Guest Editorial

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Discovering Carcinogens in the Occupational Environment: A Novel Epidemiologic Approach 8

Tens of thousands of chemicals are in common use (1). Those for which we have substantial evidence concerning human carcinogenicity number in the tens; those for which we have substantial evidence concerning experimental carcinogenicity number in the hundreds (2). For the very large majority of environmental agents to which man is exposed, we have no idea whether they may influence risk of cancer. Nevertheless the “scratching of the surface” which has been done indicates that chemical and physical agents encountered in the occupational environment may be an important class of human carcinogens, not only because of the disease produced among workers but also because many of these substances find their way into the general environment. The identification of occupational exposures that carry a long-term risk of disease or death is one of the main public health problems of our era. Most acknowledged human carcinogens in the occupational environment were first suspected on the basis of case reports by clinicians or pathologists (3). These discoveries were usually serendipitous, requiring the coincidence of a cluster of unusual cases in a practice and the insight of a perceptive clinician or pathologist. There is no reason to believe that those carcinogens already discovered represent more than a small fraction of those actually present. The number of exposures to evaluate and the extreme difficulties in the assessment of long-term effects in epidemiologic studies suggest the following question: Is it possible by epidemiologic methods to determine which of the growing list of occupational exposures increase the risk of human cancer?

Some investigators answer implicitly in the negative and suggest that we have no alternative but to accept animal experimental evidence as proxy for human evidence (4, 5). Because the financial and human resources most likely are not available for the performance of the rigorous testing necessary for each agent, other investigators go further and advocate short-term testing as a feasible proxy for animal experimentation and by implication for human evidence (6). Considerable controversy exists with regard to the applicability of animal experimental and mutagenicity evidence to humans (7-13). A major deficiency in our ability to evaluate such proxies is the lack of human evidence with which to correlate experimental evidence. Thus the rapid accumulation of human evidence concerning chemical carcinogenicity is important not only for its value in setting priorities for environmental control but also for its use in telling us more about the applicability of experimental systems to the problem of human risk assessment.

In this paper we review possible methods of detecting heretofore unsuspected risks due to occupational exposure (i.e., exposure to the environment where high levels of identifiable compounds are most likely found). A novel epidemiologic methodology is described that combines the breadth of studies based on routine reviews of occupation distributions in death certificates with the depth of studies (case-control or cohort) attempting to relate a specific exposure to cancer occurrence.

EPIDEMIOLOGIC APPROACH

Geographic Correlation Studies

Cancer maps have been published in the United States and attempts made to relate cancer mortality

ABBREVIATIONS USED: PMR = proportional mortality ratio(s); SMR = standardized mortality ratio(s).

Received May 30, 1980.

Editor’s note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.
rates at the county level to environmental and demographic data (14). This approach may be useful in the detection of hazards responsible for a large portion of the cancers in certain geographic regions. However, few occupational exposures are responsible for significant proportions of any given tumor simply because it is unusual for a large proportion of a population to be occupationally exposed to any single substance. The rare exceptions might be single-industry towns where most of the work force is exposed to a common substance [e.g., shipyard towns (15)]. The geographic correlation approach is based on an assignment of geographic units into qualitative or quantitative exposure categories, and thus all individuals within a county are assigned to the same exposure category. Thus a community in which 10% of the work force is in a certain industry may be considered a “high-exposure” community with respect to that industry. But the estimated risk of disease due to exposure is diluted by the 90% in the community who are not exposed but who nevertheless contribute to the high-exposure estimate. Further attenuation of real differences is caused by inter-county migration (16); i.e., every county includes a proportion of residents whose cancer risk was determined by conditions elsewhere. Statistical sensitivity is further limited if latency periods are not taken into account; i.e., the appropriate correlations are between today’s cancer maps and the industrial maps of many years ago. Even if a high-risk industry could be pinpointed with such an insensitive approach, identification of the carcinogen(s) responsible would usually require additional research. Finally, the number of factors that vary between counties is legion and adjustment for potentially confounding factors is at best extremely difficult. It requires a leap of faith to infer that inter-county differences in cancer rates are due to specific occupational characteristics of the population. It is even more dangerous to infer that a lack of variation in cancer rates implies that differing exposures have no effect on cancer risks. Nevertheless, when applied prudently, the approach may be useful as a guide to subsequent research (17).

Analysis of Cause of Death and Occupation as Recorded on Death Certificates

In some countries death certificates carry information on both cause of death and occupation and thus can be used to compute age- and sex-standardized PMR for different occupation categories (18, 19). Because PMR are subject to distortion due to unequal rates of disease other than the disease of interest, these records have sometimes been related to census-based occupation distributions in the population and SMR have been calculated (20). Inasmuch as death certificates tell only part of the story of cancer incidence, some investigators have supplemented these death certificates with population-based cancer registry records to obtain maximum coverage of cases in the area (21). In each such study, subjects were allocated into occupational categories and either SMR or PMR was computed for each occupation-site combination.

In addition to the capacity to scan the occupational spectrum, the main advantage of this type of routine record analysis is that it is relatively inexpensive. The main disadvantages are:

1) Occupation information may be inaccurate or misleading. Even when it is accurate the occupation listed on a death certificate is often the last one in a man’s career and may not reflect all or even the most important of his lifetime exposures (20, 22).

2) Those studies in which an SMR approach is used are subject to unpredictable bias that is due to one system of classifying and coding jobs in the numerator (death certificates or tumor registers) and another system of classifying and coding jobs in the denominator (census).

3) Those studies in which a PMR approach is used may be biased if diseases other than the cancer of interest are at high or low risk in the particular occupational grouping (20).

4) Causes of death may be inaccurate (23, 24). If the inaccuracy is equal in different occupation groups, it leads to loss of statistical sensitivity. If it is unequal, bias will ensue as well.

5) Apart from age and sex, some important cofactors, such as socioeconomic class, tobacco and alcohol consumption, and ethnic group, are unknown and cannot be adjusted for (25).

6) There is no information on duration and intensity of exposure from which “dose-response” relations can be estimated.

7) If an elevated risk is detected for a broad occupational category (e.g., machinist), it is usually impossible to infer which of many chemical exposures may be responsible for elevated risks.

8) Even within a company, a given job title typically covers a group of workers whose activities and chemical exposures are heterogeneous. The variation in exposures when workers are grouped by common job titles across industries and eras can be very substantial. Thus a risk may go undetected because only a subset of a category such as “leather workers” may have been exposed to a carcinogen and the dilution may blur the association.

9) Inasmuch as many materials are used by subsets of several occupational categories (e.g., benzene), statistical power is lost considerably if those occupations with common exposure are not pooled.

None of the human carcinogens listed in the 1978 review of the International Agency for Research on Cancer was identified in this way (2). To mitigate the problem of classifying a worker according to his last occupation and to provide a single classification of jobs in numerator and denominator, some investigators have suggested that a sophisticated system could link routinely recorded employment information of a group of workers (e.g., census returns) with subsequent routinely recorded mortality and/or morbidity information on the same workers (26, 27). Although a step in the
right direction, this approach would neither overcome the remaining problems listed above nor even assure more precise or more accurate job titles. Furthermore, such record linkage is costly.

**Occupation Title-Based Case-Control Monitoring System**

Some investigators have adapted the case-control approach from its usual hypothesis-testing function to a "fishing expedition" or monitoring system by requesting patients' complete job histories and computing relative risks for all occupation-site combinations. For each analysis, occupation can be analyzed according to any reasonable principle such as: ever worked in the occupation of interest, worked mainly in the occupation of interest, and worked in the occupation of interest between 10 and 30 years ago. By collecting data directly from cases and controls (or their close proxies), one can easily avoid the first six problems in the above list. Patients can be sought out in hospitals where diagnoses are usually adequate, and they can be interviewed to obtain reliable information on cofactors and on occupation history. Analyses can take into account alternative hypothetical latency periods. For a series of patients with cancers of a given site, the control series can be selected in various ways.

Cole et al. (28) ascertained a series of bladder cancer patients and selected general population controls. At the Roswell Park Memorial Hospital, newly admitted patients were systematically interviewed; for each site of cancer, an analysis was performed with the use of those patients with non-neoplastic disease as controls (29). In the U.S. National Cancer Study, many patients with cancers representing all sites were interviewed; for each site, an analysis was done with the use of patients with cancers of some other sites as controls (30). Although the results of such studies provide more meaningful leads than do those derived from geographic correlations or death certificate analyses, these studies were not able to avoid problems 7, 8, and 9 listed above. If workers could be categorized on the basis of common exposure rather than common job title, the contrasts would be sharper and relevant sample sizes larger. Sometimes this would reduce sample sizes (i.e., when the exposure takes place among a subset of one job category) and sometimes it would increase sample size (i.e., when exposure takes place in several job categories). In both cases the statistical power for the detection of hazards would be increased. Furthermore, it would give presumptive evidence for a specific carcinogen rather than a high-risk occupation.

**Exposure-Based Case-Control Monitoring System**

If the working histories of each patient and control can be translated into an exposure history, i.e., into a list of compounds to which the person was exposed, then a data base would be available for analyses that avoid the three major deficiencies of an occupation title-based system. Although the patient may not be able to identify chemical compounds to which he was exposed, he can usually provide detailed descriptions of the activities of the firms with which he worked, the industrial processes in which he was involved, and his specific duties. From these descriptions, experts in engineering and chemistry can, with appropriate bibliographic research and consultation, establish a list of chemicals to which the patient may have been exposed in each of his jobs. This is not a simple task, nor can it be done with precision. To be successful, the system requires the following characteristics: an efficient case ascertainment procedure that permits access to newly diagnosed cancer patients while they can still be interviewed, probing interviews with patients and controls to obtain a detailed description of each job, and review of each job by chemists and/or engineers for the purpose of inferring possible chemical exposures. In our Montreal-area pilot study we maintain a close working relationship between interviewers and the project chemist-engineer\(^9\) to ensure that the right questions are being asked of subjects. Of course, neither interviewers nor the engineer-chemist knows the subject's disease status. The most interesting exposures when one considers cancer etiology are those that occurred many years ago; thus it is of little value to perform environmental measurements in the patient's current work environment. The information required to characterize chemical environments of bygone eras can come from various sources: the knowledge and expertise of the project chemist-engineer, personal contacts and collaborations with other technically expert persons in the area, access to technical documentation, and contact with companies when necessary. The list of chemicals thus inferred becomes part of the person's data file and the basis of subsequent statistical analyses. The within- and between-chemist-engineer variation in attribution of chemical exposures is being evaluated. In essence, the analysis consists of the examination of the exposure lists of patients with a common tumor to determine whether any chemical(s) appear in an unusually high proportion of cases. As will be explained below, the fact that chemical exposures cannot be retrospectively attributed with certainty reduces but does not eliminate the statistical sensitivity of the system.

**Cases and Controls**

The following discussion of cases and controls applies equally to occupation title-based and exposure-based systems. The statistical power of the system is optimized by use of a population with a relatively high

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9 The term "chemist-engineer" will be used generically to convey the type of expertise required. Because no single person is trained to infer the chemical exposure that may be present in different jobs, a group of chemists and engineers with complementary areas of expertise is ideal.
The proportion of tumors attributable to occupational exposure. This would guide the choice of geographic location and age and sex criteria; obviously, occupational exposure should not be a selection criterion. The wider the net is cast in terms of sites the greater the chance of discovering hazards. In an area that contains several hospitals and in which their catchment areas are not strictly delimited and mutually exclusive, doing the study in only one or a few hospitals is dangerous. The comparability of cases and controls is enhanced when self-selection factors, such as those relating to choice of hospital, are minimized among cases as well as among controls. Thus the study should aim to include all patients in a given geographic area who satisfy other selection criteria.

The selection of controls is always problematic because every control group gives a different perspective on reality. The main options are a) some type of population control, b) hospital control with the use of patients having conditions believed to be unrelated to occupational exposures, or c) for one cancer site, controls selected from among patients with cancer at other sites. Population controls would be extremely expensive—fieldwork costs of interviewing controls might be higher than the cost of interviewing cases. At least as important are possible sampling and nonresponse biases due to the type of healthy persons available for interview and memory and interview biases. With a probing job-history interview, the quantity and quality of information elicited from healthy controls interviewed in their homes may differ from those elicited from ill patients. Interviewing of noncancer hospital controls would cost as much as would interviewing of patients, which would thereby double fieldwork costs, if one control is selected per case, and risks of interviewer bias would be reduced. However, it is very difficult to define a group of noncancer hospital controls with the requirement that the reason(s) for hospitalization are unrelated to occupational exposure or to correlates of occupational exposure such as socioeconomic class. In other words, even if accidents, hernias, or heart disease, for example, is not caused by occupational chemical exposures, each may be associated (not necessarily causally) with a certain occupation and thereby be unsuitable as a control for a study of cancer and occupational exposure.

Cancer controls have some attractive features for this kind of ongoing monitoring system. Each patient interviewed is a case when his site is being analyzed and a potential control when other sites are being analyzed. The risks of interviewer bias and interviewee bias are virtually eliminated so long as the interviewer is unaware of the patient’s disease. Fieldwork costs are minimized. This approach has the further advantage that, like classic systems of notifiable disease, it is self-contained and can legitimately be seen as an extension of the tumor registry concept. Although the special efforts required to set up and run a study with the use of population or noncancer hospitalized controls are feasible in the context of an ad hoc study, they would be difficult to maintain in the context of a permanent system.

The disadvantage of the use of cancer controls is that chemicals that produce cancer at many sites are less likely to be detected. Although many carcinogens may act at multiple sites, many have not been found to do so (2, 31). Even if a chemical produces cancer at multiple sites, it would have to do so to the same degree to slip through the monitoring system. For example, suppose a chemical increases the risks of bladder, liver, and pancreas cancers by factors of 5, 3, and 2, respectively, and does not affect other sites. Then an analysis of bladder cancer with the use of a variety of sites of cancers including liver and pancreas as controls would yield an observed relative risk lower than the real 5 but probably high enough to be detected as a health hazard. For statistical analyses of the association between that chemical and other sites, bladder cancer can then be excluded from the controls or, alternatively, we have developed methods to adjust for excess risk among some of the controls (Thomas DC, Siemiatycki J: Manuscript in preparation). In any case, from a public health point of view it is not important to determine all of the sites at which a material may cause cancer—one is enough to indicate the need for control measures. Table 1 shows fictitious data that might derive from such a study. When percentages are uniform across a row (i.e., for a given exposure), no elevated risk is detected. When percentages are not uniform, the site(s) with higher proportion(s) exposed are associated with the corresponding exposure.

If population controls are not used, a general population occupation distribution could still be established to serve as a general comparison before detailed case-control analyses are done. This would be useful in the detection of persons in occupations at high risk for many kinds of tumors and diseases that may not be detected when the controls represent patients with cancers at different sites or with different diseases. Such an occupation distribution might be available from the census. To compare like with like, one would have to compare the occupation distribution of the cases in the

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Bladder</th>
<th>Colon</th>
<th>Pancreas</th>
<th>Lymphoid tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1</td>
<td>0.2</td>
<td>4.0</td>
<td>0.1</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>C</td>
<td>1.0</td>
<td>1.3</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>D</td>
<td>2.0</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>E</td>
<td>4.6</td>
<td>4.8</td>
<td>4.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* Exposures may include exposures to specific chemicals, general categories of products (e.g., solvents), occupation titles, and industry titles.
year of the census (available from their respective occupational histories) with that of the population weighted to the age distribution of the cases.

Statistical Sensitivity of a Case-Control System

Statistical sensitivity depends on several factors: size of the population basin for cases, number of years of accumulation of cases, the number of controls per case, incidence of the tumor, the proportion of the population exposed to the carcinogen, accuracy in attributing exposure, accuracy in attributing disease status, the relative risk, and the statistical probabilities of type I and type II errors. High risks are more readily detectable than are low risks. Table 2 shows what would be the minimum detectable relative risk in an area with a population of 500,000 males 35-69 years old as a function of years of study, incidence of the tumor, and proportion of the population exposed to the carcinogen. The use of the table is illustrated by the following example. Product X is a bladder carcinogen, the incidence of bladder cancer in males 35-69 years old in the general population is 30/100,000, and 1% of the work force is exposed to X. Suppose that we accumulate 3 years' data. From table 2 we see that if product X increases the risk of disease by a factor of 4.2 or more, the chance of the system's detecting this hazard is 95%. This assumes that we are successfully able to attribute exposure X to all those patients who were actually exposed to it. If, however, the chemist-engineer can attribute exposure X to only one-half of the patients who were actually exposed to it, it would be tantamount to analyzing an exposure to which 0.5% of the work force was exposed and the relative risk would have to be at least 6.3 to be detectable. If exposure to X occurs in subsets of several occupation categories, one may compute the dilution effect of performing an occupation title-based case-control monitoring system. Suppose that product X is used in four different occupations, each of which represents 1% of the work force, and that about one-quarter of the workers in each occupation are exposed to X. As before, 1% of the total work force is exposed to X, but we will be conducting analyses based on occupation titles. If for workers in each of the four occupations in question we presume that three-quarters are subject to the general population risk of bladder cancer, then it can easily be shown that the relative risk for those exposed to product X would have to be greater than 13.8 to assure with 95% probability that an occupation category as a whole would show excess risk. Thus in this example relative risks for a specific chemical between 4.2 and 13.8 would be detectable in an exposure-based case-control study but not in an occupation title-based case-control study. Even when one-half of the truly exposed cases are not identified, sensitivity is still considerably greater in the exposure-based analysis, which can detect minimum relative risk of 6.3 compared with a minimum relative risk of 13.8 for the occupation title-based study. The above example is artificial and examples can be devised in which an occupation title-based analysis is superior to an exposure-based analysis. However this example indicates that a system that permits both types of analysis is optimal.

A pilot study was done in Montreal to determine the feasibility of ascertaining and interviewing patients and to check the accuracy of chemist-engineers in inferring exposures. Although a detailed analysis of the pilot study is not yet available, two aspects bear directly on the question of statistical sensitivity: What is the incidence of different sites of cancer in our study

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**Table 2.** Minimum relative risk detectable in case-control monitoring system in metropolitan Montreal for a population of 500,000 males 35-69 years old for various values of exposure rate, annual incidence, and person-years of observation

<table>
<thead>
<tr>
<th>Annual incidence per 100,000</th>
<th>Person-years of observation</th>
<th>Percentage of population exposed to carcinogen</th>
<th>Minimum detectable relative risk</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>1×500,000</td>
<td>0.1</td>
<td>345.2</td>
</tr>
<tr>
<td>3</td>
<td>1×500,000</td>
<td>0.1</td>
<td>117.0</td>
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<tr>
<td>7</td>
<td>1×500,000</td>
<td>0.1</td>
<td>51.8</td>
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<tr>
<td>30</td>
<td>1×500,000</td>
<td>0.1</td>
<td>60.0</td>
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<tr>
<td>100</td>
<td>1×500,000</td>
<td>0.1</td>
<td>19.9</td>
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<tr>
<td>3</td>
<td>5×500,000</td>
<td>0.1</td>
<td>21.8</td>
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<tr>
<td>7</td>
<td>5×500,000</td>
<td>0.1</td>
<td>10.8</td>
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<tr>
<td>100</td>
<td>5×500,000</td>
<td>0.1</td>
<td>3.8</td>
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<td>3</td>
<td>7×500,000</td>
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<td>7</td>
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<td>0.1</td>
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* It does not matter whether the person-years of observation are composed of the population and study durations shown here or some other combination (e.g., 250,000 males 35-69 yr old with study durations of 2, 6, and 14 yr).

* Exposure can be defined according to any reasonable principle such as "ever exposed."

* These computations were based on the method of Walter (32), with α=0.10 and β=0.05 or vice versa. Equal numbers of cases and controls were assumed.
area and what is the prevalence of exposure to different products? Being warned of possible underreporting in official tumor registries, we have actively ascertained cancers of 12 selected sites in all Montreal area hospitals. Among males 35-69 years old in the Montreal area, estimated annual incidence rates per 100,000 were 3-10 for six sites studied (esophagus, liver, pancreas, kidney, skin melanoma, and testis), between 15 and 30 for another (colon), and in the 90's for another (lung). As far as exposure frequencies are concerned, among the first 236 patients' histories can be determined with anything approaching completeness is inconceivable. The following circumstances preclude any hope of precise and complete exposure histories' being reconstructed even if resources to research the jobs were unlimited: Unknown chemical reactions take place in industrial environments, processes handled long ago have been forgotten or were never completely described, proprietary secrets prevent access to information, and each worker experiences an idiosyncratic environment. The strict limitation on time available to research each job history further restricts data collection and ensures that the system will fail to uncover many risks or may erroneously attribute the likelihood of detection. That workers' exposure histories' being reconstructed even if resources to research the jobs were unlimited: Unknown chemical reactions take place in industrial environments, processes handled long ago have been forgotten or were never completely described, proprietary secrets prevent access to information, and each worker experiences an idiosyncratic environment. The strict limitation on time available to research each job history further restricts data collection and ensures that the system will fail to uncover many risks or may erroneously attribute the likelihood of detection. That workers' exposure histories' being reconstructed even if resources to research the jobs were unlimited: Unknown chemical reactions take place in industrial environments, processes handled long ago have been forgotten or were never completely described, proprietary secrets prevent access to information, and each worker experiences an idiosyncratic environment. The strict limitation on time available to research each job history further restricts data collection and ensures that the system will fail to uncover many risks or may erroneously attribute the likelihood of detection. That workers' exposure histories' being reconstructed even if resources to research the jobs were unlimited: Unknown chemical reactions take place in industrial environments, processes handled long ago have been forgotten or were never completely described, proprietary secrets prevent access to information, and each worker experiences an idiosyncratic environment. The strict limitation on time available to research each job history further restricts data collection and ensures that the system will fail to uncover many risks or may erroneously attribute the likelihood of detection. That workers' exposure histories' being reconstructed even if resources to research the jobs were unlimited: Unknown chemical reactions take place in industrial environments, processes handled long ago have been forgotten or were never completely described, proprietary secrets prevent access to information, and each worker experiences an idiosyncratic environment. The strict limitation on time available to research each job history further restricts data collection and ensures that the system will fail to uncover many risks or may erroneously attribute.
excess risks to a product that is not carcinogenic itself but that happens to occur in the same job histories as a carcinogen not identified. Furthermore, as Peto (33) argues, many environmental carcinogens may cause only a small number of cancers each, which would be undiscoverable by any epidemiologic strategy. Nevertheless, if such a system can help uncover a small fraction of human carcinogens that have acted in the occupational environment, it would add very considerably to our meager knowledge.

**DISCUSSION**

Hitherto, epidemiologic research into environmental carcinogens has followed a rather anarchic path, which is not surprising in view of the recency of the notion that many environmental agents may be carcinogenic. This notion now compels a more systematic approach to the discovery of potential carcinogens. Animal testing and mutagenicity screening programs may eventually prove to be most useful components of a cancer prevention strategy. Until understanding of basic processes is sufficient to permit extrapolation or generalization from one biologic system to another, epidemiologic evidence will be necessary in its own right as a guide to cancer control and as a crucial data base for helping us to understand the relevance of animal and mutagenicity testing to the problem of human cancer. The increasing recognition of the need for a systematic approach to environmental carcinogenesis in the workplace has led to methods based on geographic correlations, analysis of death certificates to estimate PMR or SMR for occupations, and occupation title-based case-control studies. These increasingly sophisticated and costly approaches are in increasing order of likelihood of identifying harmful occupational exposures. An exposure-based case-control monitoring system opens a new dimension and, despite its greater expense, may strike the optimal balance between cost and yield. Table 3 summarizes characteristics of various systematic approaches. The various problems are not of equal value, however, and it is impossible to synthesize an overall score for each approach. Local conditions would also play a role in the determination of the potential costs and benefits of each approach, and of course, there are variations in each of the archetypal

<table>
<thead>
<tr>
<th>Circumstances</th>
<th>Type of monitoring system</th>
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<tr>
<td>Annual tumor incidence</td>
<td>Percentage of work force exposed</td>
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<tr>
<td>Low</td>
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* 0 = insensitive; *** = very sensitive; * and ** = in between.

1. Low = 10/10^5; high = 100/10^5.
2. Low = 0%; high = 5.0%.
3. A = the exposure occurs in only one occupation. All in that occupation are exposed. B = exposure occurs in subsets of different occupational categories.
4. Low = 2; high = 30.
5. Geographic correlation system with subnational county units. Cancer mortality rates were from death certificates and exposure rates were taken from recent census as proportion of work force engaged in various occupations. Assume that few geographic areas have exposed workers.
6. Routine record analysis. Death certificates provide causes of death and occupation. Census provides denominators in each occupation. SMR and PMR are computed. If the records exist for linkage of jobs during lifetime to mortality records, the cost would be much higher but the occupational data better. Assume a population basin of 500,000 for a 3-yr study.
7. Occupation title-based case-control monitoring system. Patients and controls are interviewed to obtain occupation history. Assume a population basin of 500,000 for a 3-yr study.
8. Exposure-based case-control monitoring system. Patients and controls are interviewed to obtain detailed occupation history, which in turn is translated into history of exposures. Assume that one-third of a worker's exposure can be retroactively identified with available resources. Analyses are done on exposures and on occupations. Assume a population basin of 500,000 for a 3-yr study.
studies described. An exposure-based case-control system would generally be the most statistically sensitive; i.e., any hazard detectable by one of the other methods should be detectable by this method, though the reverse is not necessarily true. Inasmuch as statistical analyses would be undertaken not only for each exposure identified in any job history but also for the occupations themselves, the system retains the strength of an occupation title-based case-control system in detecting high-risk occupations for which, through error or ignorance, the responsible carcinogen has not been identified as part of the exposure histories of the workers.

However, this method cannot uncover the entire iceberg; it can only make it somewhat more visible. No epidemiologic approach can hope to discover all human carcinogens. Nonetheless, the hazards most likely to be detected are those that cause the greatest number of cases of disease. These points are illustrated in table 4, which is based on a subjective assessment of the relative sensitivity of different approaches under various circumstances.

Properly conducted case-control studies convey as much information as do cohort studies based on the population(s) who gave rise to the cases and controls and at much lower cost (34). Inasmuch as all cases of the disease in a geographic area are being ascertained, the statistical information of the proposed system is approximately equivalent to that which would be available from multiple cohort studies based on each product noted in any patient’s job history; i.e., it would take at least hundreds of historic cohort studies with follow-up corresponding to the duration of this study to equal in a statistical sense the type of information that can be derived from the proposed exposure-based case-control study. By contrast with that expenditure of effort, our study entails investigating occupational histories of about 1,200 patients per year.

The methodology can be applied equally to a research project with a limited time period or to an ongoing monitoring system. It is a much more interventionist method of monitoring than are the notifiable disease systems developed in the 19th century and adapted recently as tumor registries. However, if significant numbers of environmental agents with which we come in contact are carcinogens, such a system may become as important a component of cancer control as the notifiable disease system was of infectious disease control. An analogous approach has been developed for surveillance of secondary effects of medication (35).

The essence of the proposal is a systematic ascertainment of newly diagnosed cases and appropriate controls in a geographic area over some period of time, a translation of job histories into exposure histories, and appropriate case-control-type analyses. The operational content—what sites to include, what criteria to employ for patient inclusion, whom to use as controls, what type of data collection to use to obtain detailed job histories, how to translate job histories to exposure histories, and what type of appropriate statistical analysis to include—may differ from one research team to another. It would nevertheless be desirable to evolve a uniform multicenter approach not only to increase effective sample size and thus increase sensitivity but also to evaluate consistency of findings.

REFERENCES


(20) The Registrar General’s decennial supplement for England and