

# Interpreting Epidemiologic Research: Lessons From Studies of Childhood Cancer

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

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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*<sup>1</sup> 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*<sup>2</sup> 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),<sup>3</sup> 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).<sup>4</sup> 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.<sup>5-7</sup> Instead of the anatomic site-based categories used for adult malignancies, a more appropriate classification system developed for pediatric neoplasms<sup>8</sup> was recently updated and designated as the International Classification of Childhood Cancer.<sup>9</sup>

This article includes 3 components. The first sec-

tion 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).

## 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.

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**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
<b>Known</b>				
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 Ionizing radiation Diagnostic, in utero Therapeutic, postnatal ALL and AML Down syndrome ALL and AML M7 Congenital disorders, ataxia telangiectasia, Fanconi syndrome, Bloom syndrome, neurofibromatosis		Monozygotic twins of young adults Affected siblings Epstein-Barr virus linked with some forms Infectious mononucleosis	Immunosuppressive therapy Congenital immunodeficiency syndromes (eg, ataxia, telangiectasia) AIDS
<b>Suggestive</b>	Maternal fetal loss Mother older than 35 years at pregnancy First born	Maternal alcohol use during pregnancy Parental occupational exposures - Benzene - Pesticides		
<b>Limited</b>	Paternal smoking before conception Parental occupational exposures Hydrocarbons Paints Motor vehicle exhaust 60-Hz magnetic fields >0.4 $\mu$ T Postnatal chloramphenicol use Clustering Decreased risk associated with breastfeeding	Maternal marijuana use during pregnancy Parental occupational exposures Pesticides Residential exposures Pesticides	Residential exposures Pesticides	

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.<sup>10-12</sup> Examples of populations for which complete lists are available include the provincial-wide health insurance listings in Canada<sup>13</sup>; population-based lists of patients assigned to a general practitioner in the United Kingdom<sup>14</sup>; and the hospitalization, cancer, or other national registries in the Nordic countries.<sup>15-17</sup> Population-based health care regis-

tries 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.<sup>18,19</sup> 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.<sup>18,20</sup>

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	Type	M:F	Age-adjusted incidence (per million)	M:F	Age-adjusted incidence (per million)
	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				
Suggestive	Turcot syndrome				
	Li-Fraumeni syndrome				
	Maternal diet during pregnancy				
Limited	Cured meats				
	Sibling or parent with brain tumor increases risk				
	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 <i>N</i> -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,<sup>21,22</sup> 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<sup>23</sup> 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	
	Type	M:F	Type	M:F	Type	M:F	Type	M:F
Known								
Gender	All bone Osteosarcoma Ewing sarcoma Chondrosarcoma	1.2 1.2 1.3 1.5	All soft tissue	1.2	All renal	0.9	All hepatic Hepatoblastoma Hepatocellular carcinoma	1.2 1.2 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								
Anatomic site	W:B = 1.3 Osteosarcoma, long bones; Ewing sarcoma, central axis		W:B = 0.9		W:B = 0.9 7% of Wilms tumors are bilateral		W:B = 1.2	
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								
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		Father employed as welder or mechanic increases risk 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	
	Type	M:F	Age-adjusted incidence per million	Type	Type	M:F	Age-adjusted incidence per million	Type	M:F	Age-adjusted incidence per million
Known Gender	All germ cell	1.1	10.1	All carcinomas	0.5	14.1	All retinoblastoma	1.0	2.8	
	Gonadal	1.5	6.1	Thyroid carcinoma	0.2	5.0				
	Testicular		8.1	Malignant melanoma	0.6	4.5				
Age peak										
Race		15-19 y							Infancy	
Other	Cryptorchidism		W:B = 1.5	Thyroid carcinoma			Parent with a history of bilateral retinoblastoma		W:B = 0.9	
Suggestive				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						
Limited				Number of nevi and dysplastic nevi			13q deletion syndrome			
				Thyroid carcinoma						
				Hormonal factors						
				Benign thyroid diseases						
				High maternal hormone levels during pregnancy						
				Family history of germ cell tumor						
				Hernia						
				Preterm birth						
				Viral infections						
				High birth weight						
				Prenatal radiographic exposure						
				Paternal occupation including health care, aircraft industry (paternal), and other work involving exposure to x-rays (paternal) or solvents (maternal)						
				Constitutional chromosome abnormalities (Klinefelter syndrome)						

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 non-ionizing 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.<sup>24</sup> 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.<sup>25–27</sup> 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.<sup>24</sup>

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.<sup>28</sup> 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).<sup>29–38</sup>

### 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.<sup>39</sup> 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.<sup>39,40</sup> 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<sup>41</sup>; acute leukemia

among children with Down syndrome<sup>42</sup>), 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.<sup>29–32</sup> 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<sup>43–45</sup> and studies of children and adults who receive therapeutic radiation.<sup>46</sup> Although high doses of ionizing radiation from environmental and therapeutic sources have been associated with several types of childhood (as well as adult) cancers,<sup>33,47</sup> 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,<sup>33–35</sup> 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,<sup>35–38</sup> and replacement of pelvimetry and other prenatal radiographic

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

The relationship of prenatal diagnostic irradiation with increased risk of childhood leukemia seems to meet most of the criteria for causality, yet some<sup>52</sup> 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<sup>53–55</sup> or twin studies<sup>56,57</sup> (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),<sup>58</sup> 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<sup>59</sup> and higher risks among beagles irradiated later in fetal development than in those irradiated earlier,<sup>60,61</sup> 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<sup>35</sup>), 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).<sup>35,58</sup>

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,<sup>15,62–64</sup> data from rigorous large epidemiologic investigations using more sophisticated exposure assessment methods<sup>13,65,66</sup> in the United States,<sup>65</sup> Canada,<sup>13</sup> and the United Kingdom<sup>66</sup> 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 ( $\mu\text{T}$ ).<sup>67,68</sup> 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  $>0.3$   $\mu\text{T}$ <sup>67</sup> and 2.0 for those with exposures  $>0.4$   $\mu\text{T}$ <sup>68</sup>

versus children whose estimated exposures were 0–0.1  $\mu\text{T}$ ; 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,<sup>69–73</sup> and nonionizing radiation from power lines has not ever been shown to cause carcinogenic changes to DNA or other parts of living cells<sup>69</sup> (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.<sup>23</sup>

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.<sup>74</sup> 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.<sup>75–77</sup> The dramatic increase in use of meta-analysis is eliciting increasing concern among some epidemiologists.<sup>78–81</sup> 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.<sup>81</sup> 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.<sup>82</sup>

### 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,<sup>83</sup> the number of requests for CT scans in children increased 63% between 1991 and 1994,<sup>84</sup> 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<sup>85</sup>). 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.<sup>86</sup> Brenner et al<sup>85</sup> calculated age-dependent lifetime cancer mortality risks per unit dose using existing databases<sup>87-91</sup> 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<sup>85,92</sup> 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<sup>85</sup> but also underscored the need for technical improvements to decrease the radiation dose while maintaining the same high-quality visualization as with current doses.<sup>93-95</sup>

### 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.<sup>96</sup> 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<sup>97</sup> and Little<sup>98</sup>) 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.<sup>99-103</sup> Maternal infection during pregnancy has long been suspected to be related to childhood ALL,<sup>104-106</sup> 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.<sup>107–111</sup> 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.<sup>112</sup>

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<sup>98</sup>]).

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<sup>113–115</sup> and statistical approaches<sup>116–119</sup>; the latter are also summarized on the Centers for Disease Control and Prevention web site ([www.cdc.gov/mmwr/preview/mmwrhtml/00001798](http://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](http://www.cdc.gov/mmwr/preview/mmwrhtml/00001797)) and a recent handbook published by the Leukemia Research Fund.<sup>96</sup>

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 socio-demographic 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<sup>5,7</sup> and a National Cancer Institute monograph on childhood cancer incidence, mortality, and survival patterns<sup>4</sup> 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.<sup>120–123</sup> 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<sup>120</sup> and 1980–1989.<sup>124</sup>

#### 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.<sup>4</sup> 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).<sup>125</sup> 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 child-

hood 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.<sup>126</sup> 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,<sup>20,26,65,111,112,127–155</sup> Canadian,<sup>13,156–162</sup> British,<sup>14,66,100,101,113,163–174</sup> German,<sup>126,175–183</sup> Nordic,<sup>15–17,74,184–187</sup> Chinese,<sup>188–191</sup> and multicenter<sup>68,192–198</sup> 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.

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*Pediatrics* 2003;112;218

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