recognized text "The Leukemias: Epidemiologic Aspects." She serves on the Advisory Group on Cancer and the Environment to the American Cancer Society and serves as the NCI liaison to the Committee on Environmental Health of the American Academy of Pediatrics.

Q. Hasn't research by Dr. Linet and her colleagues on the potential relationship between magnetic fields and childhood leukemia been mentioned before in this proceeding?

A. Yes, Dr. Linet was the lead author of an article that appeared in 1997 in the New England Journal of Medicine in 1997, entitled "Residential Exposure to Magnetic Fields and Acute Lymphoblastic Leukemia in Children," which appears as Item 12 in the Appendix to the Testimony of Dr. Leonard Bell et al. dated March 16, 2004; and the lead author of "Cancer Surveillance Series: Recent Trends in Childhood Incidence and Mortality in the United States," published in the Journal of the National Cancer Institute in 1999, which appears as Item 5 in that Appendix. Dr. Bell et al. refer to these studies at pages 11 and 12 and page 8, respectively in their March 16, 2004 pre-filed testimony. The Linet et al. (1997) study was also included in the meta-analyses of Greenland et al., Ahlbom et al., and Wartenberg, described in Exponent's report in Appendix 6 to the Application.

Q. Why is the Linet et al. (2003) article particularly relevant to the EMF issues that the Council is now confronting?

A. The article is written for an audience of pediatricians to educate them in the interpretation of epidemiologic literature and claims regarding the causation of childhood leukemia. The article sets out to help practitioners who must diagnose and treat such cases to understand and apply the teachings of sound scientific research and, at the same time, to view with appropriate rigor claims or suspicions regarding causation based on epidemiology studies "with the emotional connotations of childhood cancers." The article can serve a similar function for the Council members, as they determine whether the location of the overhead sections of the proposed lines, or the hundreds of miles of existing transmission

and distribution lines in the state pose an "undue hazard" to people, particularly children.

Q. Please summarize the overall structure of the Linet et al.. article.

A. Dr. Linet and her co-authors first explain the terminology and criteria used in evaluating whether statistical associations between risk factors and childhood cancer are causal in nature. They then suggest an approach for investigating possible pediatric cancer clusters. Finally, they discuss how patterns and trends can be translated into new "leads" to understanding causation and summarize possible causal factors of childhood leukemia.

Q. Please discuss the portions of the paper that deal specifically with transmission line magnetic fields.

A. The authors illustrate their explanation of the difference between "statistical" and "causal" associations by contrasting "two examples involving modest statistical associations." (p. 224). The first of these examples is a suggested increased risk of leukemia in the offspring of women who had X-rays taken during pregnancy, an association they regard as "likely to be causal." (*Id.)*

The second example is the relationship between exposure to power frequency magnetic fields and childhood leukemia, which they state, "does not meet the criteria for causality." (p. 225).

Q. Why, according to Dr. Linet and her co-authors, does the relationship between exposure to power frequency magnetic fields and childhood leukemia not meet the criteria for causality?

A The authors cite three reasons on pages 225-226:

- Recent large and rigorous epidemiologic investigations that followed the early positive studies did not support a causal relationship;
- Experimental studies did not support the biological plausibility of the association;
- Some of the modest increase in risk reported was likely due to selection bias.

Q. Dr. Bell and his colleagues have testified that the meta-analyses of the epidemiology of power frequency fields and childhood leukemia published in 2000 and 2001 support an inference of causality.[2] Do Dr. Linet and her co-authors caution reviewers of meta- and pooled-analyses of epidemiologic studies to be "skeptical" of such analyses?

A. Yes, they do. Dr. Linet and her co-authors address the subject of meta-analyses and pooled analyses of epidemiology studies and conclude that they are inherently less helpful than analyses of pooled observational data from *randomized clinical trials*, because, in the case of epidemiology studies, the various individual studies considered are likely to "differ in study design, types of control subjects selected, population size, methods used for exposure assessment, field work methods, and other factors." (p. 225). They further caution that "even a single study of poor quality can have a large effect on the results of a meta-analysis." (p.225).

[2] " Q. According to these large meta-analyses of the relationship between EMF and childhood cancer, what is the likelihood that EMF is truly associated with childhood cancer?
A. The likelihood that EMF is truly associated with childhood cancer in humans is extremely high." (Testimony of Dr. Leonard Bell et. al. dated March 16, 2004, p. 15).

Q. Do the authors specifically identify a concern about the reliability of meta-analyses in regard to studies of EMF and childhood leukemia?

A. Yes, at pages 225 and 226, the authors state:

> Meta-analysis may be particularly problematic when attempting to ascertain whether an exposure of great public concern (eg,. . . non-ionizing power-frequency magnetic fields…) is linked with a specific type of childhood cancer, particularly when the association is modest and inconsistently observed in different epidemiologic studies. Thus, pediatricians need to be skeptical about attempts to decrease a complex array of differing investigations to a single risk estimate.

Q. In their March 16, 2004 testimony, Dr. Bell and his colleagues describe the work reported by Dr. Linet and colleagues in their 1997 article in <u>The New England Journal of Medicine</u> as "strongly support[ing] a dose-response relationship between EMF levels and childhood leukemia. . ." (p. 12).

Does this characterization of the study conducted by Dr. Linet and co-workers accurately represent the view that Dr. Linet and her colleagues express about what their own data and that of others show as to a dose-response relationship between magnetic fields and childhood leukemia?

A. No. Dr. Linet and her colleagues neither concluded that a dose response relationship was evident in their 1997 study (Linet et al., 1997)[3] nor did they see a dose-response relationship in the Greenland and Ahlbom meta-analyses of a larger number of studies. The authors explain:

> When data from several epidemiologic studies were combined or pooled, childhood leukemia risks did not increase steadily with increasing residential magnetic field or wire code levels (ie, no consistent dose response); instead, risks did not increase with increasing exposure until

[3] "We find no significant excess risk of childhood ALL [acute lymphocytic leukemia] associated with time-weighted average summary residential magnetic-fields of 0.200 µT [2 mG] or greater, <u>nor did we observe any significant dose-response trends</u>." [*Emphasis added*] p. 5.

> estimated magnetic field exposures reached >0.3 microtesla [3 milligauss.]" (p. 225).

Q. Did Dr. Bell and his colleagues also call attention to a statistically significant association in the Linet et al. (1997) study at a cut point chosen to distinguish exposed from unexposed subjects that was part of a post hoc analysis?

A. Yes.

Q. Is this the kind of interpretation—placing undue emphasis on an isolated cut point or threshold to define an increased risk that was not identified before the data were analyzed—that Dr. Linet and her colleagues cautioned about?

A. Yes. Dr. Linet and her co-authors in their 2003 article specifically recommend that caution should be applied

> …when undue emphasis is given to a result from a post hoc analysis derived using cutoff points not included in the presumptive statistical analyses. Results that are based on presumptive criteria for analyzing data should be given substantially greater weight when interpreting findings than results that are derived from post hoc cutoff points. Results from post hoc analyses should be interpreted cautiously and questioned, because such results can be based on cutoff points that would yield the most extreme outcomes. (p. 225).

Q. For the 2003 article we have been discussing, did Dr. Linet and colleagues survey the literature on childhood cancers and classify the risk factors according to whether the scientific evidence identified them as "known", "suggestive", or "postulated" causes of childhood cancers?

A. Yes.

Q. Into what category did they assign 60-hertz power frequency magnetic fields based upon their review of the scientific evidence?

A. They classified 60-hertz power frequency magnetic fields in the "postulated" category because the "limited" supporting evidence was insufficient to classify magnetic fields as either a "suggestive" or "known" risk factor for childhood cancers (Table 1, p. 219).

Sound Public Health And Safety Policy Is Not Based On The Elimination Of All Possible Risk

Q. Let's return to the second assumption that you identified as underlying the suggestion that essentially all risk must be eliminated before an overhead line could be found to be consistent with a public health and safety standard, or to pose no "undue hazard."

Do you believe that public health and safety in this case will be protected only if there is no risk—not even a theoretical risk—that is achieved by reducing magnetic field exposure to 'background levels' or below?

A. No. The notion that public health is not adequately protected or that a risk is "undue" if there is even a theoretical risk of harm, or a chance that a risk might possibly exist, is absurd.

Q. Does a public health perspective take into account the health and welfare benefits of a reliable electric system as well as the known risks of electrical injury?

A. Yes, and I would expect that the Siting Council would also consider the benefits of proposed projects in their decision process. The difficulty is that the benefits of our electrical system are taken for granted and so are not quantified in the review process.

Maximizing public health and safety involves balancing competing real and potential risks as well as benefits. Furthermore, achieving zero potential risk is not practical in the real world. This is why the assumption that public health and safety can only be achieved by achieving zero risk, even by eliminating a risk that a risk may exist, is absurd and unrealistic from a public health perspective.

Q. Can you give another example where the public health benefits of a technology are recognized as outweighing any potential health risk?

A. Yes, the chlorination of public drinking water supplies to reduce disease risk from microbial pathogens.

Q: What are the benefits of chlorination of public drinking water supplies?

A: The U.S. Environmental Protection Agency (EPA) concludes: "Disinfection of drinking water is one of the major public health advances in the 20th century. One hundred years ago, typhoid and cholera epidemics were common through American cities; disinfection was a major factor in reducing these epidemics."[4]

Q: What are the risks of chlorination?

By-products such as chloroform, bromoform, bromodichloromethane, and chlorodibromomethane, collectively called trihalomethanes (THM), are suspected to cause cancers and birth defects in humans. These chemicals, except chlorodibromomethane, were found to have inadequate evidence for human carcinogenicity but they were classified, based on laboratory animal test results,

[4] http://www.epa.gov/safewater/mdbp/dbp1.html

as a "possible/probable human carcinogen" by the U.S. Environmental Protection Agency (U.S. EPA) and the World Health Organization.

Q: How does the EPA address these risks?

The EPA states:

> Amendments to the SDWA [Safe Drinking Water Act] in 1996 require [U.S.] EPA to develop rules to balance the risks between microbial pathogens and disinfection byproducts (DBPs) [*emphasis added*]. It is important to strengthen protection against microbial contaminants, especially *Cryptosporidium*, and at the same time, reduce potential health risks of DBPs."[5]

Q. Do the rules that the EPA has developed for the by-products of water disinfection address the potential risk of cancer and other adverse health effects from water treatments?

A. Yes. The Maximum Contaminant Level (MCL) is the highest level of a contaminant that is allowed in drinking water. MCLs are set as close to levels below which there is no known or expected risk to health but also consider the best available treatment technology and take cost into consideration. MCLs are enforceable standards. The MCL for trihalomethanes is set at 0.08 mg/L[6] yet based upon the calculated risks of its components, exposures at the MCL may approach a 1 in 10,000 risk of cancer.[7]

Q. What is the rationale provided by the EPA that addresses the acceptability of this potential risk?

[5] http://www.epa.gov/safewater/mdbp/dbp1.html
[6] http://www.epa.gov/safewater/mcl.html
[7] http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

A. Disinfection is unquestionably the most important step in the treatment of water for drinking-water supplies. Therefore, the microbial quality of drinking water should not be compromised because of concern over the potential long-term effects of disinfectants and trihalomethanes. The EPA therefore states that the goal in setting the MCL for drinking water was to "balance the risks between microbial pathogens and disinfection byproducts."

Q. Turning to the public health and safety decisions to be made by the Siting Council in this docket, does the scientific research on magnetic fields support pressure on the Siting Council to consider increasingly extraordinary and exotic means of reducing field levels outside the right-of-way?

A. No, particularly if such means would not lead to a more reliable transmission system. The entirety of the scientific research to date has not established a likely risk from exposure to children or adults.

Q. From a scientific perspective, what actions have other agencies recommended as commensurate with the research findings to date?

A. I have previously stated that "The recommendations of NIEHS … and the Connecticut EMF Best Management Practices both embrace the strategy of encouraging responses and expenditures that are proportionate to the degree of scientific evidence that there might be a risk, and responsive to public concern." (Supplemental Testimony of Dr. William H. Bailey Concerning Passive Regulatory Responses with Respect To 60 Hz Electric And Magnetic Fields, May 3, 2004, p. 7).

In this docket the Applicants have presented some site-specific alignments of the route and a variety of transmission line configurations for consideration in reducing magnetic field levels. However, a requirement that such measures be implemented in the extreme so as to achieve some arbitrary field level or distance setback at great cost would be counter to the public health policies that have been applied by state, national, and international agencies to address EMF concerns.

Q. Does this conclude this testimony?

A. Yes.

SERVICE LIST
Docket: 272

Ms. Pamela B. Katz
Chairman
Connecticut Siting Council
10 Franklin Square
New Britain, CT 06051

Anthony M. Fitzgerald, Esq.
Brian T. Henebry, Esq.
Carmody & Torrance, LLP
50 Leavenworth Street
P. O. Box 1110
Waterbury, CT 06721-1110

Linda L. Randell, Esq.
Bruce L. McDermott, Esq.
Wiggin and Dana, LLP
One Century Tower
New Haven, CT 06508-1832

The Honorable Robert W. Megna
State Representative – 97th District
40 Foxon Hill Rd. #54
New Haven, CT 06513

The Honorable Al Adinolfi
State Representative – 103rd District
235 Sorghum Mill Dr.
Cheshire, CT 06410

Eric Knapp, Esq.
Branse & Willis, LLC
41-C New London Turnpike
Glen Lochen East
Glastonbury, CT 06033-2038

Julie Donaldson Kohler, Esq.
Hurwitz, Sagarin & Slossberg LLC
147 North Broad St.
Milford, CT 06460

Peter G. Boucher, Esq.
Halloran & Sage, LLP
225 Asylum Street
Hartford, CT 06103

Janice M. Small, Esq.
Town Attorney
Wallingford Town Hall
45 South Main Street
Wallingford, CT 06492

Ms. MaryAnn Boord
First Selectwoman
Durham Town Hall
30 Townhouse Rd.
Durham, CT 06422

Mr. Louis S. Ciccarello
Corporation Counsel
P. O. Box 798
Norwalk, CT 06856-0798

Town of Westport
c/o Ira W. Bloom, Esq.
27 Imperial Ave.
Westport, CT 06880

The Honorable Mary G. Fritz
State Representative – 90th District
43 Grove St.
Yalesville, CT 06492

David A. Ball, Esq.
Cohen & Wolf, P.C.
1115 Broad Street
Bridgeport, CT 06604

Deborah L. Moore, Esq.
Legal Department
Meriden City Hall
142 East Main St.
Meriden, CT 06450

Atty. Michael C. Wertheimer
Assistant Attorney General
Office of the Attorney General
10 Franklin Square
New Britain, CT 06051

The Honorable Raymond Kalinowski
State Representative – 100th District
P.O. Box 391
Durham, CT 06422

Ms. Melanie J. Howlett
Associate City Attorney
Office of the City Attorney
999 Broad Street
Bridgeport, CT 06604

Ms. Trish Bradley, President
Mr. Ed Schwartz, Treasurer
Communities for Responsible Energy, Phase II
45 Ironwood Lane
Durham, CT 06422

Mr. Bruce Johnson
Litigation Attorney
Office of Consumer Counsel
10 Franklin Square
New Britain, CT 06051

The Honorable Themis Klarides
State Representative – 114th District
23 East Court
Derby, CT 06418

Charles Walsh
Assistant Attorney General
Attorney General's Office
Juris. No. 402623
55 Elm Street, P.O. Box 120
Hartford, CT 06106

Lawrence J. Golden, Esq.
Pullman & Comley, LLC
90 State House Square
Hartford, CT 06103-3702

Anthony M. MacLeod, Esq.
Whitman, Breed, Abbott & Morgan, LLC
100 Field Point Road
Greenwich, CT 06830

Franco Chieffalo
General Supervisor
First District Water Department
P.O. Box 27
Norwalk, CT 06852

The Honorable Kenneth A. Flatto
First Selectman
Independence Hall
725 Old Post Rd.
Fairfield, CT 06824

David A. Reif
Jane K. Warren
Joel B. Casey
McCarter & English, LLP
CityPlace I
Hartford, CT 06103

Monte E. Frank, Esq.
Cohen & Wolf, P.C.
158 Deer Hill Avenue
Danbury, CT 06810

Andrew W. Lord, Esq.
Murtha Cullina LLP
CityPlace I, 29th Floor
185 Asylum Street
Hartford, CT 06103-3469

Brian M. Stone, Esq.
Sousa, Stone & D'Agosto, LLC
375 Bridgeport Avenue
Shelton, CT 06484

Robert E. Earley
Connecticut Business & Industry Assoc.
350 Church Street
Hartford, CT 06103-1106

Richard J. Buturla, Esq.
Town Attorney
Berchem, Moses & Devlin, P.C.
75 Broad Street
Milford, CT 06460

Joaquina Borges King
Assistant Town Attorney
Hamden Government Center
2750 Dixwell Avenue
Hamden, CT 06518

Timothy P. Lynch
Deputy City Attorney
City Attorney's Office
245 deKoven Drive, P.O. Box 1300
Middletown, CT 06457-1300

The Honorable Derrylyn Gorski
First Selectwoman
Bethany Town Hall
40 Peck Road
Bethany, CT 06524-3378

William J. Kupinse, Jr.
First Selectman
Easton Town Hall
225 Center Road, P.O. Box 61
Easton, CT 06612

The Honorable William A. Aniskovich
State Senate—12th District
15 Grove Avenue
Branford, CT 06405

David J. Monz
Updike, Kelly & Spellacy, P.C.
One Century Tower
265 Church Street
New Haven, CT 06510

David R. Schaefer, Esq.
Brenner Saltzman & Wallman, LLP
271 Whitney Avenue
New Haven, CT 06511

Senator Joseph J. Crisco, Jr.
17th District
State Capitol
Hartford, CT 06106-1591

Honorable Leonard A. Fasano
State Senator – 34th District
7 Sycamore Lane
North Haven, CT 06473

Elizabeth Gilson, Esq.
383 Orange Street
New Haven, CT 06511

Karyl Lee Hall, Esq., Co-Chairman
Branford Conservation and Environment Commission
c/o Box 3072
Branford, CT 06405

Honorable John E. Opie
First Selectman
Branford Town Hall
P.O. Box 150, Town Hall
Branford, CT 06405

Interpreting Epidemiologic Research: Lessons From Studies of Childhood Cancer

Martha S. Linet, MD; Sholom Wacholder, PhD; and Shelia Hoar Zahm, ScD

ABBREVIATIONS. ALL, acute lymphoblastic leukemia; CT, computed tomography.

In recent years, the public has shown concern about trends in incidence rates, the occurrence of clusters, and the role of certain environmental exposures in the cause of childhood cancers. A front-page news story in the *New York Times*[1] stimulated a dramatic upswing of public anxiety about these issues. Hearings by the US Senate Environment and Public Works Committee on a cluster of 11 childhood acute lymphoblastic leukemia (ALL) cases (since increased to 13) among the 8200 residents of a town in Nevada over a 3-year period led to a featured article in *USA Today*[2] describing legislation under consideration to enhance the federal government's role in responding to apparent cancer outbreaks in US communities.

Compared with 1.22 million cancers (excluding non-melanoma skin cancers) diagnosed annually among adults in the United States (corresponding to an average annual incidence rate for all cancers of 398 per 100 000 person-years),[3] there are only ~8700 diagnosed per year among children younger than 15 years and 12 400 among children and adolescents younger than 20 years (corresponding to average annual incidence rates of 13.4 per 100 000 and 14.9 per 100 000 person-years, respectively).[4] Carcinomas predominate among adults, and the major pediatric tumors are nonepithelial. The most common pediatric neoplasms are the leukemias (representing 30.2% of all cancers diagnosed in children younger than 15 years), brain and central nervous system cancers (21.7%), and lymphomas (10.9%); these 3 categories (together constituting 63%) and the remaining 37% of pediatric malignancies are characterized by substantial histologic and biological diversity.[5–7] Instead of the anatomic site-based categories used for adult malignancies, a more appropriate classification system developed for pediatric neoplasms[8] was recently updated and designated as the International Classification of Childhood Cancer.[9]

This article includes 3 components. The first section focuses on terminology and criteria to evaluate whether statistical associations between risk factors and childhood cancer are causal in nature. The second section suggests a general approach for investigating possible pediatric cancer clusters. The third section considers how distinctive patterns and trends can be translated into new etiologic leads and summarizes potential causal factors (Tables 1–4).

From the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.
Received for publication Jul 26, 2002; accepted Jan 17, 2003.
Reprint requests to (M.S.L.) Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS Rm 7054, Bethesda, MD 20892-7238. E-mail: linetm@exchange.nih.gov

TERMINOLOGY AND CRITERIA FOR CAUSALITY

The major objectives of most epidemiologic studies are to determine whether a specific exposure or factor (eg, ionizing radiation, or a medical condition) is likely to cause a given disease and to quantify the strength of the relationship. Two major study designs are used to evaluate whether an exposure is linked with a given disease: the cohort and the case-control study designs. In a cohort study, exposed (eg, an occupational group, or people with a common environmental or medically related exposure) and unexposed (often the general population but sometimes a similar occupational group without the exposure) populations are ascertained then followed up (prospectively or retrospectively) to compare risks of developing particular disease outcomes. In an ideal case-control study, cases are those who have developed a particular disease in a specified population during the study period, and control subjects are a random sample of those in the population who have not developed disease; in practice, the investigator's efforts to select control subjects may be affected by logistic issues. The case-control design is essential for economy in studies of rare diseases but requires retrospective collection of exposure information. An example of an ideal case-control study is one nested within a cohort, in which all cases are ascertained, but a randomly selected sample of the cohort is used for controls.

Epidemiologists typically evaluate the association between exposure and disease by estimating the ratio of rates of disease in people who had previous exposure to the agent with unexposed people. By convention, an association between exposure and disease is considered to be statistically significant if the probability is less than an estimate of association as strong or stronger than the one observed that would arise if, in fact, there were no association; if the probability is 5% or greater, then the association is considered too likely to be attributable to random variation to be considered solid. Many scientists are unhappy with this evaluation criterion, but no satisfactory alternative has been widely adopted.

TABLE 1. Risk Factors (Known, Suggestive, Limited) Associated With Childhood Leukemias and Lymphomas

Exposure or Characteristic	Leukemia		Lymphoma	
	Acute Lymphoblastic	Acute Myeloid	Hodgkin Disease	Non-Hodgkin Lymphoma
Known				
Gender	M:F = 1.3	M:F = 1.1	M:F = 1.3	M:F = 3.0
Age peak	2–4 years	Infancy	Adolescence	Adolescence
Age-adjusted incidence	26.3 per million	6.5 per million	13.8 per million	9.9 per million
Race	W:B = 2.0	W:B = 1.0	W:B = 1.3	W:B = 1.4
Other factors	Birth weight >4000 g		Monozygotic twins of young adults	Immunosuppressive therapy
	Ionizing radiation		Affected siblings	Congenital immunodeficiency syndromes (eg, ataxia, telangiectasia)
	Diagnostic, in utero		Epstein-Barr virus linked with some forms	AIDS
	Therapeutic, postnatal ALL and AML		Infectious mononucleosis	
	Down syndrome			
	ALL and AML M7			
	Congenital disorders, ataxia telangiectasia, Fanconi syndrome, Bloom syndrome, neurofibromatosis			
Suggestive	Maternal fetal loss	Maternal alcohol use during pregnancy		
	Mother older than 35 years at pregnancy			
	First born	Parental occupational exposures		
		- Benzene		
		- Pesticides		
Limited	Paternal smoking before conception	Maternal marijuana use during pregnancy	Residential exposures	
	Parental occupational exposures	Parental occupational exposures	Pesticides	
	Hydrocarbons	Pesticides		
	Paints			
	Motor vehicle exhaust			
	60-Hz magnetic fields >0.4 μT	Residential exposures		
		Pesticides		
	Postnatal chloramphenicol use			
	Clustering			
	Decreased risk associated with breastfeeding			

M:F indicates male-to-female ratio of incidence; W:B, white-to-black ratio of incidence; AML, acute myeloid leukemia; AIDS, acquired immunodeficiency syndrome.

Results or conclusions from different studies of a specific exposure and disease or from different investigators examining the same data sometimes seem to be contradictory. Pediatricians are better equipped to make an informed decision if they are familiar with key concepts and principles of interpretation particularly pertinent to epidemiologic studies of childhood cancer as described in this report.

Source Population and Selection of Cases and Control Subjects

Critical to interpreting epidemiologic studies are the source population and the methods of selecting study subjects. In case-control studies, cases (ie, people with the disease of interest) and control subjects (ie, people without that specific disease) should be identified from the same population; ideally, control subjects should be chosen randomly from a complete list of the entire population from which cases arose.[10–12] Examples of populations for which complete lists are available include the provincial-wide health insurance listings in Canada[13]; population-based lists of patients assigned to a general practitioner in the United Kingdom[14]; and the hospitalization, cancer, or other national registries in the Nordic countries.[15–17] Population-based health care registries are limited in the United States, because even the nationwide Medicaid or Medicare lists are restricted to population groups defined by income or age. The rarity of childhood cancers limits the utility of large health maintenance organizations or most insurance plans for epidemiologic studies of pediatric tumors in the United States. Epidemiologic studies of childhood cancer have been conducted within US clinical trials consortia, because a high proportion of all children younger than 15 years (but not older adolescents) in whom cancer is diagnosed are seen by pediatric oncologists affiliated with these consortia.[18,19] However, epidemiologic studies of pediatric cancer have not always included a substantial number of children from ethnic minorities, because regions with larger proportions of minorities are not always included, the proportion of pediatric cancer cases whose families agree to participate is smaller for minority than for nonminority children, and the proportion of minorities among control subjects has been lower than the percentage among cases.[18,20]

Registration of patients who are treated by pediatric oncologists within the consortia often occurs within days of diagnosis, but the choice of control subjects is not so straightforward. One possibility might be selection of controls with other cancers or diseases from the same institution as cases if the

TABLE 2. Risk Factors (Known, Suggestive, Limited) Associated With Childhood Brain Tumors and Sympathetic Nervous System Tumors

Exposure or Characteristic	Brain Tumors			Sympathetic Nervous System	
Known					
Gender		M:F	Age-adjusted incidence (per million)	M:F	Age-adjusted incidence (per million)
	Type				
	All brain tumors	1.2	25.9	1.1	7.9
	Astrocytomas	1.1	13.4		
	Primitive neuroectodermal tumors	1.7	5.0		
	Other gliomas	1.0	4.4		
	Ependymomas	2.0	2.1		
Age peak	Infancy			Infancy	
Race	W:B = 1.2			W:B = 1.8	
Other factors	Ionizing radiation				
	Genetic disorders				
	Neurofibromatosis				
	Tuberous sclerosis				
	Nevoid basal cell syndrome				
	Turcot syndrome				
	Li-Fraumeni syndrome				
Suggestive	Maternal diet during pregnancy				
	Cured meats				
	Sibling or parent with brain tumor increases risk				
Limited	Some paternal occupations, including aircraft industry; agriculture; electronics manufacturing; petroleum industry; painting; paper or pulp mill work; printing; metal-related occupations; and occupations involving exposure to paint, ionizing radiation, solvents, and electromagnetic fields			Selected medications taken during pregnancy	
				Fertility drug use before pregnancy	
	Use of products containing *N*-nitroso compounds, including beer, incense, makeup, antihistamines, etc			Maternal smoking and alcohol use during pregnancy	
	Residential pesticides			Selected paternal occupational exposures	
	Family history of epilepsy, mental retardation			Agricultural, pesticides	
				Hydrocarbons, rubber, paint	
				Dusts, electrical components	

M:F indicates male-to-female ratio of incidence; W:B, white-to-black ratio of incidence.

exposures of interest do not cause the cancers or diseases in control subjects; if the exposure being evaluated is statistically or causally associated with the cancers or other diseases of control children, then the estimated risks using this control group tend to be lower than the actual risks. Because the major causes of most childhood cancers are unknown and the few known causes (high doses of ionizing radiation and certain inherited genetic disorders) are associated with more than 1 type of cancer or other serious pediatric disease, selecting control subjects with cancer or other serious pediatric disease is probably not a good choice. An alternative is to select otherwise healthy control subjects from the general population.

For many years, control subjects for most US epidemiologic studies of childhood cancer have been selected by a telemarketing technique called random-digit dialing. Randomized listings of telephone numbers with the same area code and exchange as the cases are generated and systematically evaluated to identify households that contain children of similar age, gender, or racial or ethnic group as the pediatric cancer cases. Although reasonable in the United States, where telephone coverage has been nearly universal, this method was not appropriate for countries in which substantial numbers of households lack telephones. During the past decade, random-digit dialing in the United States has been less successful than it had been in previous decades,[21,22] because increasing numbers of answering machines are used to screen telephone calls, and there are more telephone lines per household, more lines dedicated to fax or modem use in residences and businesses, more cellular telephones, and rapidly decreasing levels of participation by potentially eligible control subjects. These trends have also led to increasing sociodemographic differences between cases and control subjects; concern about the potential for selection bias[23] has led to consideration of alternative approaches for selecting control subjects.

Definition of Risk Factor

A risk factor is a specific agent statistically associated with a disease. Risk factors can be exogenous exposures, such as pesticides; endogenous characteristics, such as high hormone levels; lifestyle factors, such as dietary constituents or level of physical activity; treatments, such as medications; predisposition to particular familial diseases; or genetically determined features. The extent to which the evidence of causality supports a relationship between a risk factor and a disease determines whether the weight of the evidence should be considered as established, suggestive, or limited. Risk factors may be positively associated (ie, increase incidence) or negatively associated (ie, decrease incidence) with the disease. If increasing levels of exposure to a specific risk factor

TABLE 3. Risk Factors (Known, Suggestive, Limited) Associated With Childhood Malignant Bone Tumors, Soft Tissue Sarcomas, Renal Tumors, and Hepatic Tumors

Exposure or Characteristic	Malignant Bone Tumors	Soft Tissue Sarcomas	Renal Tumors	Hepatic Tumors
Known				
Gender	Type M:F All bone 1.2 Osteosarcoma 1.2 Ewing sarcoma 1.3 Chondrosarcoma 1.5	Type M:F All soft tissue 1.2	Type M:F All renal 0.9	Type M:F All hepatic 1.2 Hepatoblastoma 1.2 Hepatocellular carcinoma 1.0
Age peak	13–18 y	Infancy for rhabdomyosarcoma; 15–19 years for others	Infancy for Wilms tumor; 15–19 y for renal cell carcinomas	Infancy for hepatoblastoma; 15–19 y for hepatocellular carcinoma
Age-adjusted incidence (per million)	8.6	10.8	6.4	1.5
Race	W:B = 1.3	W:B = 0.9	W:B = 0.9	W:B = 1.2
Anatomic site	Osteosarcoma, long bones; Ewing sarcoma, central axis		7% of Wilms tumors are bilateral	
Other factors	Radiation therapy for childhood cancer Treatment with alkylating agents High doses of radium Genetic disorders Hereditary retinoblastoma Li-Fraumeni syndrome Rothmund-Thomson syndrome	Some concordance between anatomic location of rhabdomyosarcoma and major birth defects Up to one third of patients with rhabdomyosarcoma have at least 1 congenital anomaly Genetic disorders Li-Fraumeni syndrome Neurofibromatosis	Notably decreased incidence in Asians, compared with whites and blacks Genetic disorders WAGR Beckwith-Wiedemann syndrome Perlman syndrome Denys-Drash syndrome	Genetic disorders Beckwith-Wiedemann syndrome Hemihypertrophy Familial adenomatous polyposis Gardner syndrome
Suggestive	—	—	Father employed as welder or mechanic increases risk	—
Limited	Taller stature Trauma Short birth length Some parental occupations, including chicken farming Exposure to pesticides	Low socioeconomic status Diagnostic radiographs during pregnancy Parents' use of recreational drugs	High birth weight Parental occupational exposure to pesticides Maternal consumption of coffee and/or tea during pregnancy Maternal hair dye use Maternal occupational exposures, including hairdressing and electronic and laboratory work	Parental occupational exposures to metals, petroleum products, paints, and pigments Low birth weight

M:F indicates male-to-female ratio of incidence; W:B, white-to-black ratio of incidence; WAGR, Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation.

TABLE 4. Risk Factors (Known, Suggestive, Limited) Associated With Childhood Germ Cell Tumors, Carcinomas and Other Malignant Epithelial Tumors, and Retinoblastoma

Exposure or Characteristic	Germ Cell Tumors			Carcinomas and Other Malignant Epithelial Tumors			Retinoblastoma		
Known									
Gender	Type	M:F	Age-adjusted incidence	Type	M:F	Age-adjusted incidence	Type	M:F	Age-adjusted incidence
	All germ cell	1.1	10.1 per million	All carcinomas	0.5	14.1 per million	All retinoblastoma	1.0	2.8 per million
	Gonadal	1.5	6.1	Thyroid carcinoma	0.2	5.0			
	Testicular		8.1	Malignant melanoma	0.6	4.5			
	Ovarian		5.3						
Age peak		15–19 y			15–19 y			Infancy	
Race		W:B = 1.5			W:B = 1.5			W:B = 0.9	
Other	Cryptorchidism			Thyroid carcinoma Ionizing radiation exposure during childhood from environmental and medical sources Inherited cancer susceptibility syndromes (familial polyposis multiple endocrine neoplasia types I, II-A, II-B) Malignant melanoma Ultraviolet sunlight exposure Number of nevi and dysplastic nevi			Parent with a history of bilateral retinoblastoma		
Suggestive	High maternal hormone levels during pregnancy Family history of germ cell tumor Hernia Preterm birth			Thyroid carcinoma Hormonal factors Benign thyroid diseases			13q deletion syndrome		
Limited	Viral infections High birth weight Prenatal radiographic exposure Parental occupation including health care, aircraft industry (paternal), and other work involving exposure to x-rays (paternal) or solvents (maternal) Constitutional chromosome abnormalities (Klinefelter syndrome)						Paternal occupation including military, metal manufacturing and welding, machining, or related occupation		

M:F indicates male-to-female ratio of incidence; W:B, white-to-black ratio of incidence.

result in steadily increasing or decreasing incidence of the disease, then causation is more likely.

A broad definition of risk factor should be considered when evaluating environmental or exogenous agents that may be important in the cause of childhood cancer. Sources of such agents can include the residential, child care, or school environment. Environmental agents can be transmitted by inhalation, ingestion, or dermal routes. Types of agents identified as risk factors for childhood (and/or adult) cancers include radiation (including ionizing and nonionizing forms), metals (eg, arsenic, platinum), fibers (eg, asbestos), individual chemicals (eg, benzene, or a drug such as aspirin), mixtures (eg, paints, cigarette smoke, pharmaceutical agents containing several chemicals), dietary constituents (including mixtures such as food groups, macronutrients such as specific types of fat, and micronutrients), physical activity, and familial and genetic disorders (eg, neurofibromatosis type 1, Down syndrome, ataxia telangiectasia).

Exposure Assessment

Exposure assessment is always important, particularly in case-control studies. In general, poor measurement of exposure for cases and control subjects makes it more difficult to observe an effect. By contrast, if exposures cannot be measured and the investigator must rely on questionnaire data, then risk estimates may be too high if past exposures are systematically overreported by cases but not control subjects or underreported by control subjects but not cases.

In case-control studies of children and adults, by definition, the relevant exposures occurred before (sometimes many years before) diagnosis. Because childhood cancers are rare, a prospective study would need to collect exposure information from hundreds of thousands, if not millions, of children over several years to identify adequate numbers of pediatric cancers for assessing statistical associations; such a study would be too expensive to be feasible. Hence, for case-control studies, improved methods are needed to estimate past exposures and to test for validity. Ideally, investigators should attempt to obtain objective environmental, occupational, or biological measurements. Objective measurements taken after diagnosis, however, may not reflect exposure levels during the relevant prediagnosis period (eg, preconception or prenatal exposures). It may not be possible to use a single measurement obtained for each subject after diagnosis to estimate accurately exposures that may vary by day, month, season, year, or age. If measurements are not feasible, then epidemiologists must rely on proxy measures, such as interview data obtained from mothers or fathers of subjects. Interview data may be subject to reporting, recall, or rumination effects, because parents of children with cancer will expend extensive effort to remember exposures that are often forgotten or only partially remembered by parents of healthy children. If exposures (eg, diet, physical activity, other habits) change subsequent to onset of childhood cancer, then it may be difficult for the parent to recall accurately the child's prediagnostic exposures in postdiagnostic interviews.

Exposure assessment methods used in epidemiologic investigations of childhood cancer have improved with time, but studies continue to require collection of substantial exposure information from interviews with parents, yet there are relatively few comparisons of different measurement or interview approaches for retrospectively assessing exposures potentially relevant to the cause of childhood cancer. In general, most efforts have relied on maternal interview, an approach fraught with potential for misclassification and differential recall between cases and control subjects.[24] For example, most of the published epidemiologic investigations evaluating residential pesticide exposures and childhood cancer risk used very crude exposure assessment with little detailed information about pesticide type, amount, number of applications, or year of application.[25–27] Some case reports have included this type of detail, but the exposure assessment measures generally used in epidemiologic studies were broad. A recent report also indicated that the risk estimates could vary notably for the different interview-based exposure assessment strategies used.[24]

In the absence of environmental or biological measurements or, more ideal, molecular "fingerprints" of a specific exposure, it is difficult to interpret responses of a parent about a child's exposure to many agents or devices, particularly because exposure levels and use change over time with growth, development, and behavioral change. Efforts to develop new methods for assessing exposures are under way. Epidemiologists should use rigorous, standardized methods for measuring exposures, for assessing reproducibility of measurements over time and among data collectors, for evaluating validity and accuracy of exposure measurements, and for incorporating appropriate quality control measures within data collection protocols. When possible, epidemiologists should incorporate blinding strategies, as used in clinical trials, to keep data collectors uninformed about the disease or cancer and exposure status of each subject to increase the likelihood of objective exposure assessment. Laboratories that are responsible for testing environmental exposures (eg, residential radon or pesticide levels measured in dust from carpets) or clinical parameters (eg, hormone or micronutrient levels) should require standardized protocols with stringent quality control measures. In addition, the accuracy of laboratory quantification of an exposure can be evaluated by submitting additional samples accurately loaded with a known level of a given substance for testing by the laboratory.

Critical Windows of Exposure

In children, as in adults, there seem to be discrete windows of vulnerability to exogenous exposures. There is evidence from animal and human epidemiologic studies of causal relationships for preconception, in utero, perinatal, infancy, and postinfancy exposures and cancer occurrence in children.[28] One example is the statistical association between prenatal exposure to diagnostic radiographs, particularly

during the last trimester of pregnancy, and subsequent small increase in childhood leukemia risk (discussed in more detail below).[29–38]

Measures for Estimating Risk

The measure used to estimate risk in most epidemiologic studies is relative risk, defined as the ratio of the incidence of disease in exposed individuals to the baseline incidence of disease in unexposed individuals.[39] The concept of relative risk is not an intuitive statistic to most people. A relative risk of 1.5 among exposed versus unexposed individuals, a 50% increase over disease rates in unexposed individuals, sounds important. Indeed, a causal 50% increase in a common disease would be very important. However, an unconfirmed 50% increase in a rare disease may not be particularly meaningful. One way to consider communicating the meaning of a relative risk is to translate this measure to the concept of probability. For example, suppose a rare disease occurs in unexposed individuals at the annual incidence rate of 3 per 100 000 people and that the relative risk for that disease among people with a specified exposure is 1.6 (eg, a 60% increase in annual incidence of the rare disease to 4.8 per 100 000 is observed in exposed compared with unexposed people in that population). The rate of developing the disease among exposed people would be almost 5 per 100 000 people per year in contrast to the baseline rate of 3 per 100 000 per year among unexposed people. This type of translation may be helpful for interpreting the risk estimate. The same relative risk would arise if the rates in unexposed and exposed people were 30 and 48 per 100 000 per year, respectively. In case-control studies, epidemiologists typically report the odds ratio; for risks of rare diseases such as childhood cancer, the odds ratio and the relative risk are virtually identical, and the distinction between these 2 measures can be disregarded.

Statistical Versus Causal Associations

Even when a statistically significant association is observed, it is still possible that the association may be attributable to chance, study design, features of the data collection process, or the effects of factors closely related to exposure. Criteria used to judge whether an association is a mere statistical association or a causal association with biological or public health implications include the magnitude of the risk (relative risks between 1.0 and 1.5 or 2.0 are viewed with caution), whether the risk increased with increasing exposure level, consistency across studies, the appropriate temporal relationship between the exposure and the disease (ie, the exposure must precede the disease, with a biologically appropriate interval for carcinogenesis between first exposure to a cancer-causing agent and development of the first malignant cells of a tumor), and the biological plausibility of the hypothesis.[39,40] Each of these factors should be considered, but sufficient evidence for causation does not require that each criterion be established. With large relative risks (eg, the 10-fold or greater excesses of lung cancer among heavy, long-term cigarette smokers[41]; acute leukemia among children with Down syndrome[42]), it is much less likely that chance or undetected bias could explain the entire increase.

With small relative risks, it can be difficult to distinguish a true cause-and-effect relationship from a chance or undetected bias. Essentially, all other explanations for the finding, including chance, must be unlikely. For small increases in relative risk to be accepted as real, many studies of excellent quality that consistently report the statistical association in diverse populations (in addition to the criteria listed previously) are needed.

Two examples involving modest statistical associations illustrate several pertinent points. The first describes a statistical association likely to be causal, and the second describes a relationship for which clear evidence of causality is lacking. Since the mid-1950s, large epidemiologic studies from different countries reported small increases in risk (relative risks ranging from 1.2 to 1.8, with an overall estimate of 1.4 [ie, risks that were 40% higher than expected]) of leukemia in offspring of women who were radiographed during pregnancy.[29–32] Much of the diagnostic radiography was conducted toward the end of a pregnancy (eg, pelvimetry) to evaluate potential problems during delivery. Current understanding of the long-term carcinogenic effects of radiation exposure is largely derived from studies of cancer incidence and mortality among the atomic bomb survivors in Hiroshima and Nagasaki[43–45] and studies of children and adults who receive therapeutic radiation.[46] Although high doses of ionizing radiation from environmental and therapeutic sources have been associated with several types of childhood (as well as adult) cancers,[33,47] the magnitude of the risk associated with lower doses of ionizing radiation, such as that from diagnostic radiography during pregnancy, is difficult to estimate.

The possibility that the indication of diagnostic or treatment intervention may confound a statistical association between the intervention and disease outcome must be considered in evaluating the expected and unexpected effects of a medical intervention. Some epidemiologists postulated that modest increases of cancer in offspring of women exposed to diagnostic radiography during pregnancy may have been a consequence of fetal or maternal health problems rather than the ionizing radiation exposure. In the past, obstetricians ordered diagnostic radiography to examine pregnant women for a variety of conditions, including many unrelated to the health of the fetus. Subsequent analyses demonstrated that cancer risks were increased even among children with no evidence of poor health in utero,[33–35] ruling out fetal health problems as the likely cause of the increased incidence of childhood cancer.

With awareness of the increased childhood cancer risk among offspring of women radiographed during pregnancy, 3 developments led to a decrease in exposures: improvements in radiologic techniques resulting in high-quality radiographic films using lower radiation doses, decreasing use of radiographic testing during pregnancy,[35–38] and replacement of pelvimetry and other prenatal radiographic

tests with diagnostic ultrasound.[48] Epidemiologic studies documented a decline in childhood cancer risks between 1936–1959 and 1960–1967 in Sweden,[49] between 1940–1956 and 1957–1969 in the United Kingdom,[50] and between 1947–1957 and 1958–1960 in the northeast United States.[51]

The relationship of prenatal diagnostic irradiation with increased risk of childhood leukemia seems to meet most of the criteria for causality, yet some[52] have raised doubts about the evidence of causality, arguing that diagnostic radiography during pregnancy has been linked with excesses of solid pediatric tumors in addition to leukemia (ie, lack of specificity), that the association is restricted to case-control but not cohort[53–55] or twin studies[56,57] (ie, lack of consistency), that there was an absence of elevated risks among Japanese children exposed in utero to radiation from the atomic bombs dropped in Hiroshima and Nagasaki (ie, lack of increased risks associated with higher doses or lack of dose response),[58] and that there is no support from experimental evidence linking cancer risks in animals with low-dose radiation exposures late in pregnancy (ie, lack of biological plausibility). Counterarguments include that there was experimental evidence of increased benign and malignant neoplasms after perinatal irradiation of young beagles[59] and higher risks among beagles irradiated later in fetal development than in those irradiated earlier,[60,61] that there is a lack of evidence of associations in cohort (including the Japanese atomic bomb survivors) and twin studies explained by limited statistical power (see Table 4 in Doll and Wakeford[35]), and that there is an absence of information about early mortality in Japanese atomic bomb survivors (mortality from childhood leukemia was unrecorded from 1946 to 1949 because the Japanese survivors were systematically monitored only from 1950).[35,58]

The second example illustrates a relationship between an environmental exposure and childhood leukemia that does not meet the criteria for causality. After publication of results from relatively small investigations linking high-level proxy or direct measures of residential 60-Hz power-frequency magnetic fields with small increases in risk of childhood leukemia,[15,62–64] data from rigorous large epidemiologic investigations using more sophisticated exposure assessment methods[13,65,66] in the United States,[65] Canada,[13] and the United Kingdom[66] did not support a causal relationship (ie, for direct and proxy measures, the strength of the statistical associations observed did not support causality). When data from several epidemiologic studies were combined or pooled, childhood leukemia risks did not increase steadily with increasing residential magnetic field or wire code levels (ie, no consistent dose response); instead, risks did not increase with increasing exposure until estimated magnetic field exposures reached >0.3 microtesla (μT).[67,68] In the pooled analyses, a very small proportion of children with high residential magnetic field exposures had modest excess risks of leukemia (relative risk estimated as 1.7 for children whose estimated exposures were >0.3 μT[67] and 2.0 for those with exposures >0.4 μT[68] versus children whose estimated exposures were 0–0.1 μT; ie, the strength of the association was weak). The results of experimental studies did not support the biological plausibility of the association. Exposure to power-frequency magnetic fields did not lead to cancer occurrence in laboratory animals,[69–73] and nonionizing radiation from power lines has not ever been shown to cause carcinogenic changes to DNA or other parts of living cells[69] (both types of findings revealing lack of biological plausibility). Finally, some of the modest increase in risk among US children was likely attributable to selection bias; that is, among families that resided in homes with high magnetic field or wire code levels, those with a child who developed leukemia were more likely to participate fully in the large US epidemiologic study than those with a comparison (control) child; the latter were more likely to participate only partially in the study.[23]

Whether evaluating the results of a single study, a body of work, or a pooled analysis, pediatricians must evaluate the weight of the evidence when deciding whether small statistical associations are likely to be causal. A similar caution should also be applied when reading abstracts of medical papers, particularly when undue emphasis is given to a result from a post hoc analysis derived using cutoff points not included in the presumptive statistical analyses.[74] Results that are based on presumptive criteria for analyzing data should be given substantially greater weight when interpreting findings than results that are derived from post hoc cutoff points. Results of post hoc analyses should be interpreted cautiously and questioned, because such results can be based on cutoff points that would yield the most extreme outcomes.

Meta-analyses or Pooled Analyses

Consistency of findings across observational studies can be judged informally or, increasingly, with a technique called meta-analysis or pooled analysis.[75–77] The dramatic increase in use of meta-analysis is eliciting increasing concern among some epidemiologists.[78–81] Pooling of data across randomized clinical trials investigations has proved very helpful, particularly to clarify whether there is a benefit and to quantify the overall improvement for a clinically important outcome when a relatively small effect is seen in many but not all studies. Pooling of observational data from epidemiologic studies to summarize results with a single number can be helpful when the studies have similar methods and characteristics. However, this is rarely the situation, because epidemiologic studies often differ in study design, types of control subjects selected, population size, methods used for exposure assessment, field work methods, and other factors. Because there are no standardized ways to weigh studies according to quality or exclude those studies that do not attain a minimum level of quality, the meaning of a single-summary risk estimate becomes unclear when studies with diverse methodology and limitations are pooled, because even a single study of poor quality can have a large effect on the results of a meta-analysis. Meta-

analysis may be particularly problematic when attempting to ascertain whether an exposure of great public concern (eg, environmental sources of ionizing radiation, nonionizing power-frequency magnetic fields, arsenic as a natural contaminant in drinking water) is linked with a specific type of childhood cancer, particularly when the association is modest and inconsistently observed in different epidemiologic studies.[81] Thus, pediatricians need to be skeptical about attempts to decrease a complex array of differing investigations to a single risk estimate.

Are there meaningful types of meta-analyses or statistical approaches for systematically evaluating a body of epidemiologic studies? At present, this is an active area of statistical research with a variety of methods under development. Until internationally recognized methods have been validated, such efforts should be viewed with appropriate caution.[82]

Population Impact

Once causality is established between a specified exposure and a disease, it is important to consider the impact, that is, the number of individuals who will develop the disease (incidence) or die (mortality) as a result of the exposure. A recent example is provided. As use of pediatric computed tomography (CT) examinations has rapidly increased, driven in part by technical improvements and the speed of examination made possible by the helical CT,[83] the number of requests for CT scans in children increased 63% between 1991 and 1994,[84] and the number of abdominal and pelvic CT examinations among children in a major children's hospital increased ~100% from 1996 through 1999 (shown by Brenner et al[85]). It has been clearly demonstrated that use of helical CT decreases the need for sedation of children and improves the quality and precision of diagnostic evaluation of the pediatric abdomen in acute illnesses, particularly in young, sick, and uncooperative children. Although CT examinations constitute a relatively small proportion of all diagnostic radiologic examinations in children, the contribution to a child's cumulative radiation dose is substantial because of the notably higher lifetime risk per unit dose of radiation for children, compared with adults. For example, in Britain, pediatric CT scans constitute ~4% of all diagnostic radiologic procedures but contribute ~40% of the total radiation dose from diagnostic examinations.[86] Brenner et al[85] calculated age-dependent lifetime cancer mortality risks per unit dose using existing databases[87–91] and estimated that lifetime risk of death from cancer was 1 in 600 or 0.18% increased in a 1-year-old child undergoing a CT scan of the abdomen; lifetime risk of death from cancer was estimated to be 0.07% increased in a 1-year-old undergoing head CT scan. These estimated cancer risks were 1 order of magnitude higher than for adults receiving comparable doses. Approximately 1.6 million CT scans of the abdomen and head are currently administered annually to children younger than 15 years in the United States. If a lifetime follow-up study were conducted to assess the causes of death among all children currently younger than 15 years in the United States, investigators[85,92] estimated that of the 373 000 expected deaths from cancer in this population, ~1500 would be attributable to childhood radiation exposure from the CT examinations. The authors noted that the current benefit of pediatric CT examination strongly outweighs the small increase in lifetime cancer mortality[85] but also underscored the need for technical improvements to decrease the radiation dose while maintaining the same high-quality visualization as with current doses.[93–95]

CONSIDERATIONS IN INVESTIGATING A POTENTIAL CLUSTER OF CHILDHOOD CANCER CASES

Public health practitioners are periodically faced with reports of seemingly high local incidences of childhood cancers. Post hoc childhood cancer clusters are defined as notable aggregations of cases occurring in geographic proximity or with similar temporal onset and representing a seemingly statistically higher incidence, compared with expected rates for the geographic region and time period or chance fluctuations.[96] A priori childhood cancer clusters are those found as a result of a specific statistical exercise evaluating the childhood cancer incidence in a particular geographic area. Clusters can be transient (ie, occurring during a given period but disappearing with continued surveillance) or prolonged (ie, persisting with long-term monitoring).

The approach and initial steps for investigating possible childhood cancer clusters include distinguishing between homogeneous and heterogeneous types of pediatric cancers in the cluster, determining whether the cluster includes newly diagnosed cases only or a mixture of incident (new onset) and prevalent (existing) cases plus deaths, and designation of the temporal and geographic boundaries of the cluster. Although place of residence at diagnosis is often used to define the geographic characteristics of cases that compose a potential cluster, a biologically more meaningful definition may be place of residence during the etiologically relevant period. Because neither the causes nor the etiologically relevant time periods are known for most childhood cancers, the characterization of the cases according to geographic boundaries may be difficult. Progress may be achieved in clarifying the etiologically relevant period as investigators increasingly obtain lifetime residential histories.

An extensive literature (reviewed in Linet[97] and Little[98]) suggests an infectious cause for childhood ALL. Potentially supporting this hypothesis are a growing number of reports confirming higher incidence of childhood ALL in areas of population growth (eg, rapidly developing new towns, growing suburbs) and regions with increased population movements or social contact attributable to new construction in formerly isolated regions; rising levels of commuting; or influxes related to war, major disasters, or tourism.[99–103] Maternal infection during pregnancy has long been suspected to be related to childhood ALL,[104–106] but findings have not been consistent and specific organisms have not been

identified. Immunization during pregnancy and infancy has been linked with increased and sometimes decreased risks of childhood ALL.[107–111] The possible role of social contact during infancy and early childhood has been explored, using enrollment in child care, number and spacing of siblings, and other indirect proxy measures of exposure to infectious organisms.[112]

Childhood cancer clusters have also been linked with postulated environmental hazards, including ionizing or nonionizing radiation; benzene, solvents, pesticides, or other chemicals; or residential or school proximity to known or suspected carcinogens in manufacturing facilities, waste sites, underground storage tanks, or environmental or industrial accidents (eg, Chernobyl in the former Soviet Union or Seveso, Italy [reviewed in Little[98]]).

There are no internationally recognized systematic approaches for evaluating a putative cluster, but cluster investigations are generally led by state and local health departments with additional guidance from federal agencies and academic specialists. The reader is referred elsewhere for detailed descriptions of methods[113–115] and statistical approaches[116–119]; the latter are also summarized on the Centers for Disease Control and Prevention web site (www.cdc/gov/mmwr/preview/mmwrhtml/00001798). Two useful references for step-by-step approaches for evaluating a putative cluster include the Centers for Disease Control and Prevention web site (www.cdc.gov/mmwr/preview/mmwrhtml/00001797) and a recent handbook published by the Leukemia Research Fund.[96]

Briefly, after notification about a potential cluster, the key first steps should include confirmation of the existence of the reported cases; identification of any additional cases (from hospitals, pediatric oncologists and other relevant physician practices, cancer registries, and other sources); and systematic collection of standardized clinical, residential, and sociodemographic information for each case. This initial data should guide the investigators in establishing geographic boundaries and defining the diagnoses of concern. The investigators need to balance requirements for strict confidentiality with frequent communication of progress and activities to the concerned community. If the investigation goes forward, then important components include validation of diagnoses of cases, selection of an appropriate reference area for calculation of expected numbers, and establishing temporal boundaries to include the longest time interval during which all potential cases can be confirmed and validated.

Methodologic considerations should include awareness that the detailed amount and quality of data collected on suspected cases will likely be notably superior to the corresponding data available for cases in populations used to calculate expected rates; such discrepancy could lead to biased results (attributable to underestimates of childhood cancer incidence in the regions used to calculate expected rates and corresponding overestimates of the excess of cases in the study area). Methodologic problems to avoid include the temptation to fit the results to a preconceived pattern, possible errors in estimating the population at risk, use of inappropriate statistical tests, and recognition that evaluation of a large number of putative causative exposures will result in some statistical associations that occur by chance alone. The minimum number of cases that constitute a cluster is unclear, but the rarity of childhood cancer suggests that numbers will be fairly small.

If the investigators determine that the cluster represents a significant excess, then potential causes must be evaluated. Investigators should recognize that epidemiologic methods are limited when studying small numbers of subjects, particularly when no plausible exposure can explain the occurrence of the childhood cancer cluster.

CHARACTERISTIC FEATURES AND KNOWN, SUGGESTIVE, AND POSTULATED CAUSES OF CHILDHOOD CANCERS

Recent analyses of childhood cancer trends[5,7] and a National Cancer Institute monograph on childhood cancer incidence, mortality, and survival patterns[4] in the geographic regions covered by the institute's Surveillance Epidemiology and End Results Program have clarified understanding of trends in these areas for the period 1975–1995 and have pointed to notable differences in patterns by age, gender, racial or ethnic group, and histologic subtypes within major cancer categories. Efforts to compare incidence trends in childhood cancers among populations internationally, however, can be problematic because of differences in population census quality, completeness and accuracy of childhood cancer ascertainment, the rarity of childhood cancer, and geographic and temporal variation in coding and classification.[120–123] International childhood cancer incidence data have been systematically collated in monographs published by the International Agency for Research on Cancer for the periods 1970–1979[120] and 1980–1989.[124]

Distinctive Patterns and Trends Can Be Translated Into New Etiologic Leads

In Tables 1 to 4, some characteristic features of the major categories (and a limited number of subtypes) are shown. More detailed characterization of childhood cancers can be found elsewhere.[4] Some noteworthy features of childhood leukemia include the notable peak at 2 to 3 years of age for the common form of ALL; the much lower incidence and absence of a striking age peak at 2 to 3 years of age in blacks compared with US whites; the long-term, changing trends for common ALL in whites, with little evidence of a peak at very young ages until the 1920s in Britain and until the 1930s in the United States; and the relatively flat incidence of acute myeloid leukemia throughout childhood, with the only small peak apparent in infancy (Table 1).[125] The current presence of a notable age peak among whites and absence of such a peak among blacks may suggest a role for genetic factors in occurrence of common ALL, but the absence of an age peak among whites early in the 20th century followed by evidence of such a peak first in Britain and subsequently in the

United States implicates unknown exogenous or environmental exposures in initiating such a change. In addition to ALL, ethnic or racial differences are apparent for sympathetic nervous system cancers (low in blacks), renal tumors (notably decreased in Asians), and Ewing sarcoma (notably decreased in blacks). Such differences may be linked with genetic factors or exogenous exposures that differ by racial or ethnic group; racial or ethnic differences in genetic modulators of carcinogen metabolism, immune function, or other functional processes may also be important.

Although the male-to-female (M:F) age-adjusted incidence is >1.0 for all types of leukemias and lymphomas, the ratio is highest (M:F: 3.0) for non-Hodgkin lymphoma, similar for ALL and Hodgkin disease (both M:F: 1.3), and lowest for acute myeloid leukemia (M:F: 1.1 [Table 1]). The M:F incidence also varies among the subtypes of central nervous system tumors, with the highest ratio apparent for ependymomas (M:F: 2.0) and primitive neuroectodermal tumors (M:F: 1.7), but there is little difference between male and female age-adjusted incidences for astrocytomas and other gliomas (Table 2). The 2 major categories of carcinomas and other epithelial tumors are characterized by higher incidences among females than among males (Table 4). Reasons are unknown for the male predominance in incidence of non-Hodgkin lymphoma and ependymomas; the higher incidences among young females for thyroid cancer and malignant melanoma; and the lack of gender-related differences in incidences of acute myeloid leukemia, astrocytomas, and other gliomas, but etiologic leads to consider include exposures that differ by gender, effects of hormonal influences, and gender-related genetic differences.

Incidence of sympathetic nervous system tumors is highest during infancy. When incidence is evaluated according to onset by month during the first year, the highest rate is seen in the first month and subsequently decreases with increasing age, suggesting a prenatal origin for these tumors (Table 2). Incidence of malignant bone tumors is highest in the latter part of adolescence, with a somewhat later increase during adolescence for males than for females, particularly for osteosarcomas (Table 3); this pattern may suggest a role for adolescent hormonal effects in the cause of this type of tumor. The peak age for incidence of rhabdomyosarcoma is during infancy, and the highest incidence for other forms of soft tissue sarcoma occurs during late adolescence (Table 3). The peak age for incidence of Wilms tumor is infancy, but incidence of renal cell carcinoma does not begin to increase until late adolescence. The variation in age of onset patterns for rhabdomyosarcoma versus other forms of soft tissue sarcoma and for Wilms tumor versus renal cell carcinoma may point toward causative differences.

Known, Suggestive, and Postulated Causes of Childhood Cancers

Epidemiologic studies of pediatric cancers have evaluated a relatively large number of postulated risk factors. Little is known about the cause of childhood cancers, particularly the rarer forms of these cancers. Familial and genetic factors seem to occur in no more than 5% to 15% of different categories of childhood cancer.[126] Known environmental exposures and exogenous factors explain <5% to 10% of the occurrence of childhood cancer. Some risk factors are known to cause specific forms of childhood cancers, and other exposures have been statistically linked with several types of childhood cancers (Tables 1–4). Several types of pediatric cancers have increased incidences in children with genetic syndromes or congenital disorders. Moderate to high doses of ionizing radiation are associated with increased risks of acute lymphoblastic and myeloid leukemias, central nervous system tumors, malignant bone tumors, and thyroid carcinoma. Suggestive or limited data link certain maternal reproductive factors, parental occupational exposures, residential pesticides (prenatal and postnatal exposures), cured meats (prenatal exposures), paternal smoking (preconception), and other exposures with increased risk of some types of childhood cancers.

A small but expanding number of environmental or exogenous risk factors have been linked with childhood cancer in the past decade from large and influential US,[20,26,65,111,112,127–155] Canadian,[13,156–162] British,[14,66,100,101,113,163–174] German,[126,175–183] Nordic,[15–17,74,184–187] Chinese,[188–191] and multicenter[68,192–198] epidemiologic studies of leukemia, brain tumors, neuroblastoma, and other childhood cancers. Although the burgeoning literature from these and other recent investigations has offered some new insights, the causes of most childhood cancers remain unexplained.

CONCLUSIONS

Epidemiologic studies in humans, including those that focus on childhood cancers, are primarily observational, not experimental, investigations. The weight of the entire body of epidemiologic evidence and, in particular, the quality and rigor of the methodologic aspects of individual studies are critical to interpreting the results. Epidemiologic studies, regardless of the main hypotheses, must take into account a complex interplay of exogenous exposures, human behaviors, and endogenous physiologic characteristics, all mediated in part by genetic determinants. The science of epidemiology is undergoing constant transformation as new methods are developed for exposure assessment, outcome designation, and data analysis. Unlike the experimental approaches used by laboratory scientists or even the methods used in randomized treatment trials in humans, data collection efforts in epidemiologic studies, particularly those with the emotional connotations of childhood cancers, can be strongly influenced on a day-to-day basis by scientific or media reports implicating the specific exposures under evaluation with the childhood cancer (or other serious disease). Epidemiologists who investigate postulated determinants for childhood cancers must strike a fine balance between objective (as well as accurate and reproducible) ascertainment of past exposures without regard to disease status while empathizing

with distraught families and an anxious public. Interpretation of results requires sensitivity to individual and public fears but must not lose sight of the key objective: identification of the causes of childhood malignancies.

REFERENCES

1. Cushman JH Jr. US reshaping cancer strategy as incidence in children rises. *New York Times*. 1997;September 29, Section A, page 1, column 2
2. Ritter J. Cancers haunt town, defy science. *USA Today*. 2001;April 12:8A
3. Howe HL, Wingo PA, Thun MJ, et al. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. *J Natl Cancer Inst*. 2001;93:824–842
4. Ries LAG, Smith MA, Gurney JG, et al, eds. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995.* Bethesda, MD: National Cancer Institute; 1999 (NIH Publication No. 99-4649)
5. Chow WH, Linet MS, Liff JM, Greenberg RS. Cancers in children. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York, NY: Oxford University Press; 1996:1331–1369
6. Miller RW, Myers MH. Age distribution of epithelial and non-epithelial cancers [letter]. *Lancet*. 1983;2:1250
7. 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;91:1051–1058
8. Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer*. 1987;40:620–624
9. Kramarova E, Stiller CA. The international classification of childhood cancer. *Int J Cancer*. 1996;68:759–765
10. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol*. 1992;135:1019–1028
11. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. II. Types of controls. *Am J Epidemiol*. 1992;135:1029–1041
12. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. III. Design options. *Am J Epidemiol*. 1992;135:1042–1050
13. McBride ML, Gallagher RP, Theriault G, et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. *Am J Epidemiol*. 1999;149:831–842
14. UK Childhood Cancer Study Investigators. The United Kingdom Childhood Cancer Study: objectives, materials, and methods. *Br J Cancer*. 2000;82:1073–1102
15. Feychting M, Ahlbom A. Magnetic fields and cancer in children residing near Swedish high-voltage power lines. *Am J Epidemiol*. 1993;138:467–481
16. Cnattingius S, Zack MM, Ekbom A, et al. Prenatal and neonatal risk factors for childhood lymphatic leukemia. *J Natl Cancer Inst*. 1995;87:908–914
17. Cnattingius S, Zack M, Ekbom A, Gunnarskog J, Linet M, Adami HO. Prenatal and neonatal risk factors for childhood myeloid leukemia. *Cancer Epidemiol Biomarkers Prev*. 1995;4:441–445
18. Ross JA, Severson RK, Pollock BH, Robison LL. Childhood cancer in the United States. A geographical analysis of cases from the Pediatric Cooperative Clinical Trials groups. *Cancer*. 1996;77:201–207
19. Bleyer WA, Tejeda H, Murphy SB, et al. National cancer clinical trials: children have equal access; adolescents do not. *J Adolesc Health*. 1997;21:366–373
20. Shu XO, Linet MS, Steinbuch M, et al. Breast-feeding and risk of childhood acute leukemia. *J Natl Cancer Inst*. 1999;91:1765–1772
21. Greenberg ER. Random digit dialing for control selection. A review and a caution on its use in studies of childhood cancer. *Am J Epidemiol*. 1990;131:1–5
22. Olson SH, Kelsey JL, Pearson TA, Levin B. Evaluation of random digit dialing as a method of control selection in case-control studies. *Am J Epidemiol*. 1992;135:210–222
23. Hatch EE, Kleinerman RA, Linet MS, et al. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? *Epidemiology*. 2000;11:189–198
24. Savitz DA. Environmental exposures and childhood cancer: our best may not be good enough. *Am J Public Health*. 2001;91:562–567
25. 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;151:639–646
26. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer*. 2000;89:2315–2321
27. Daniels JL, Olshan AF, Teschke K, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology*. 2001;12:20–27
28. Olshan AF, Anderson L, Roman E, et al. Workshop to identify critical windows of exposure for children's health: cancer work group summary. *Environ Health Perspect*. 2000;108(suppl 3):595–597
29. Stewart A, Webb J, Giles D, Hewitt D. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet*. 1956;2:447
30. MacMahon B. Pre-natal x-ray exposure and childhood cancer. *J Natl Cancer Inst*. 1962;28:1173–1191
31. Graham S, Levin ML, Lilienfeld AM, et al. Preconception, intrauterine and postnatal irradiation as related to leukemia. *Natl Cancer Inst Monogr*. 1966;19:347–371
32. MacMahon B, Hutchison GB. Pre-natal x-ray and childhood cancer. A review. *Acta Ujion Int Contre le Cancer*. 1964;20:1172–1174
33. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation. Annex I. Epidemiological Evaluation of Radiation-Induced Cancer.* New York, NY: United Nations Scientific Committee on the Effects of Atomic Radiation; 2000:297–450 (United Nations Publication No. E. 00. IX. 3)
34. Harvey EB, Boice JD Jr, Honeyman M, Flannery JT. Prenatal x-ray exposure and childhood cancer in twins. *N Engl J Med*. 1985;312:541–545
35. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol*. 1997;70:130–139
36. Bithell JF, Stewart AM. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. *Br J Cancer*. 1975;31:271–287
37. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation.* New York, NY: United Nations Scientific Committee on the Effects of Atomic Radiation; 1986 (United Nations Publication No. E. 86. IX. 9)
38. Cox R, MacGibbon BH. *Diagnostic Medical Exposures: Exposures to Ionizing Radiation of Pregnant Women. Biological Basis of the Board's Statement.* Chilton, England: National Radiological Protection Board; 1993 (NRPB Document No. 4, Vol 4)
39. MacMahon B, Pugh TF. *Epidemiology: Principles and Methods.* Boston, MA: Little Brown & Co; 1970:1–16
40. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:7–28
41. US Department of Health, Education, and Welfare. *Smoking and Health. Report of the Advisory Committee to the Surgeon General*. Washington, DC: US Government Printing Office; 1964 (Public Health Service Publication No. 1103)
42. Neglia JP, Robison LL. Epidemiology of the childhood acute leukemias. *Pediatr Clin North Am*. 1988;35:675–692
43. Preston DL, Kusumi S, Tomonaga M, et al. Cancer incidence of atomic bomb survivors. Part III. Leukemia, lymphoma, and multiple myeloma, 1950–1987. *Radiat Res*. 1994;137(2 suppl):S68–S97
44. Thompson DL, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958–1987. *Radiat Res*. 1994;137(2 suppl):S17–S67
45. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, part I. Cancer: 1950–1990. *Radiat Res*. 1996;146:1–27
46. Inskip PD. Second cancers following radiotherapy. In: Neugat AI, Meadows AT, Robinson E, eds. *Multiple Primary Cancers.* Philadelphia, PA: Lippincott Williams & Wilkins; 1999:91–135
47. Boice JD Jr, Land CE, Preston DL. Ionizing radiation. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York, NY: Oxford University Press; 1996:319–354
48. Moore RM Jr, Jeng LL, Kaczmarek RG, Placek PJ. Use of diagnostic ultrasound, X-ray examinations, and electronic fetal monitoring in perinatal medicine. *J Perinatol*. 1990;10:361–365
49. Rodvall Y, Pershagen G, Hrubec Z, Ahlbom A, Pedersen NL, Boice JD. Prenatal x-ray exposure and childhood cancer in Swedish Twins. *Int J Cancer*. 1990;46:362–365
50. Mole RH. Childhood cancer after prenatal exposure to diagnostic x-ray examinations in Britain. *Br J Cancer*. 1990;62:152–168
51. Monson RR, Mac Mahon B. Pre-natal x-ray exposure and cancer in children. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation Carcinogenesis: Epidemiology and Biological Significance.* New York, NY: Raven Press; 1984:97–105

52. Boice JD Jr, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology*. 1999;59:227–233
53. Court Brown WM, Doll R, Hill AB. Incidence of leukaemia after exposure to diagnostic radiation in utero. *Br Med J*. 1960;2:1539–1545
54. Lewis TLT. Leukaemia in childhood after antenatal exposure to X-rays. A survey at Queen Charlotte's Hospital. *Br Med J*. 1960;2:1551–1552
55. Diamond EL, Schmerler H, Lilienfeld AM. The relationship of intrauterine radiation to subsequent mortality and development of leukemia in children. A prospective study. *Am J Epidemiol*. 1973;97:283–313
56. Inskip PD, Harvey EB, Boice JD Jr, et al. Incidence of childhood cancer in twins. *Cancer Causes Control*. 1991;2:315–324
57. Rodvall Y, Hrubec Z, Pershagen G, Ahlbom A, Bjurman A, Boice JD Jr. Childhood cancer among Swedish twins. *Cancer Causes Control*. 1992; 3:527–532
58. Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950–May 1992. *Radiat Res*. 1997;147:385–395
59. Benjamin SA, Lee AC, Angleton GM, Saunders WJ, Keefe TJ, Mallinckrodt CH. Mortality in beagles irradiated during prenatal and postnatal development. II. Contribution of benign and malignant neoplasia. *Radiat Res*. 1998;150:330–348
60. Benjamin SA, Lee AC, Angleton GM, et al. Neoplasms in young dogs after perinatal irradiation. *J Natl Cancer Inst*. 1986;77:563–571
61. Gilman EA, Kneale GW, Knox EG, Stewart AM. Pregnancy x-rays and childhood cancers: effects of exposure age and radiation dose. *J Radiol Prot*. 1988;8:3–8
62. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. *Am J Epidemiol*. 1979;109:273–284
63. 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
64. 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;134:923–937
65. Linet MS, Hatch EE, Kleinerman RA, et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. *N Engl J Med*. 1997;337:1–7
66. UK Childhood Cancer Study Investigators. Exposure to power-frequency magnetic fields and the risk of childhood cancer. *Lancet*. 1999;354:1925–1931
67. Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh M. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. *Epidemiology*. 2000;11:624–634
68. Ahlbom A, Day N, Feychting M, et al. A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer*. 2000;83:692–698
69. Portier CJ, Wolfe MS, eds. *Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields.* Research Triangle Park, NC: National Institute of Environmental Health Sciences; 1998 (NIH Publication No. 98-3981)
70. McCormick DL, Boorman GA, Findlay JC, et al. Chronic toxicity/oncogenicity evaluation of 60 Hz (power frequency) magnetic fields in B6C3F1 mice. *Toxicol Pathol*. 1999;27:279–285
71. Boorman GA, McCormick DL, Findlay JC, et al. Chronic toxicity/oncogenicity evaluation of 60 Hz (power frequency) magnetic fields in F344/N rats. *Toxicol Pathol*. 1999;27:267–278
72. Boorman GA, Rafferty CN, Ward JM, Sills RC. Leukemia and lymphoma incidence in rodents exposed to low-frequency magnetic fields. *Radiat Res*. 2000;153(suppl):627–636
73. Boorman GA, Owen RD, Lotz WG, Galvin MJ Jr. Evaluation of in vitro effects of 50 and 60 Hz magnetic fields in regional EMF exposure facilities. *Radiat Res*. 2000;153(suppl):648–657
74. Olsen JH, Nielsen A, Schulgen G. Residence near high voltage facilities and risk of cancer in children. *BMJ*. 1993;307:891–895
75. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol*. 1994;140:290–296
76. Petitti DB. *Meta-Analysis, Decision-Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine.* New York, NY: Oxford University Press; 1994
77. Petitti DB. *Meta-Analysis, Decision-Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine.* 2nd ed. New York, NY: Oxford University Press; 1999
78. Shapiro S. Meta-analysis/shmeta-analysis. *Am J Epidemiol*. 1994;140: 771–778
79. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol*. 1994;140: 783–787
80. Petitti DB. Of babies and bathwater. *Am J Epidemiol*. 1994;140:779–782
81. Shapiro S. Bias in the evaluation of low-magnitude associations: an empirical perspective. *Am J Epidemiol*. 2000;151:939–945
82. Blair A, Burg J, Foran J, et al. Guidelines for application of meta-analysis in environmental epidemiology. ISLI Risk Science Institute. *Regul Toxicol Pharmacol*. 1995;22:189–197
83. Frush DP, Donnelly LF. Helical CT in children: technical considerations and body applications. *Radiology*. 1998;209:37–48
84. Coren ME, Ng V, Rubens M, Rosenthal M, Bush A. The value of ultrafast computed tomography in the investigation of pediatric chest disease. *Pediatr Pulmonol*. 1998;26:389–395
85. Brenner DJ, Elliston CD, Hall EJ, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol*. 2001;176:289–296
86. Shrimpton PC, Edyvean S. CT scanner dosimetry. *Br J Radiol*. 1998;71: 1–3
87. National Research Council, Committee on the Biological Effects of Ionizing Radiations. *Health Effects of Exposure to Low Levels of Ionizing Radiation*. Washington, DC: National Academy Press; 1990
88. International Commission on Radiological Protection. *1990 Recommendations of the International Commission on Radiological Protection*. Oxford, England: Pergamon Press; 1991 (ICRP Publication No. 60)
89. Shrimpton PC, Jones DG, Hillier MC, Wall BF, Le Heron JC, Faulkner K. *Survey of CT Practice in the UK. Part 2. Dosimetric Aspects.* Chilton, England: National Radiological Protection Board; 1991 (NRPB Report No. 249)
90. National Radiological Protection Board. *Survey of CT Practice in the United Kingdom. Part 1. Aspects of Examination Frequency and Quality Assurance.* Chilton, England: National Radiological Protection Board; 1991
91. Huda W, Scalzetti EM, Roskopf M. Effective doses to patients undergoing thoracic computed tomography examination. *Med Phys*. 2000;27: 838–844
92. Bahador B. *Trends in Diagnostic Imaging to 2000.* Camborne, England: Financial Times Pharmaceuticals and Healthcare Publishing; 1996
93. Ambrosino MM, Genieser NB, Roche KJ, Kaul A, Lawrence RM. Feasibility of high-resolution, low-dose chest CT in evaluating the pediatric chest. *Pediatr Radiol*. 1994;24:6–10
94. Zeman RK, Baron RL, Jeffrey RB Jr, Klein J, Siegel MJ, Silverman PM. Helical body CT: evolution of scanning protocols. *AJR Am J Roentgenol*. 1998;170:1427–1438
95. Chan CY, Wong YC, Chau LF, Yu SK, Lau PC. Radiation dose reduction in paediatric cranial CT. *Pediatr Radiol*. 1999;29:770–775
96. Arrundale J, Bain M, Botting B, et al. *Handbook and Guide to the Investigation of Clusters of Diseases.* London, England: Leukaemia Research Fund; 1997
97. Linet MS. *The Leukemias: Epidemiologic Aspects.* New York, NY: Oxford University Press; 1985
98. Little J. *Epidemiology of Childhood Cancer*. Lyon, France: International Agency for Research on Cancer; 1999 (IARC Scientific Publication No. 149)
99. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet*. 1988;2:1323–1327
100. Kinlen LJ, Clarke K, Balkwill A. Paternal preconceptional radiation exposure in the nuclear industry and leukaemia and non-Hodgkin's lymphoma in young people in Scotland. *BMJ*. 1993;306:1153–1158
101. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. *BMJ*. 1995;310:763–768
102. Stiller CA, Boyle PJ. Effect of population mixing and socioeconomic status in England and Wales, 1979–85, on lymphoblastic leukaemia in children. *BMJ*. 1996;313:1297–1300
103. Alexander FE, Leon DA, Cartwright RA. Isolation, car ownership, and small area variation in incidence of acute lymphoblastic leukaemia in children. *Paediatr Perinat Epidemiol*. 1996;10:411–417
104. Till M, Rapson N, Smith PG. Family studies in acute leukaemia in childhood: a possible association with autoimmune disease. *Br J Cancer*. 1979;40:62–71
105. van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, van Zanen GE. Are maternal fertility problems related to childhood leukaemia? *Int J Epidemiol*. 1985;14:555–559
106. Roman E, Ansell P, Bull D. Leukaemia and non-Hodgkin's lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? *Br J Cancer*. 1997;76:406–415
107. Salonen T, Saxen L. Risk indicators in childhood malignancies. *Int J Cancer*. 1975;15:941–946
108. Comstock GW, Martinez I, Livesay VT. Efficacy of BCG vaccination in prevention of cancer. *J Natl Cancer Inst*. 1975;54:835–859
109. Snider DE, Comstock GW, Martinez I, Caras GJ. Efficacy of BCG

vaccination in prevention of cancer: an update. *J Natl Cancer Inst*. 1978;60:785–758
110. Hoover RN. Bacillus Calmette-Guerin vaccination and cancer prevention: a critical review of the human experience. *Cancer Res*. 1976;36:652–654
111. Groves FD, Gridley G, Wacholder S, et al. Infant vaccinations and risk of childhood acute lymphoblastic leukaemia in the USA. *Br J Cancer*. 1999;81:175–178
112. Neglia JP, Linet MS, Shu XO, et al. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer*. 2000;82:234–240
113. Draper GJ, Stiller CA, Cartwright RA, Craft AW, Vincent TJ. Cancer in Cumbria and in the vicinity of the Sellafield nuclear installation, 1963–90. *BMJ*. 1993;306:89–94
114. Alexander FE. Clusters and clustering of childhood cancer: a review. *Eur J Epidemiol*. 1999;15:847–852
115. Blumenstock J, Fagliano J, Bresnitz E. The Dover township childhood cancer investigation. *N J Med*. 2000;97:25–30
116. Knox J. The detection of space-time interaction. *Appl Stat*. 1964;13: 25–29
117. Chen R, Mantel N, Klingberg MA. A study of three techniques of time-space clustering in Hodgkin's disease. *Stat Med*. 1984;3:173–184
118. Boyle P, Alexander RE, eds. *Statistical Methods in Cancer Research. Vol IV: Methods of Analysis of Disease Clustering*. Lyon, France: International Agency for Research on Cancer; 1996
119. Reynolds P, Smith DF, Satariano E, Nelson DO, Goldman LR, Neutra RR. The four county study of childhood cancer: clusters in context. *Stat Med*. 1996;15:683–697
120. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. *International Incidence of Childhood Cancer*. Lyon, France: International Agency for Research on Cancer; 1988 (IARC Scientific Pub No. 87)
121. Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer Surv*. 1994; 19–20:493–517
122. Blair V, Birch JM. Patterns and temporal trends in the incidence of malignant disease in children: I. Leukaemia and lymphoma. *Eur J Cancer*. 1994;30A:1490–1498
123. Blair V, Birch JM. Patterns and temporal trends in the incidence of malignant disease in children: II. Solid tumours of childhood. *Eur J Cancer*. 1994;30A:1498–1511
124. Parkin DM, Kramarova E, Draper GJ, et al, eds. *International Incidence of Childhood Cancer, Volume II*. Lyon, France: International Agency for Research on Cancer; 1998 (IARC Scientific Publication No. 144)
125. Smith MA, Simon R, Strickler HD, McQuillan G, Ries LA, Linet JS. Evidence that childhood acute lymphoblastic leukemia is associated with an infectious agent linked to hygiene conditions. *Cancer Causes Control*. 1998;9:285–298
126. Birch JM. Genes and cancer. *Arch Dis Child*. 1999;80:1–3
127. Bunin GR, Kuitjten RR, Buckley JD, Rorke LB, Meadows AT. Relation between maternal diet and subsequently primitive neuroectodermal brain tumors in young children. *N Engl J Med*. 1993;329:536–541
128. Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group. *Cancer Causes Control*. 1996;7:581–590
129. Preston-Martin S, Gurney JG, Pogoda JM, Holly EA, Mueller BA. Brain tumor risk in children in relation to use of electric blankets and water bed heaters. Results from the United States West Coast Childhood Brain Tumor Study. *Am J Epidemiol*. 1996;143:1116–1122
130. 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;143:105–119
131. Preston-Martin S, Pogoda JM, Mueller BA, Holley EA, Lijinsky W, Davis RL. Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors. *Cancer Epidemiol Biomarkers Prev*. 1996;5:599–605
132. Gurney JG, Preston-Martin S, McDaniel AM, Mueller BA, Holly EA. Head injury as a risk factor for brain tumors in children: results from a multicenter case-control study. *Epidemiology*. 1996;7:485–489
133. 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;5:127–133
134. Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Children's Cancer Group study. *J Natl Cancer Inst*. 1996; 88:24–31
135. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: the Children's Cancer Group epidemiology program. *Environ Health Perspect*. 1995; 103(suppl 6):111–116
136. Gurney JG, Mueller BA, Preston-Martin S, et al. A study of pediatric brain tumors and their association with epilepsy and anticonvulsant use. *Neuroepidemiology*. 1997;16:248–255
137. Gurney JG, Pogoda JM, Holly EA, Hecht SS, Preston-Martin S. Aspartame consumption in relation to childhood brain tumor risk: results from a case-control study. *J Natl Cancer Inst*. 1997;89:1072–1074
138. Kleinerman RA, Linet MS, Hatch EE, et al. Magnetic field exposure assessment in a case-control study of childhood leukemia. *Epidemiology*. 1997;8:575–583
139. Bunin GR. Maternal diet during pregnancy and risk of brain tumors in children. *Int J Cancer Suppl*. 1998;11:23–25
140. McKean-Cowdin R, Preston-Martin S, Pogoda JM, Holly EA, Mueller BA, Davis RL. Parental occupation and childhood brain tumors: astroglial and primitive neuroectodermal tumors. *J Occup Environ Med*. 1998;40:332–340
141. Holly EA, Bracci PM, Mueller BA, Preston-Martin S. Farm and animal exposures and pediatric brain tumors: results from the United States West Coast Childhood Brain Tumor Study. *Cancer Epidemiol Biomarkers Prev*. 1998;7:797–802
142. Hatch EE, Linet MS, Kleinerman RA, et al. Association between childhood acute lymphoblastic leukemia and use of electrical appliances during pregnancy and childhood. *Epidemiology*. 1998;9:234–245
143. Lubin JH, Linet MS, Boice JD Jr, et al. Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure. *J Natl Cancer Inst*. 1998;90:294–300
144. Buckley JD, Pendergrass TW, Buckley CM, et al. Epidemiology of osteosarcoma and Ewing's sarcoma in childhood: a study of 305 cases by the Children's Cancer Group. *Cancer*. 1998;83:1440–1448
145. 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;85:1380–1388
146. Steinbuch M, Weinberg CR, Buckley JD, Robison LL, Sandler DP. Indoor residential radon exposure and risk of childhood acute myeloid leukaemia. *Br J Cancer*. 1999;81:900–906
147. Olshan AF, De Roos AJ, Teschke K, et al. Neuroblastoma and parental occupation. *Cancer Causes Control*. 1999;10:539–549
148. Olshan AR, Smith J, Cook MN, et al. Hormone and fertility drug use and the risk of neuroblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. *Am J Epidemiol*. 1999;150: 930–938
149. Shu XO, Stewart P, Wen WQ, et al. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. *Cancer Epidemiol Biomarkers Prev*. 1999;8:783–791
150. Kleinerman RA, Kaune WT, Hatch EE, et al. Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia? *Am J Epidemiol*. 2000;151:512–515
151. Wen WQ, Shu XO, Linet MS, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control*. 2000;11:303–307
152. Wen WQ, Shu XO, Steinbuch M, et al. Paternal military service and risk for childhood leukemia in offspring. *Am J Epidemiol*. 2000;151: 231–240
153. Yang O, Olshan AF, Bondy ML, et al. Parental smoking and alcohol consumption and risk of neuroblastoma. *Cancer Epidemiol Biomarkers Prev*. 2000;9:967–972
154. Daniels JL, Olshan AF, Teschke K, Hertz-Picciotto I, Savitz DA, Blatt J. Comparison of assessment methods for pesticide exposure in a case-control interview study. *Am J Epidemiol*. 2001;153:1227–1232
155. Freedman DM, Stewart P, Kleinerman RA, et al. Household solvent exposures and childhood acute lymphoblastic leukemia. *Am J Public Health*. 2001;91:564–567
156. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology*. 1999;10:481–487
157. Infante-Rivard C, Mathonnet G, Sinnett D. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. *Environ Health Perspect*. 2000;108:495–498
158. Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). *Cancer Causes Control*. 2000;11:547–553
159. Infante-Rivard C, Fortier I, Olson E. Markers of infection, breastfeeding and childhood acute lymphoblastic leukaemia. *Br J Cancer*. 2000;83:1559–1564
160. Infante-Rivard C, Olson E, Jacques L, Ayotte P. Drinking water contaminants and childhood leukemia. *Epidemiology*. 2001;12:13–19

161. Green LM, Miller AB, Villeneuve PJ, et al. A case-control study of childhood leukemia in southern Ontario, Canada, and exposure to magnetic fields in residences. *Int J Cancer*. 1999;82:161–170
162. Armstrong BG, Deadman J, McBride ML. The determinants of Canadian children's personal exposures to magnetic fields. *Bioelectromagnetics*. 2001;22:161–169
163. Kinlen LJ. Can paternal preconceptional radiation account for the increase of leukaemia and non-Hodgkin's lymphoma in Seascale? *BMJ*. 1993;306:1718–1721
164. Bithell JF, Dutton SJ, Draper GJ, Neary NM. Distribution of childhood leukaemias and non-Hodgkin's lymphomas near nuclear installations in England and Wales. *BMJ*. 1994;309:501–505
165. Doll R, Evans HM, Darby SC. Paternal exposure not to blame. *Nature*. 1994;367:678–680
166. Draper GJ, Little MP, Sorahan T, et al. Cancer in the offspring of radiation workers: a record linkage study. *BMJ*. 1997;315:1181–1188
167. Sorahan T, Prior P, Lancashire RJ, et al. Childhood cancer and parental use of tobacco: deaths from 1971 to 1976. *Br J Cancer*. 1997;76:1525–1531
168. McKinney PA, Juszczak E, Findlay E, Smith K. Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. *BMJ*. 1998;316:173–177
169. Westerbeek RM, Blair V, Eden OB, et al. Seasonal variations in the onset of childhood leukaemia and lymphoma. *Br J Cancer*. 1998;78:119–124
170. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer*. 1998;77:825–829
171. Maconochie N, Doyle P, Roman E, Davies G, Smith PG, Beral V. Nuclear industry family study: methods and description of a United Kingdom study linking occupational information held by employers to reproduction and child heath. *Occup Environ Med*. 1999;56:798–808
172. Roman E, Doyle P, Maconochie N, Davies G, Smith PG, Beral V. Cancer in children of nuclear industry employees: report on children aged under 25 years from nuclear industry family study. *BMJ*. 1999;318:1443–1450
173. UK Childhood Cancer Study Investigators. Childhood cancer and residential proximity to power lines. *Br J Cancer*. 2000;83:1573–1580
174. Sorahan T, McKinney PA, Mann JR, et al. Childhood cancer and parental use of tobacco: findings from the inter-regional epidemiological study of childhood cancer (IRESCC). *Br J Cancer*. 2001;84:141–146
175. Michaelis J, Schuz J, Meinert R, et al. Childhood leukemia and electromagnetic fields: results of a population-based case-control study in Germany. *Cancer Causes Control*. 1997;8:167–174
176. Michaelis J, Schuz J, Meinert R, et al. Combined risk estimates for two German population-based case-control studies on residential magnetic fields and childhood acute leukemia. *Epidemiology*. 1998;9:92–94
177. Kaattsch P, Kaletsch U, Meinert R, et al. German case control study on childhood leukaemia—basic considerations, methodology and summary of the results. *Klin Padiatr*. 1998;210:185–191
178. Schuz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol*. 1999;28:631–639
179. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. *Br J Cancer*. 1999;80:585–590
180. Meinert R, Kaletsch U, Kaatsch P, Schuz J, Michaelis J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. *Cancer Epidemiol Biomarkers Prev*. 1999;8:793–799
181. Kaletsch U, Kaatsch P, Meinert R, Schuz J, Czarwinski R, Michaelis J. Childhood cancer and residential radon exposure—results of a population-based case-control study in Lower Saxony (Germany). *Radiat Environ Biophys*. 1999;38:211–215
182. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Risk of childhood leukemia and parental self-reported occupational exposure to chemicals, dusts, and fumes: results from pooled analyses of German population-based case-control studies. *Cancer Epidemiol Biomarkers Prev*. 2000;9:835–838
183. 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;91:728–735
184. Verkasalo PK, Pukkala E, Hongisto MY, et al. Risk of cancer in Finnish children living close to power lines. *BMJ*. 1993;307:895–899
185. Linet MS, Gridley G, Cnattingius S, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control*. 1996;7:437–448
186. Tynes T, Haldorsen T. Electromagnetic fields and cancer in children residing near Norwegian high-voltage power lines. *Am J Epidemiol*. 1997;145:219–226
187. Naumburg E, Bellocco R, Cnattingius S, Hall P, Ekbom A. Prenatal ultrasound examinations and risk of childhood leukaemia: case-control study. *BMJ*. 2000;320:282–283
188. Shu XO, Gao YT, Brinton LA, et al. A population-based case-control study of childhood leukemia in Shanghai. *Cancer*. 1988;62:635–644
189. Shu XO, Jin F, Linet MS, et al. Diagnostic x-ray and ultrasound exposure and risk of childhood cancer. *Br J Cancer*. 1994;70:531–536
190. Shu XO, Clemens J, Zheng W, Ying D-M, Ji BT, Jin F. Infant breastfeeding and the risk of childhood lymphoma and leukemia. *Int J Epidemiol*. 1995;24:27–32
191. Ji BT, Shu X-O, Linet MS, et al. Paternal cigarette smoking and the risk of childhood cancer among offspring of non-smoking mothers. *J Natl Cancer Inst*. 1997;89:238–244
192. Preston-Martin S, Pogoda JM, Mueller BA, et al. Prenatal vitamin supplementation and risk of childhood brain tumors. *Int J Cancer Suppl*. 1998;11:17–22
193. Preston-Martin S, Pogoda JM, Mueller BA, et al. Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk. *Childs Nerv Syst*. 1998;14:551–557
194. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environ Health Perspect*. 1998;106(suppl 3):803–908
195. McCredie M, Little J, Cotton S, et al. SEARCH international case-control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. *Paediatr Perinat Epidemiol*. 1999;13:325–341
196. Kheifets LI, Sussman SS, Preston-Martin S. Childhood brain tumors and residential electromagnetic fields (EMF). *Rev Environ Contam Toxicol*. 1999;159:111–129
197. Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. *Environ Health Perspect*. 2001;109:193–196
198. Alexander FE, Patheal SL, Biondi A, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res*. 2001;61:2542–2546