

Methodologic Approaches to Studying Environmental Factors in Childhood Cancer

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Little is known about environmental causes of childhood cancer. This is probably due to the relative rarity of cancer in children. In the United States, cancer incidence in adults is over 20 times greater than cancer incidence in children. The situation is compounded by the fact that two groups of cancers, leukemias and brain and spinal tumors, account for half of all childhood cancers. The rarity of childhood cancer renders the conduct of most cohort studies infeasible. The majority of studies assessing potential environmental risk factors for childhood cancers have been case-control studies, which are highly efficient for studying rare diseases. Case-control studies of childhood cancers have been greatly facilitated by using cooperative clinical trial groups for case identification. The national studies that have emerged utilize random-digit telephone dialing and telephone interviewing as feasible and economic means of identifying and interviewing controls. Other approaches such as descriptive epidemiology, ecologic studies, and studies of cancer clusters have proven to be disappointing in elucidating environmental causes of childhood cancer. Descriptive and ecologic studies provide no information on specific exposures of study subjects; rather, they use population levels as surrogates for individual exposure. Studies of cancer clusters have also proven to be disappointing. Although there are numerous difficulties in conducting research on the causes of childhood cancer, these difficulties can be remedied by using carefully designed and conducted studies. It should be remembered that the epidemiologic approach is probably the most likely research venue for uncovering environmental causes of childhood cancer. — *Environ Health Perspect* 106(Suppl 3):881-886 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/881-886grufferman/abstract.html>

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Introduction

Relatively little is known about the causes of cancer in childhood. In the 1950s, interest was focused on *in utero* diagnostic radiation exposure and risk of childhood leukemia (1-3). Research interest next focused on the genetics of selected childhood cancers (4,5). The mechanism of transplacental carcinogenesis was demonstrated in the early 1970s (6). In reviewing

knowledge of the etiology of childhood cancer up until the 1980s, one is struck by the paucity of published etiologic studies relative to those of adult cancers. In large part, this is due to the relative rarity of cancer during childhood. Difficulty in the accrual of sufficiently large numbers of childhood cancer cases beyond leukemia (the type most frequent in childhood) has probably impeded research on the etiology of cancers in children. More recently, pediatric cooperative clinical trial groups have been identified and tapped as an important means for conducting etiologic research on cancers of childhood (7). This has mitigated greatly the primary problem of having sufficient numbers of subjects to study childhood cancers properly. However, there remain significant problems in conducting research on environmental (and other) causes of cancer in children. This paper will review several methodologic issues that arise in conducting research on environmental causes of childhood cancer.

The Rarity Issue

The overall annual incidence of cancer in U.S. children 0 to 14 years of age at diagnosis is 143.9 per million for white males and 126.9 per million for white females. The comparable incidence rate for black males and females is 107.2 and 107.9 per million, respectively (8). This is in contrast to 330.4 and 277.0 per 100,000 in white males and females, respectively, of all ages (9). The comparable figures for black males and females of all ages are 351.3 and 227.1 per 100,000, respectively. Thus, adult incidence of cancer (all ages) in the United States is over 20 times greater than the cancer incidence in children 0 to 14 years of age at diagnosis. The rarity issue becomes even more salient when one looks at the incidence of childhood cancers beyond acute leukemias and brain cancers. The U.S. annual incidence of all leukemia is 47.8 per million in white males and 29.5 per million in white females, and for brain and spinal tumors it is 26.4 and 23.3 in white male and female children, respectively (8). Thus, leukemias account for 51.6 and 49.5% of all cancers in 0- to 14-year-old white males and females, respectively. Once we go beyond these two cancer groups, other groups are more truly rare diseases. For example, the incidence of rhabdomyosarcoma (RMS) in children is 5.0 and 4.4 per million in white males and females, and that of osteosarcoma is 2.3 and 2.7 per million in white males and females, respectively (8). Accrual of subjects for studies of less common subsets of an already rare group of diseases becomes difficult even through the use of large cooperative treatment groups as sources of subjects. As will be discussed, the rarity issue has major impact on methodologic approaches to the study of childhood cancers.

Rarity: A Basic Problem in Childhood Cancer Research

The major difficulties encountered in attempting to do epidemiologic research on childhood cancer result from the relative rarity of individual childhood cancers. This becomes a particular problem if one wishes to study cancers other than acute leukemia and brain tumors in children. This factor has perhaps played the single most important role in limiting our information on the causes of childhood cancer.

The relative rarity of childhood cancers has led to the development of large multicenter cooperative clinical trial groups for

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Abbreviations used: DES, diethylstilbestrol; RMS, rhabdomyosarcoma.

the conduct of cancer treatment research in children. The two major U.S. groups are the Children's Cancer Group (Arcadia, CA) and the Pediatric Oncology Group (Chicago, IL). A large proportion of all U.S. children with cancer is treated with protocols from the two groups. This very practical approach to dealing with the rarity issue in childhood cancer research has proven invaluable for developing new information on cancer treatment.

A Further Problem

A further problem in conducting epidemiologic research on childhood cancers, and for many adult cancers as well, is that many environmental exposures are hard to measure and validate and their links with disease are often hard to detect. This has been a particular problem in case-control research, where information is collected on a wide variety of potential environmental exposures. The issue is further compounded by the reliance on cases' and controls' recall of environmental exposures. Usually there are few, if any, means for validating exposures and even fewer biomarkers of exposure available to provide better quantification of exposures.

Some Exceptional Environmental Causes of Cancer

Sometimes the astute clinical observation of the concordance of a rare form of cancer and an uncommon environmental exposure can lead to breakthroughs in knowledge of cancer causation. Little confirmation of such findings is needed when extremely strong associations are observed. An example of this is the striking causal association between vinyl chloride exposure and angiosarcoma of the liver. The initial report of this association was the result of astute occupational health workers observing three cases of this extremely rare cancer at manufacturing facilities producing vinyl chloride (10). The detection of such linkages is enhanced when they are noted for extremely rare cancers associated with extremely rare exposures. For example, the rarity of both disease and causal exposure led to a breakthrough finding of an association between diethylstilbestrol (DES) and clear cell vaginal adenocarcinoma in young women (6). An astute obstetrician/gynecologist observed an unusual occurrence of these rare vaginal cancers in young women in his practice (6). A case-control study was conducted to assess potential exposures that might be associated with risk of these rare cancers. This classic study found a striking

association between the use of DES during pregnancy and subsequent development of vaginal adenocarcinoma in the young women exposed to DES *in utero* (6). This observation provided considerable impetus to awareness of the mechanism of transplacental carcinogenesis. Unfortunately, observations such as these, which link extremely rare exposures with extremely rare malignancies, are themselves rare. For the vast majority of cancers, more difficult traditional epidemiologic methods must be used to uncover new potential risk factors.

Descriptive Epidemiology

A fundamental approach frequently used to study the epidemiology of a disease is assessment of the way a disease occurs in a population. This is often termed descriptive epidemiology (11). One looks for unusual patterns of disease occurrence in terms of time, place, and person characteristics. For example, is there seasonal variation in the occurrence of a disease? Is there a higher incidence of a disease in some places than in others? Are women affected more than men? The answers to such questions can provide ideas (hypotheses) regarding the underlying cause of the disease.

An example of the use of descriptive epidemiology for developing causal hypotheses would be the observation of an unusual occurrence of cancer cases in proximity to a hazardous waste dump site. This observation, which might well be due to chance, can lead to further epidemiologic study of associations between substances in the dump site and risk of the cancers observed. One of the difficulties with descriptive epidemiology is that it usually does not provide us with information regarding the specific exposures of the cases.

The Texas Sharpshooter Effect

One of the fallacies in certain descriptive epidemiologic observations of clusters is termed the Texas sharpshooter effect (12). This problem can best be illustrated by the anecdote about the Texas sharpshooter. A traveler passing through a small town in Texas noted a remarkable display of sharpshooting. On almost every barn he passed there was a target with a single bullet hole that uncannily passed through the center of the bull's-eye. He was so intrigued by this that he stopped at a nearby gas station to ask about the sharpshooter. With a chuckle, the attendant told him that the shooting was the work of Old Joe. Old Joe would first shoot at the side of a barn and then paint targets centered over his bullet holes

so that each shot appeared to pass through the center of the target.

Clusters and the Sharpshooter Effect

In a random distribution of cases of cancer over a geographic area, some cases will appear to occur very close together just on the basis of random variation. The occurrence of a group of cases of a disease close together in time and place at the time of their diagnosis is called a cluster. If such a cluster is observed in relation to a suspected causal environmental factor, it often becomes a cause of concern.

The usual way the cluster is investigated is that the time frame selected for study is the period between the diagnosis of the first case and the last. The geographic frame for study is often the distance between the two cases living farthest apart. When the incidence of the disease in these time and geographic frames is computed, it is often alarmingly high. This approach is similar to the Texas sharpshooter. In a cluster investigation, the time and space intervals become the target that is painted around the observed cluster. It is this post hoc definition of the study population and time frame that leads to spurious and often alarming reports of clusters greatly in excess of normal expectation.

However, not all studies of childhood cancer clustering are done in this post hoc fashion. Excellent statistical methods have been developed for assessing whether cases occur more closely together than would be expected by chance. These approaches usually are based on analysis of all cases of a disease occurring in large defined populations selected without prior observation of clustering (13,14).

Ecologic studies

Another type of descriptive epidemiologic study is the so-called ecologic study. Ecologic studies examine data on a population basis without specific assessment of individual exposures. For example, childhood cancer incidence could be assessed in counties in which there are chemical dump sites and comparison made with the incidence in counties without dump sites. The difficulty with this approach is that it is not known whether cancer cases were actually exposed to the dump site and/or what their levels of exposure might have been. There is also a likelihood that children living near dump sites will differ in socioeconomic status from children living in areas without dump sites. Although ecologic studies may

have some value in developing new hypotheses, they provide little in the way of the ability to test causal hypotheses.

The Cohort Study

In a cohort study, subjects are defined on the basis of their exposure status (15). Usually a group of individuals who have been exposed to some environmental factor are followed over time to see whether or not they develop a disease (or diseases). A comparable group of unexposed individuals is followed similarly over time to see whether they develop the disease(s) of interest. This allows for comparison between the rates of disease occurrence in exposed and nonexposed persons. Often, general population rates of disease occurrence are used for comparison rather than control groups. Cohort studies involving childhood cancers are infrequently done. The childhood cancer cohort studies that have been done usually involve well-defined large groups of children that have had an uncommon exposure such as to ionizing radiation.

Advantages and Limitations of Cohort Studies

A major advantage of the cohort study approach is that it works best for evaluating the health effects of rare exposures. Selecting and following a group of people who have had a very uncommon exposure is more likely to yield meaningful results than would a case-control study. It is most unlikely that in a case-control study of usual size, many subjects will have had a history of a rare exposure. Another advantage of cohort studies is that they allow for evaluating a variety of outcomes in relationship to a particular exposure or a category of exposures. Thus, in a cohort study of an occupational exposure, many outcomes can be evaluated in relation to the exposures being studied. This is in contrast to the case-control study approach in which only a single disease is studied, but multiple potential environmental exposures can be assessed.

A major limitation of cohort studies is that often it is difficult to determine the exposure status of people. It is not by accident that most cohort studies are of occupationally exposed people, as they can be identified relatively easily and the quality and quantity of their environmental exposures can often be determined. Another problem is posed by the inefficiency of cohort studies for assessing rare diseases or outcomes. To find enough cases of the rare

disease, even if the risk is high following the exposure, extremely large cohorts of exposed individuals would have to be followed.

Perhaps the greatest problem posed by cohort studies is that they allow for the assessment of associations between the studied exposures and many different diseases. By looking at a large number of potentially associated diseases, some associations will be observed purely on the basis of chance. Thus, many associations reported in the literature might be due to chance rather than to a valid association, let alone a causal association.

The Case-Control Study

Case-control studies are the type of epidemiologic study most frequently used by epidemiologists to assess potential causes of childhood cancer (16). In the case-control study, subjects with a disease (or health condition) are the cases. Comparisons are then made with a group of subjects without the disease—the controls. Generally, cases and controls are matched on age, gender, and race. In studies of rare diseases such as childhood cancers, case-control studies are efficient, as subjects are selected because they have the disease of interest. In contrast to this, in a cohort study, very large numbers of exposed individuals would have to be studied to detect an elevated risk of an extremely rare cancer.

Cases and controls are usually interviewed and data are collected on a variety of exposures they might have had prior to the onset of the cases' disease. Thus, case-control studies are retrospective. Case-control studies allow for study of many potential risk factors for disease but usually permit the study of only one disease at a time.

Advantages and Limitations of Case-Control Studies

Case-control studies are most advantageous for the study of uncommon diseases such as childhood cancers. Generally, case-control studies are relatively inexpensive because lengthy follow-up of subjects, often the case in cohort studies, is not necessary. However, most modern case-control studies of childhood cancers tend to be expensive and time-consuming because of difficulties in collecting sufficient numbers of cases for study and then in identifying sufficient numbers of matched controls. Also, data collection usually involves personal interviews of subjects or surrogates, which adds to the expense of such studies.

A key advantage of case-control studies is that they allow for the evaluation of

many possible causes of a disease. By studying many potential causes, analyses can search for interactions between environmental causes and also allow for evaluation of potential confounding variables. Confounding variables are variables (exposures) that are associated both with the disease and with another exposure observed to be associated with the disease. The other exposure may appear to be associated with the disease when it is really the joint association with the confounder that is the underlying risk factor for the disease. Case-control studies have proven over the years to be valuable tools for the generation and testing of hypotheses regarding the causes of cancer.

However, case-control studies are fraught with difficulties, as are most epidemiologic study designs. For reasons mentioned previously, case-control studies are not efficient for evaluating the role of uncommon exposures in the etiology of a disease. Additionally, cases and controls have different levels of motivation for participating in the study and may have differential reporting or recall of exposure histories. For example, the cancer patient might be more apt to recall remote relatives that have had cancer than would a healthy community control. Part of this problem also results from the fact that when a person develops a cancer, relatives often remind that individual of other family members who have had the same or similar cancers. This is an example of selective recall. Another problem relates to the fact that in many instances, controls for case-control studies are biased subsets of the population and thus not truly comparable to cases. Increasingly, in case-control studies of childhood cancer, random-digit telephone dialing is used to select controls from the same telephone area as the cases. Thus, these controls represent comparable individuals living in the same communities. However, if the telephone calls are only made during the daytime, the likelihood of being reached for inclusion in the study could be affected by such factors as unemployment of family members, family size, and whether or not a mother stays home to provide care for her children. As a result, in most case-control studies of childhood cancers, random-digit dialing is done on evenings and weekends to avoid such potential sources of bias.

The Nested Case-Control Study

A hybrid of case-control and cohort studies, the nested case-control study, has been

developed (15). In this study approach, a cohort study is used as a venue for conducting a subsequent case-control study. Cases who have developed a particular disease are identified within the cohort. Comparable cohort members without the disease are selected as controls for these cases. Cases and controls are compared with regard to prior exposure history, laboratory data, or other previously collected information. There are many efficiencies afforded by this design. First, information on potentially causal exposures are usually obtained well in advance of the development of the disease of interest. Thus, such information is less subject to the imperfections of remote memory and biased recall of information. Second, when laboratory risk factors (or markers) are assessed, they need only be studied in cases and controls rather than in the entire cohort, thereby reducing costs considerably, particularly when the laboratory studies are done on previously collected biologic specimens.

Early Experience Using a Case-Control Approach

In response to observations in 1976 that there appeared to be an epidemic of childhood RMS in North Carolina, a case-control study was conducted to search for underlying causes (17). Because there was no state cancer registry at the time, cases were identified through North Carolina hospitals. Thirty-three RMS cases were collected over a 10-year period. Controls were identified via state birth certificates because it was felt that hospital controls might be a biased subset of North Carolina children. This study attempted to uncover some possible environmental risk factors (causes) for RMS. Because few hypotheses existed regarding the causes of this rare malignancy, information on a wide variety of potential causes was collected. We asked about smoking as well as several other exposures that also have adverse health effects. The most important finding emerging from this study was a strong association between fathers' cigarette smoking and RMS in their children. There was no association between mothers' smoking and RMS in their children. A biologically based hypothesis was developed to explain the finding and there seemed to be an important need to confirm or refute it (18).

Because RMS is such a rare disease, we searched for ways to identify larger numbers of cases. We contacted the Intergroup Rhabdomyosarcoma Study (Omaha, NE), a cooperative clinical trials group, and they

were extremely interested in doing a second case-control study. Although we finally had access to large numbers of cases, we could not come up with an economical and feasible means of identifying controls. Our first attempt was to have case parents select control families for us. This fared poorly in peer review because it was felt to be likely to yield a biased (nonrandom) group of controls. Our problem was finally solved by the use of random-digit telephone dialing to obtain controls. This technique uses a random number based on the case's telephone number. The random number is then called to see if a comparable child resides there and if the family is willing to participate.

We were then able to conduct a second, very large case-control study of over 300 RMS cases and a matched number of controls. It is likely that over 50% of all U.S. RMS cases were in our study. We found no association between fathers' (or mothers') cigarette smoking and RMS in their children. However, when we asked about smoking, we asked about several other exposures that also might have adverse health effects. These dummy variables were used to camouflage the questions about cigarette smoking. Much to our surprise, we found that parents' use of recreational drugs (marijuana and cocaine) was strongly associated with RMS risk in their children. Thus, one of our dummy variables was associated with risk of RMS (19).

What Can Be Learned from This Experience?

The most important lesson emerging from this experience was that cooperative clinical trial groups are excellent venues for the conduct of case-control studies of childhood cancer, particularly for the extremely rare cancers of childhood (7). It also demonstrated that techniques for control selection such as random-digit dialing render the conduct of national case-control studies feasible. The reason for the conduct of studies that are national in scope and use subjects from cooperative clinical trial groups is that it allows for the accession of sufficiently large numbers of subjects with extremely rare cancers to allow for proper statistical analyses. It also yields a relatively representative group of cases.

This experience also illustrates that case-control studies can assess many potential causes of a disease and some of the suspected risk factors will prove to be associated with the disease merely on the basis of chance—the Achilles heel of

case-control research. Although there has been much criticism of case-control studies regarding the assessment of so many potential risk factors that they often generate false leads, the problem lies not in the methodologic approach but in how the analyses are done and how the data are interpreted and promulgated to the public. Simply stated, results from case-control studies must be confirmed by other case-control studies in other populations before they can be accepted. Case-control studies are excellent tools for developing new etiologic hypotheses. They are also excellent tools for generating chance associations that may then result in misleading hypotheses. Investigators conducting case-control studies must exert prudence in their analyses and interpretation of their data. Good scientific investigation requires a healthy degree of skepticism for one's own as well as others' new scientific findings. Thus, investigators should not rush out and hold press conferences when they find a new and sensational association that may or may not be due to chance and has yet to be confirmed. The downside of this is that the process of doing epidemiologic research on rare cancers via case-control studies is a slow one requiring testing and retesting of hypotheses. Given the rarity of most childhood cancers, the accrual of sufficient numbers of subjects for study often takes years. Thus, the entire process from the observation of a new association to its confirmation may be a matter of a decade or more. Unfortunately, for many rare cancers, this process cannot be accelerated; great patience is required.

Recommendations for Future Studies of Childhood Cancer

My first recommendation is that breakthroughs in our understanding of the environmental causes of childhood cancer are just as likely to result from studies of rare cancers as from studies of more common cancers. Thus, studies of diseases that may be of little public health impact can yield important knowledge regarding the causation of childhood cancer.

Over the years there has been great interest in studying unusual clusters of disease, particularly clusters of cancer. Almost all of the clustering studies done have failed to yield new knowledge about the environmental causes of childhood cancer. The post hoc nature of most cluster investigations has yielded results suggesting striking excesses of cancers in certain locales. However, these reports generally tend to be meaningless and serve to alarm the public unnecessarily.

There has also been increasing interest in conducting ecologic studies of environmental factors in childhood cancer. Such studies might look at the relationship between residence near a dump site and the occurrence of childhood cancer in its immediate vicinity. These studies suffer from a lack of specific exposure data for the subjects involved. They are also likely to be confounded by socioeconomic and other factors. Thus, it is highly unlikely that useful information can be obtained on environmental causes from such studies.

Cohort studies of environmental causes of childhood cancer would be extremely difficult and unlikely to yield important new information other than in special situations. Usually, it is very difficult to identify a large enough cohort of children with a common set of exposures for study. It should be remembered that childhood cancers are extremely rare and thus huge cohorts would have to be assembled to generate sufficient numbers of children with the cancer at issue to derive meaningful results. Cohort studies of parents' occupational exposures and risk of cancer in their children should only be done when specific exposure data are available. Numerous such studies have been published (20). However, these studies have tended to be lacking in information on the type, dose, and timing of the parents' occupational exposures. Thus, if further studies are to be done and not add to the confusion in the literature, they should only be done in situations in which precise exposure information can be obtained.

Traditional case-control studies that rely predominantly on interview data are

unlikely to yield new information on environmental causes of childhood cancer. Most childhood cancers have already been studied in this manner. Well-designed large case-control studies that involve biologic information or that validate exposure information are likely to yield important new information. Such studies should be multidisciplinary and large in size to allow for proper evaluation of causal interactions and potential confounding variables. Such studies would be relatively expensive because of their increased complexity; however, this expense would be well justified.

Because it is often the case that the specific level of exposure of a child to a suspected environmental risk factor is unknown, it would be highly desirable to have some biologic measure of past exposure. Unfortunately, few biomarkers of exposure levels are currently available. Biomarkers of cancer risk following environmental exposures would be high on many epidemiologists' wish lists. The availability of inexpensive, reliable, and valid laboratory measures of environmental exposures, cancer risk, or individual susceptibility would greatly strengthen epidemiologic studies of environmental risk factors for childhood cancer (21). It would particularly facilitate ecologic and case-control studies. Development of such biomarkers should be a priority area for future research.

It is likely that genetic factors (i.e., hereditary susceptibility) play an important role in the etiology of many cancers of childhood. Children with a genetic predisposition for cancer may be particularly

sensitive to environmental carcinogenic exposures. The Knudson two-mutation hypothesis of familial cancer occurrence is consistent with this notion (4). Thus, it should be fruitful in future epidemiologic research on childhood cancer to consider genetic-environmental interactions. The difficulty in conducting such research hinges on the rarity of most genetically related cancers of childhood. Again, the availability of a useful and economical laboratory measure of genetic susceptibility to childhood cancer would be a boon to epidemiologic research.

Another area for future research is the role of environmental factors in the causation of second malignancy in cancer patients. As treatment of childhood cancer becomes more successful, many patients will survive into adulthood. Some of these patients will develop second cancers, most of which are believed to be due to cancer therapy effects or to genetic predisposition. The question arises as to whether a cancer survivor's risk of second cancer might be increased further by environmental factors such as occupational exposures. This is a potentially fruitful area for new research.

In summary, there are numerous difficulties in conducting research aimed at elucidating the causes of childhood cancer. However, these difficulties are not insurmountable and can be remedied by the conduct of carefully designed and conducted studies. It must be remembered that the epidemiologic approach is probably the most likely research venue for uncovering the causes of childhood cancer.

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