Clarification of hypotheses can improve research design, measurements, data analysis, and interpretation of results. I will describe how hypotheses could be clarified during the design of an epidemiologic study of cancer risks near nuclear facilities in the United States. Based on what is known about age variation in radiation sensitivity and difficulties in evaluating other cancer risk factors and tracking people over long time periods, my conclusion is that knowledge about this topic can be most effectively advanced by studying childhood cancer incidence and in utero exposures.

First it may be worthwhile to note that an epidemiologic study is being considered because we do not understand all the mechanisms, and we do not have all the measurements, that would allow us to infer cancer risks from deterministic models. If we knew the necessary and sufficient factors that combine to produce cancer cases in populations near nuclear facilities, and could measure them well, we could determine cancer risks without conducting an epidemiologic study. Although we don’t know all the mechanisms and can’t measure all the factors, incorporating this kind of thinking into the design of an epidemiologic study can increase its scientific value.

Descriptive and analytic studies

Some of the literature on cancer risks near nuclear facilities draws a distinction between descriptive studies and analytic, or hypothesis-testing, studies.¹,² This distinction is disingenuous. So-called descriptive studies are of interest because of an underlying hypothesis, whether or not it is explicit. We are not here to discuss cancer risks near baseball stadiums or supermarkets, despite the fact that it would be much easier to evaluate facilities in populated areas where the numbers of cancer cases are larger. Study of disease around a specific type of facility usually implies a hypothesis that something released by that type of facility causes disease. We are here to discuss cancer risks near nuclear facilities because these facilities emit radionuclides, and because ionizing radiation causes cancer.

General vs. specific causation

Most epidemiologic studies are about general causation. The hypotheses in such studies are about exposure-response relationships, not about the source of the exposure, why the exposure occurs, or about any particular population’s risks. A major consideration in choosing populations for studies of general causation is that their exposures and responses can be measured accurately. Populations that have been enumerated to evaluate the question of radiation and cancer include A-bomb survivors whose doses were estimated as a function of
distance from hypocenter and shielding, patients exposed to medical or diagnostic radiation procedures recorded in clinical records, and workers whose occupational exposures have been monitored by individual dosimeters. Results from general causation studies are often used to estimate risks in specific populations that have not, or cannot, be studied.

Other epidemiologic studies are designed to evaluate specific causation relevant to particular people in a particular place and time. The aim is to address the causes of disease in a given population and similar populations. The hypotheses in these studies rely on knowledge of general causation, but populations for study are chosen for reasons other than the ability to quantify their exposures and responses. The question of cancer risks near nuclear facilities is specific because it concerns people who live near this category of facilities. An even more specific question is about cancer risks near a particular nuclear facility.

Design of epidemiologic studies

Although usually non-experimental, most epidemiologic studies are based on the model of an experiment in which subjects are randomized to be exposed or not, and all other conditions are kept identical in the two groups, including the assessment of responses. Although it is not necessary to know the mechanisms by which the exposure produces the response, knowledge about mechanisms is important for choosing factors to measure, measuring them correctly, and for deciding the extent to which the evidence supports the hypothesis that the exposure causes the response. As in an experiment, sample size must be chosen so that the response occurs with sufficient frequency to permit comparison of the groups.

Because exposures are not randomized, large sample size does not provide confidence that other conditions that influence the response are similarly distributed in the exposed and unexposed groups, and these potential confounders must be considered in the data analysis and interpretation of results. Studies of cancer risks around nuclear facilities typically adjust for demographic factors that differ between near-by populations and groups to which they are compared.

Assumptions required for testable hypotheses

An epidemiologic hypothesis might be that the response is higher in the exposed than the unexposed group. However, the scientific value of the hypothesis is not merely numerical; it depends on assumptions about the level of the exposure, the shape and magnitude of the exposure-response relationship, and the sample size, all of which combine to determine the study power.

Dose assumptions

To be testable, there must be a non-trivial difference in exposure between the groups being compared. Otherwise, evidence that the response is higher in the exposed than the unexposed is not interpretable as supporting the hypothesis. This may seem obvious; however some studies of cancer around nuclear facilities have been conducted under the assumption that the exposure is too low to cause the response. For example, Jablon et al. quote UK researchers: “the increased
occurrence of cancers in persons living near nuclear facilities could not have resulted from radioactive emissions from the facilities” because the doses were too low. Based in part on estimates of doses from the 1979 accident at Three Mile Island which were described as having been made “for educational, public relations and defensive epidemiology purposes,” Hatch et al. reported elevated cancer incidence in downwind areas, but went on to study stress as an explanation because radiation doses were known to be “a fraction of the average US exposure.”

Kaatch et al., who found elevated childhood cancer risk near German nuclear facilities, concluded, “the observed positive distance trend remains unexplained,” noting that, “radiation exposure near German nuclear power plants is a factor of 1,000 – 100,000” below background. These authors tested hypotheses but assumed that the exposure was too small to cause the response. They did not expect to find positive relationships. When they did, they could not conclude that the evidence supported the hypothesis. Although numerical hypotheses were posited and data collected to address them, the evidence produced was not believed. We must ask, why conduct a study if the results cannot be interpreted as providing evidence in support of the hypothesis? Of course we must consider potential sources of bias that can produce the appearance of an effect when none in fact exists. Skepticism is critical. Empirical evaluation of alternative explanations is one of the most important parts of science. Unfortunately, the most popular alternative explanation for excess cancers near nuclear facilities, increased viral exposures due to population mixing, is not supported by evidence that such a virus exists or that it affects nuclear facility communities more than others.

The British epidemiologist Geoffrey Rose described radiation dose assumptions in the Sellafield inquiry in the UK: “We were given information (which, it later transpired, was incorrect) of the total radioactive emissions from the plant, but the exposure levels of the children were a matter of speculation. The radiation experts on the committee calculated ‘best estimates’ and they concluded, on theoretical grounds, that these could not have caused any major excess risk: ‘It couldn’t have happened, so it didn’t happen.’” False assumptions can lead to false conclusions.

Assumptions about doses to populations near nuclear facilities are based on estimated releases, environmental dispersion, human uptake, and estimates of the relative biological effectiveness of different forms of radiation. Except in the case of short-term exposures during an accident, environmental assumptions involve average emission estimates, distances from facilities, and sometimes prevailing winds. Most epidemiologic studies of populations near nuclear facilities have not considered the spatial pattern of ingestion of radionuclides from food or water, nor have they evaluated radiation doses to individuals. All have been based on emission estimates that come from industries responsible for the releases and agencies responsible for regulating them.

Dose-response assumptions

The importance of assumptions about dose levels depends on another assumption, the dose response, which is the increase in cancer for each unit increase in radiation dose. When excess cancer near nuclear facilities cannot be interpreted as evidence of an effect of releases, it is because the expected response from the estimated dose is too small to detect. For example, authors of the study of cancer incidence following the accident at Three Mile Island believed that the relative risk of cancer at the maximum environmental dose was 1.005. A relative risk of 1.0
indicates no effect of exposure. The fact that a relative risk of 1.005 would not be detectable in this study means that evidence of a dose response relationship cannot be interpreted as supporting the hypothesis.

When Stewart and colleagues reported that obstetric x-rays were associated with childhood cancer the findings were dismissed because it was assumed that diagnostic radiation doses were not capable of producing such a response. Following many confirmatory studies it is now widely assumed that the effect of fetal irradiation is orders of magnitude higher (on a relative risk scale) than adult exposure. As in the assumptions made today about the magnitude of dose response, initial dismissal of the in utero exposure findings was based primarily on studies of acute penetrating radiation exposures of A-bomb survivors.

The Life Span Study of A-bomb survivors is important because of its large size and inclusion of females and males of all ages. However the cohort was assembled 5 yr after exposure, and cancer incidence data are not available until 12 years after exposure. There are no data for the time period of most interest in studies of cancer risk near nuclear facilities, early childhood. Health-related selection in survivors of nuclear war is a particular concern for susceptible ages, including the in utero exposed and young children. Dose assessments rely on interviews and do not include assessment of fallout or residual radiation. Caution should be used in extrapolating dose response relationships from A-bomb studies to populations near nuclear facilities that may be chronically exposed to inhaled or ingested radionuclides.

Study power

The power or sensitivity of an epidemiologic study to detect an exposure response relationship is a function of the magnitude of the relationship and the sample sizes in the exposure groups. The weaker the relationship, the larger the sample size needed to detect it. This is why combining small populations near multiple US nuclear facilities is important in cancer studies. Power also depends on the ability to accurately measure the exposure and the response. If an exposure response relationship does exist, it will be underestimated and may not be detected at all if people in the exposed and unexposed groups are mixed together.

Recommendations

Many studies of cancer near nuclear facilities have been conducted since the 1990 NCI study. Rather than repeating that study, the new effort should build on what has been learned since. Recent seminal publications that address many of the critical issues are Baker and Hoel’s meta-analysis of childhood leukemia in proximity to nuclear facilities, and the case control studies of childhood leukemia and all childhood cancers in the vicinity of German nuclear facilities (see also discussions of the German study by Nussbaum and Fairlie).

1. Focus on children
In their meta-analysis Baker and Hoel include only populations under age 25, and they focus on children under age 10. The German study includes only children under age 5. The focus on young ages is justified because of theory and evidence that radiation-cancer dose response relationships are steeper for fetal and childhood than adults exposures, because the temporal lag
between exposure and cancer is shorter for children, because children are less exposed to potentially confounding occupational and lifestyle carcinogens than are adults, and because previous studies have found the strongest associations for children. The shorter exposure lag for children than for adults limits the time period for which exposure must be assessed and affords less opportunity for residential mobility, which increases the difficulty of measuring exposure and ascertaining incident cancers.

2. Focus on areas within 10 km of nuclear facilities
Baker and Hoel focused on populations within 16 km (10 miles) of nuclear facilities. Studies based on large administrative districts like US counties, such as the 1990 NCI study, do not have sufficient spatial specificity. The German study compared the distance from the nearest nuclear facility of the residences of childhood cancer cases at the time of diagnosis to distances of residences of disease-free controls. Residence at birth or during the period of gestation would have been a better measure of fetal dose, and residential history from conception to diagnosis would provide a more complete assessment of exposure history. Although the German researchers analyzed risk as a continuous function of the reciprocal of distance up to 70 km, the distance effects in these studies primarily reflect excesses within 5 or 10 km of nuclear facilities.

3. Consider population size
Childhood cancer occurs infrequently, so nuclear facilities with few children nearby cannot contribute many cases to an epidemiologic study. However, population size has little effect on the research effort required to evaluate historical releases and environmental pathways. Therefore, the most efficient expenditure of time and money would be to give priority to inclusion of facilities with larger nearby populations. Although population size is an important consideration, selection of facilities with larger nearby populations could be problematic if it led to systematic exclusion of facilities with larger estimated releases.

4. Evaluate releases, environmental pathways, uptake, and dose
Past studies have classified exposure based on distance to facilities. In order to be relevant to potential exposure, time period must be factored into the distance measure in order to avoid misclassification of exposure. For example, a child diagnosed with cancer at age 4 who lived near a nuclear power plan that began operations 2 years earlier could not have experienced in utero exposure to emissions. Similarly, air emissions from an operating reactor could not affect a child diagnosed at age 4 if the plant ceased operation 5 years earlier, however, drinking water contaminated by radionuclides with sufficient half-lives could have affected that child from conception through the date of diagnosis. These scenarios underscore how considering time periods of operation, releases, environmental pathways, uptake, and internal doses could help to improve a study of cancer in populations near nuclear facilities. A key component of this assessment is consideration of specific radionuclides, their physical half-lives, transformations in the environment, and biokinetics. Such efforts have been made for studies of radioiodine and thyroid cancer near Chernobyl and Hanford, WA.

Consideration of these factors would require acquisition of operations and environmental data for specific facilities. Because facilities differ in the magnitudes and types of releases to air and water, doses and cancer risks to nearby populations may differ. Even if we assume that radiation doses have roughly the same relationship with cancer in different populations, the risks near
facilities may differ due to differences in releases and human exposure. One way to deal with this problem would be to conduct individual dose assessments so that all study subjects can be considered on the same dose scale. However, lack of data makes individual dose reconstruction difficult. Therefore, analysis of data should take account of the expectation that the distance-cancer relationship should be expected to vary between facilities.

5. Focus on areas and time periods with incidence data
Only cancer mortality data are available nationally for the locations and time periods of operation of all nuclear facilities in the nation. Unlike most countries where this research question has been addressed, the United States lacks a national medical insurance system that could help track cancer incidence nationally. States have instituted cancer registries at different times. This means that the choice of study facilities should place priority on locations and time periods for which cancer incidence data can be assembled.

6. Collect data that could be used to consider alternative hypotheses
If a leukemogenic virus that is spread through population mixing is discovered before data collection, it would be important to measure it directly or obtain a proxy measure so that potential confounding by this factor could be considered in analysis of data. Similarly, if there is reason to suspect a strong or moderate correlation between distance from nuclear facilities and exposure to medical radiation, other sources of radiation, or other causes of cancer, these factors should be measured and considered as potential sources of bias.

Conclusions

The literature on cancer near nuclear facilities provides evidence of elevations in childhood cancer, in particular childhood leukemia. In some cases researchers have concluded that there is no explanation for these elevations and speculated that they must be caused by some unknown factor. However, it is not logical to test a hypothesis of elevated cancer near facilities that release carcinogens if results cannot be interpreted as evidence in support the hypothesis. This situation can be avoided by careful engagement with issues of the mechanisms and selection of populations for study where adequate measurements and sample sizes can be obtained.

References: