

Occupational Epidemiology: Detection of Cancer in the Workplace

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There are fundamental approaches that can be used by health professionals to study the contribution of occupational exposures to cancer occurrence. It would be helpful for clinicians who see patients with cancer to be aware of the methods used to identify those types of cancer that are related to work. Such physicians may be asked by companies or unions to collaborate on the design of epidemiologic studies in work settings or to assist in interpreting results, or they may be consulted by patients from such work environments. Understanding these approaches is essential in order to anticipate, detect and prevent cancer caused by occupational exposures.

That certain types of occupational exposure cause cancer has been known for years. The best known examples involve rare tumors or epidemics so severe that they are easy to recognize; for example, scrotal cancer in chimney sweeps and bladder cancer affecting 60 percent to 70 percent of dye workers. In recent years other unusual tumors have been associated with occupational exposures; for example, mesothelioma in asbestos workers, oat-cell lung cancer in chloromethyl-methyl ether workers and angiosarcoma of the liver in vinyl chloride workers. The clustering of these rare tumors did not escape the attention of alert clinicians. These examples represent situations in which the risks are extremely high.

A more difficult problem is to relate occupational exposures to common tumors or to uncommon tumors when the risk is not enormous. These approaches involve quantitative techniques rather than clinical vigilance. For example, showing the relationship between radon daughter exposure in uranium mining and an excess risk of lung cancer required the study of a relatively large population of uranium miners and the use of epidemiologic and biostatistical techniques. This paper will focus on quantitative techniques that can be applied to the study of cancer in the workplace and to observations of associations of tumors with exposures previously thought not to be hazardous. It is written to inform physicians of the uses, applications and

limitations of epidemiologic techniques and to demystify some of the epidemiologic jargon.

The debate about how much cancer in humans is caused by occupational exposures usually pits the prototype industrialist, who claims that occupational exposures contribute in a minor way, against the prototype environmentalist, who claims that a large proportion of cancer is caused by environmental or occupational exposure. In our opinion, this debate is fueled largely by ignorance. No one knows. The studies have not been done; the data are not available. Systematic and comprehensive studies, with the involvement of industry, organized labor, government and universities, would begin the work of determining how much cancer is caused by occupational factors. Each discovery of a connection between occupational exposure and tumor production provides basic information that can be applied to reduce the incidence of cancer. This article describes processes and approaches that can be used toward that purpose. The reader who wishes to go beyond the limited scope of this paper is referred to the book *Occupational Epidemiology*.¹

Conceptual Approach

Epidemiology is a word that many people misunderstand. In this paper, we are simply talking about trying to relate an occupational exposure to a measure of disease, namely cancer incidence or mortality. Does

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chemical X cause tumor Y? To answer that question we need a measure of exposure and we need a measure of cancer incidence or mortality. Optimally we would like information that would allow us to establish a dose-response relationship: How much X causes how much Y?

Exposure or Dose

In most studies of the relationship of a working population to cancer, the exposure or dose side of the dose-response relationship has been neglected or underemphasized. Too little effort has been expended toward categorizing relevant exposure by type, intensity and duration. The exposure that is relevant to cancer is that which occurred years before the onset of the cancer. However, in most work environments few retrospective data on exposure exist. If we walk into a rubber factory, it is difficult to ascertain what the exposure levels have been for the last 20 or 30 years. However, we can estimate the type and intensity of exposures if we know how the industrial processes have changed. Sometimes an epidemiologist can find factories that have not changed or can simulate previous work conditions so that exposure measurements can be made. By characterizing present and future exposures, we can provide valuable information for medical surveillance and prospective studies. Often the best an epidemiologist can do is to determine whether exposure took place—that is, classify workers into exposed and nonexposed groups. The duration of exposure is usually known, so this index of exposure can represent an estimate of lifetime dose.

Tumor Outcome or Response

A simpler part of the equation is counting the cases of cancer. Sources of data on cancer occurrence in populations include local cancer registries, death certificates for a group of workers or death benefit forms in company or union files. While some death certificates are inaccurate and there can be some misclassification of cancer by histologic type, these sources of cancer incidence and cancer mortality information are a solid enough basis to make the associations that are important.

Inherent Difficulties in Population Approach

The importance of assessing exposure has already been stressed, but there are difficulties that must be considered. For example, the *induction period* for tumor development is usually years long. This makes the relevant exposure remote from the incidence or onset of the tumor. Most malignant lesions caused by occupational exposures have induction periods ranging from 12 to 50 years. Because the causative exposure can have occurred during a long period, there may have been many changes in the working environment. In addition, records are often lost, or the worker may have forgotten the materials and processes used in the work. Job mobility also complicates estimation of exposure; that is, the worker may have had several jobs in several locations during the induction period. Frequently, to

protect trade secrets, companies are reluctant to release a list of ingredients in materials. In many instances, information on industrial hygiene has not been routinely collected over the last 30 or 40 years, making quantification of exposures difficult. When quantitative data are not available, we often rely on qualitative information; that is, someone was exposed to asbestos at unknown levels for a known period of time.

Other complications in relating exposures to disease result from confounders and competing risks. For example, to ascertain the relationship between an occupational exposure and the incidence of lung cancer, epidemiologists must consider smoking habits. In retrospective studies, detailed information on smoking habits is rarely available although more generalized studies, such as population surveys ascertaining smoking habits by occupation and by socioeconomic status, allow estimation of the effect of smoking. By knowing the smoking patterns of specific occupations and by knowing the relationship between smoking levels and lung cancer incidence, adjustment for smoking factors can be made in any population.

There are several other potential confounders; for example, diet as it relates to the incidence of stomach cancer or other tumors of the alimentary tract. Avocational exposures are frequently important and can confound any apparent result between occupational exposure and tumor incidence. For example, a person who has a hobby of restoring furniture may be exposed to solvents such as benzene that could result in the development of leukemia. Other possible confounders include air pollution, physical activity, stress and drugs.

Another important issue is threshold versus nonthreshold relationships. Policymakers are currently debating about how to deal with carcinogens. If a certain amount of exposure is needed to increase the incidence of cancer, exposure might be permitted at levels below the point at which risk is increased. On the other hand if any exposure increases the risk, no exposure should be allowed. Rarely do data exist that allow scientists to determine whether there is a threshold or nonthreshold situation.

Uses of the Quantitative or Epidemiologic Approach

As noted earlier in this paper, rare tumors occurring at great excess can frequently be detected in clusters; however, common tumors cannot. By following the population in a certain occupational setting, tumor incidence and mortality can be determined. Given the right population and information on exposure, relatively small risks can be detected by the population approach and researchers can ascertain whether occupational exposures are causing common tumors. Although a large population with possible exposure to some substance or substances might have an excess risk, knowledge of specific exposure within the population might allow the identification of a subpopulation with much higher risks. For example, when a large cohort of rubber workers was studied, results showed no striking excess in cancer frequency for any tumor site. However, when the population was broken down by department in

which they worked (where exposure becomes more discrete), excesses of stomach and colon cancer cases were found in those working in the rubber-compounding area, and lung cancer was excessive in workers from the tire-curing area.

Well-done epidemiologic studies frequently provide information on dose-response relationships, such as the studies relating work in uranium mines and with asbestos to increases in lung cancer. Population approaches allow epidemiologists to examine latency or induction periods.

Types of Population Studies

There are three common approaches to studying populations that might be occupationally exposed to elements that possibly increase tumor risk.

1. A population exposed to a specific substance or substances can be followed to determine the number of tumors that develop. Such a *cohort* study allows an epidemiologist to relate all possible health outcomes to a specific exposure or set of exposures.

2. On the other hand, the starting point can be persons with a specific type of tumor. Here the epidemiologist would attempt to determine what exposures have occurred in that group of persons that might explain the cancer. In this instance, the patients with cancer (*cases*) would be compared with similar persons without cancer (*controls*) and past exposures would be ascertained. This approach is called a *case-control* study.

3. In some instances records may exist of the deaths of all workers from a certain company, union or other group. By using the death certificates, cause of death can be compared with the expected *proportions* of mortality based on age, race, sex and time of death. This is called a *proportional mortality* study.

There are advantages and limitations to these three basic approaches that will be discussed in the next section.

Cohort Studies

Most studies of working populations aimed at identifying the relationship between occupational exposure and cancer use the cohort approach. A cohort study has the advantage of providing information on which cancer rates (new cases or deaths) can be computed. By starting with a denominator population with no cancer and following it, a researcher can determine the number of cancer cases that occur and how many deaths result from cancer within that population, thus providing a rate of cancer incidence or mortality. The occurrence of nonmalignant disease can also be examined by this approach. The major disadvantages are that cohort studies can be very time consuming and expensive because many persons must be traced and mortality information collected. Most cohort studies are done by epidemiologists attempting to identify a cohort exposed to some substance of interest 20 or 30 or 40 years earlier, and to follow that cohort forward in time to the present.

In order to do the cohort study a researcher needs a

TABLE 1.—Example of Cohort Study*
Observed and Expected† Deaths Among a
Cohort of 13,571 Rubber Workers‡

Cause of death	ICD No.‡	Observed Deaths	Expected Deaths	SMR§
ALL CAUSES		5,079	6,090.6	83
All cancer	140-205	986	1,064.9	93
Digestive	150-159	368	364.1	101
Stomach	151	98	90.4	108
Large intestine ..	153	104	103.4	101
Respiratory	160-164	255	293.4	87
Genitourinary	177-181	155	159.6	97
Bladder	181	48	39.5	122
Lymphatic and hematopoietic ...	200-205	105	94.4	111
Leukemia	204	55	42.7	129
Vascular diseases of central nervous system	330-334	493	524.0	94
Circulatory diseases ..	400-468	2,448	2,871.8	85
Respiratory diseases ..	470-527	218	327.0	67
Digestive diseases	530-587	217	279.0	78
Genitourinary diseases	590-637	75	135.8	55
Accidents, poisoning, violence	800-999	279	440.1	63
Residual		363	448.0	81

*The results are presented on a large cohort of rubber workers.² While none of the standard mortality ratios (SMR's) for the entire group are very remarkable, further analysis by type of job showed excesses of cancer that could be explained by exposures in those jobs. Note that the starting point is a cohort of 13,571 rubber workers of whom 5,079 died over about 25 years.

†Expected deaths computed on basis of age-time-cause specific mortality rates for US white men.

‡International Classification of Disease, 7th Revision.

§Standardized mortality ratio = $100 \times \text{observed number of cases} / \text{expected number of cases}$.

cohort defined in time. For example, all of the shipyard workers employed from 1942 through 1945 might be followed to determine the incidence of mesothelioma that could be related to asbestos exposure in the shipyards during World War II. Once the cohort is identified, the basic procedure is to follow all of those workers to determine their vital status and to collect death certificates or other tumor incidence information for comparison with a reference population. The reference population might be the entire United States, the state in which the cohort lived or, in some instances, the county of work or residence when county data are available for comparison. A cohort study is normally done when there is an exposure of interest and the suspected outcome is a common tumor.

The more precisely exposure can be identified, the better the chance of relating exposure to disease. The example given in the previous section on the "Uses of the Quantitative or Epidemiologic Approach" illustrates this point. Table 1 shows the results of a large cohort study that classified exposure by (1) work in a company and (2) work in specific departments of the company. The mortality (standard mortality ratio) is expressed as a simple ratio of the observed number ($\times 100$) of deaths in cohort to the expected number of deaths in white men in the United States.

Case-Control Studies

While cohort studies are based on company (and sometimes union) records, case-control studies are

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TABLE 2.—Example of Case-Control Study*

Factor	Concordant Pairs: Both Exposed	Discordant Pairs		Relative Risk	One-sided Test (P)
		Cases Exposed	Controls Exposed		
Mother					
Got chemicals on skin	0	10	3	3.3	.05
Inhaled chemicals or fumes	1	12	4	3.0	.04
One or both of the above	1	14	5	2.8	.03
Father					
Exposed to chemical solvents	3	17	6	2.8	.02
Exposed to paints	0	7	1	7.0	.04
Worked in aircraft industry	2	10	0	..	.001

P = probability of result occurring by chance.

*A total of 92 mothers of children who were under 10 years of age and had brain tumors were interviewed along with 92 matched control mothers. The exposures of interest are the occupational exposure of both parents. The table shows that exposure of both parents results in a risk of central nervous system tumors in the offspring (no excess risk would be a relative risk of 1.0). Note that the starting point was 92 cases recorded in the Los Angeles County Tumor Registry.³

Matched-pair comparison of parental occupational exposure of cases and controls. The mother was considered to have been exposed if exposed at any time from 1 year before conception through lactation. The father was considered to have been exposed if exposed during that period or at the time of diagnosis of a case.

usually not. The case-control study examines an uncommon tumor. If a cohort study were done following 1,000 workers in whom leukemia might develop, the ascertainment of an excess of leukemia would be extremely difficult because the rate of leukemia is low and the number of cases expected in a population of 1,000 is small. However, a sufficient number of leukemia cases can be collected from a tumor registry, which can sometimes supply information on where the patients with leukemia worked and what their job was. Aside from serving as a useful tool in the study of uncommon tumors, the case-control study can assess multiple exposures (more than one cause). The principal disadvantages relate primarily to the dependence on interview information and the fact that only one disease is being examined.

In order to do case-control studies there must be a way of identifying cases from the population of interest. Tumor registries can be used for this purpose. For example, the University of Southern California School of Medicine operates a tumor registry for Los Angeles County. This registry collects all new cases of cancer occurring among the more than 7 million persons residing in the county, approximately 28,000 new cases per year. One can use the tumor registry to identify all of the cases of leukemia, for example, find a suitable control group and interview the patients with leukemia and the controls for past exposure that might account for the leukemia incidence. Case-control studies should be done when the cause of a specific tumor is of interest. The example in Table 2 provides further details of the case-control approach.

Proportional Mortality Studies

In many instances information is not available to establish a cohort for follow-up. One may, however, have access to the death certificates on a group of workers with known exposure. Analyzing the death certificates without cohort information can very often provide valuable information. The principal advantages are those of speed and cost. Computer programs allow

TABLE 3.—Example of a Proportional Mortality Study*
Observed and Expected Deaths Among Vinyl Chloride Workers in a Proportional Mortality Study†

Cause of Death	Observed	Expected	SPMR‡
All causes	161	161.0	100
All cancer	41	27.9	150
Digestive	13	8.3	160
Liver and biliary	8	0.7	1,100
Lung	13	7.9	160
Brain	5	1.2	420
Other	10	10.5	95
Central nervous system			
vascular	8	9.5	80
Circulatory	66	68.6	96
External	22	24.5	90
All other causes	24	30.5	79

*Death certificates of 161 workers who worked in a vinyl chloride manufacturing facility were analyzed. The table shows an excess in liver, lung and central nervous system tumors.⁴ Note that the starting point was an accumulation of death certificates.

†Expected numbers based on proportional mortality ratios for white men in the United States.

‡SPMR = standardized proportional mortality ratio = $100 \times \text{observed} / \text{expected}$.

very rapid analysis of a collection of death certificates. While some epidemiologists deprecate the value of this approach, the answers provided by this type of study almost always parallel the results of the more complicated cohort studies. An example of this form of study is shown in Table 3. Note that mortality is expressed as a simple ratio ($\times 100$) of observed deaths to expected deaths.

Application of These Techniques

The approaches discussed have a variety of applications, including etiologic research and medical surveillance. The ultimate goal of all professionals in occupational medicine should be to prevent disease caused by occupational exposures. This requires detection of the adverse effects, reducing or eliminating the exposure responsible for the problem and monitoring the population for early identification of other problems. The approaches described in this paper can assist physicians,

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nurses and other health professionals immensely in identifying hazardous work environments. With training and consultation with epidemiologists, these techniques can be and should be used by most companies to detect problems (if they exist) or to demonstrate a healthy working population and to assure (through continuous monitoring) that no deterioration of health related to work occurs. Expertise in occupational epidemiology exists in several large universities in the West. Most of these academically based epidemiologists are more than willing to help interested companies or unions develop and implement these programs. It is through this kind of cooperation that problems can be anticipated and

prevented. If the techniques and epidemiologic methods that currently exist are applied in many work settings, we should be able to identify causes of cancer, reduce exposures to prevent many cases of cancer from occurring and avert future epidemics of cancer caused by occupational exposure.

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Medical Practice Questions

EDITOR'S NOTE: From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.

Human Tumor Stem Cell Assay

QUESTION:

Is a human tumor stem cell assay considered an effective technique in the treatment of cancer or is it considered investigational?

OPINION:

In the opinion of the Advisory Panels on Chest Diseases, General Surgery, Internal Medicine, Neurosurgery and Pathology, human tumor stem cell assays must be considered investigational at this time, although they appear to offer promise as a valuable in vitro test of tumor sensitivity to chemotherapeutic agents. At present, there are problems in methodology, in standardization and in interpretation of the data derived.

These assays effectively predict drug resistance, and thereby can safeguard patients from the toxic effects of drugs known to be ineffective. However, the test is limited in its ability to predict sensitivity reliably. Prospective correlative data remain scant and limited to a few tumors and drugs. Most of these data have been accumulated for ovarian carcinoma, which grows relatively well in soft agar systems, tends to be moderately responsive to chemotherapy and often has relatively accessible tumor cells in ascites fluid. The correlations may not apply to other types of tumors and may differ from drug to drug. Further, many of the published reports are retrospective, or, when prospective, are not true correlations for individual drugs since patients may be treated with combination therapy after in vitro testing of single agents.

There is as yet no controlled study that indicates that treatment selected by assay is superior to a clinician's choice or that patients' survival is significantly increased by use of the assays.

Long-term clinical studies, carried out in controlled research settings, are required to validate the reliability and clinical application of this technique. Once the methodological differences among laboratories are resolved, and better cell growth for various tumor types and more reliable end points for measuring the effects of drugs are achieved, the clinical studies needed to assess the role of this type of assay will be possible. Until such time as its clinical utility fulfills its theoretical expectations, human tumor stem cell assays merit continued investigation.