Future Etiologic Research in Occupational Cancer

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Research focused on occupational exposure has been one of the cornerstones of epidemiological research into the etiology of cancer. It is appropriate to critically assess the contribution of this research effort and to assess the potential for making significant progress in the future in unraveling the etiology of cancer by studying the occupational environment. The study of the occupational environment has indeed been very fruitful. It is likely that there remain many more carcinogens to be discovered, but we have not deployed adequately sensitive study methods. The two major obstacles to quality research have been inadequate exposure assessment and insufficient sample sizes. Quality exposure assessment requires the participation of trained experts (industrial hygienists, chemists, etc.); it also requires an adequate information base on the exposures that occur in different workplaces. We need structures and career paths that facilitate the participation of exposure experts in epidemiological research. We need active large-scale industrial hygiene surveys to better characterize the U.S. workplace. This will be useful for epidemiological studies and for public health purposes. Community-based case–control studies will need to be much larger than they have been traditionally, with 1000 as a minimum number of cases and controls. — Environ Health Perspect 103(Suppl 8):209–215 (1995)

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Introduction

Early in the 20th century, two important parallel developments were reshaping the scientific view of the etiology of cancer. Based mainly on observed clusters of cases by physicians, certain groups of industrial workers were found to have high risks of certain types of cancer. At the same time, experimentalists were showing that chemicals of the types found in workplaces were capable of causing cancer in laboratory animals. Consequently, the scientific community was increasingly receptive to the notion that workplace chemicals could be carcinogenic. The 1960s saw the flowering of a popular ideology of environmentalism that recognized the dangers of environmental degradation, and that fostered an attitude of vigilance about chemical exposure. All this led to a widespread belief, both inside and outside the scientific community, that the occupational environment is an important one on which to focus when searching for causes of cancer. As a result, a large body of research on occupational causes of cancer has been conducted over the past 25 years. My intention in this paper is to reflect on the field of occupational cancer epidemiology, namely, how successful it has been and the potential for making significant progress in the future in unraveling the etiology of cancer by studying the occupational environment. I will try to address three questions: *a*) What is the legacy of several decades of research in this field? *b*) Is it still important to carry out research in this field? *c*) What are the structural or methodological constraints that must be tackled and overcome if we are to make progress?

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The Legacy of Past Research

Examination of recent lists or reviews of known human carcinogens will reveal that many known risk factors for human cancer are chemical or physical agents that were discovered in the occupational environment (*1–3*). In fact, when simply listing the known human carcinogens and ignoring their quantitative importance as causes of cancer, occupational carcinogens make up if not a majority at least a sizable minority of known human carcinogens.

Paradoxically, most of the recognized occupational carcinogens were first discovered before 1970 before the marked increase in the amount and quality of research devoted to investigating occupational cancer. Because the rhythm of discovery of solidly established occupational carcinogens has decreased despite new methodological advances and improved data sources, it is legitimate to question whether research into occupational carcinogens is at a dead end. It may be claimed, for instance, that in contrast with the situation earlier in this century, occupational carcinogens with high enough quantitative impact to be detectable no longer exist, either because the most potent carcinogens already have been discovered or because regardless of inherent carcinogenic potency, exposure levels now are much lower than before. While these are plausible claims, and not strictly testable, I believe it unlikely that the discoveries of the first half of the century represent all the important occupational carcinogens, and this belief is based in large part on how those discoveries were made.

Most known carcinogens were discovered by chance. Typically, an occupational risk factor for cancer was discovered by an astute clinician observing a cluster of three or four cases in his practice who all worked in the same place, and the lead was followed and eventually confirmed (*4*). A typical example is represented by the discovery of nickel carcinogenesis. Clinicians noticed clusters of cases of nasal and lung cancer in a Welsh nickel refinery and followed up this observation with a cohort study that confirmed the association (*5*). Subsequent research in other countries has confirmed that excess risks have occurred in other nickel refining environments (*6,7*)

but not in all (*8*). A recent attempt to determine which chemical agent was responsible for the apparent excesses in some nickel-exposed workers has not produced clear-cut results (*9*). Many of the known occupational carcinogens were similarly identified, by a combination of case–cluster observations followed by fairly prosaic cohort studies.

Among the circumstances necessary for such discoveries to take place are *a*) relatively high relative risk so as to produce an observable excess in the work force; *b*) an obvious commonality of experience, such as working in the same plant, among the cases; *c*) the confluence of multiple cases into a single medical practice; *d*) a rare tumor that would catch the attention of an attending physician; *e*) an astute physician to realize that something unusual is going on; *f*) a persistent physician to evaluate and follow up on the initial realization. In light of the above, it appears that many discoveries were exceptional and that there must be other carcinogens that were not discovered because one or more of the necessary conditions were absent. Thus, it is probable that the known carcinogens represent merely the tip of the iceberg.

If, as mentioned above, there has been a vast increase in the amount of research on occupational cancer in the past 25 years, and if past methods only gave us the tip of the iceberg, why has that research effort not paid off in a corresponding increase in the visible part of the iceberg? There are a few reasons. First, the bulk of research in this area has been aimed not at discovering the hidden part of the iceberg but rather at better characterizing already known or suspect carcinogens. Second, much of the research that was done to monitor the work environment to identify occupational risk factors has been deficient, either in terms of poor quality exposure assessment or in terms of hopelessly small sample sizes. I will expand on these problems below.

In the late 1970s and early 1980s, there was a heated debate, fueled by sociopolitical as much as scientific considerations, about the relative importance of occupational exposures in producing cancer. Several investigators tried to address the following question: What proportion of cancer in the population is attributable to occupational exposures (referred to as the population-attributable risk percent)? This question had great social importance; the answer would affect both the disbursement of cancer research funds and the priority to be given to cleaning up the workplace.

The answer to the above question depends on several factors, including the number of occupational carcinogens that have been in the occupational environment, their carcinogenic potencies, and their prevalence. Obviously, the more occupational carcinogens there are, the greater their prevalence and the greater the risks due to exposure to them, the greater the resulting number of cases will be and the greater the population attributable risk percent.

Very divergent estimates were made by various authors, ranging from less than 1 to about 40% [(*2,10–14*); K Bridbord, unpublished data]. The major reason for the wide variability of published estimates was the variety of the methods used to derive the estimates. The methods used to estimate the proportions of cancer attributable to occupational carcinogens have for the most part been very crude and even subjective. To illustrate the variability in estimates due to differences in approach, we used three different approaches employing the same data set (a large multicancer case–control study to be described below). Table 1 shows the three different estimates for each of nine sites of cancer. The three methods are described in detail elsewhere (*15*) but can be summarized as follows: *a*) a method based on the relative risk and prevalence of exposure in our data for a set of substances that have been shown in previous research to be human carcinogens at the site of interest; *b*) a method based on the relative risk and prevalence of exposure in our data for a set of substances that were found to be significantly associated with the site of interest in our own data set; *c*) a method not based on any identified list of substances but rather on the fitted regression equation between cancer risk and a quantitative estimate of the "blue-collaredness" of the job history. For each site, the three estimates tended to be quite diverse.

Table 1. Population-attributable risk percent due to occupational exposure for each of nine sites of cancer by three different methods.

Site	Based on recognized carcinogens	Based on significant associations in our data	Based on regression of risk on dirtiness scale
Esophagus	3.5	20.4	0
Stomach	4.0	14.1	5.6
Colon	0.4	3.4	0
Rectum	0	21.8	0
Pancreas	0	20.6	26.1
Lung	8.0	20.3	17.2
Prostate	0.2	9.9	11.6
Bladder	1.2	10.8	0
Kidney	0	20.8	16.7

The methods used in the past to estimate the proportions of cancer attributable to occupational carcinogens have for the most part been very crude and even subjective. Some were based on the erroneous assumption that for a given type of cancer, the sum of the proportions due to individual risk factors cannot exceed 1.0. The most valid methods are those based on lists of recognized carcinogens, such as those in the first column of Table 1. However, implementation of this method is subject to vastly different assumptions about the number of occupational carcinogens already identified, their carcinogenic potencies, and their prevalence. Further, some of these parameters, especially prevalence but also potency, may well differ from population to population. Not only is our knowledge deficient in providing a complete listing of occupational carcinogens, but for those already discovered, there is very little reliable quantitative information available on their potency or their prevalence. For these reasons, the data have not been available to make valid estimates of the proportion of cancer attributable to occupational carcinogens, and therefore the estimates that have been based on lists of known occupational carcinogens probably have been underestimates.

Importance of Investigating Occupational Carcinogens

Workers continue to be exposed to substances that may be dangerous. It is not known whether the as-yet undiscovered carcinogens consist of a few dominant ones like asbestos, each of which cause many cases of cancer, or a plethora of agents, each of which may cause a few cases. As a general rule, epidemiology can only detect those agents that cause a reasonably large number of cases of disease. Despite the ostensible decline in the pace of discovery of occupational carcinogens, there are several reasons that this should remain an important area of research (*16*).

One of the characteristics that enhances the value of discovering occupational carcinogens is that unlike many other types of risk factor, they often are amenable to effective public health intervention. For instance, whereas the discovery that asbestos is an important occupational carcinogen has led to dramatic reductions in occupational exposure to asbestos and thereby to reductions in the incidence of asbestos-related cancers, there have not been

analogously dramatic reductions in exposure to some demonstrated lifestyle risk factors such as tobacco smoke and nulliparity.

A second favorable characteristic is that, other things equal (e.g., relative risk, prevalence of exposure), the likelihood of detecting an occupational carcinogen may be greater than the likelihood of detecting a nonoccupational carcinogen. This is because one of the key factors in the success of detecting a true risk factor is the ability to measure it accurately. In general, exposure circumstances are relatively more circumscribed and more easily identifiable in the industrial environment than in the general environment, which improves chances for detection.

A third argument for the importance of research on occupational causes of cancer is that the hazardous materials identified are not always limited to the workplace. Substances found in occupational environments often become exposures to the general population, either because of industrial emissions or accidental spills, or because of their incorporation into consumer products.

A fourth reason is that there is a great deal of evidence from animal tests that chemicals occurring in the workplace can cause cancer in mammalian systems. Still another reason is that our knowledge of the biology of carcinogenesis has been crucially influenced by the nature and variety of known occupational causes of cancer. This critical contribution is in part due to some of the features mentioned above, namely the greater opportunity for defining exposure circumstances in the occupational milieu.

Not only is it important to invest in occupational cancer research but there is an urgency to it. Given the changing picture in advanced industrial societies, in the future there will be fewer blue-collar workers and greater occupational mobility. These factors, combined with improving industrial hygiene practices, may well reduce the hazards of occupational exposure and ultimately result in less occupation-related cancer. Epidemiology generally is a fairly blunt instrument; i.e., it is capable of detecting hazards that cause many cases of disease but not those that cause few. Without wishing for more victims, we must nonetheless take advantage of unfortunate situations that have occurred. If we do not detect hazards in situations in which they caused large enough problems to be detectable, we may condemn future generations to suffer risks. If we wait 20 years, we may have missed an opportunity to discover environmental and occupational risk factors that continue to cause cancer, albeit at lower rates than in the past.

Constraints to Progress

We might say that occupational cancer epidemiology has at least two functions. One is to discover previously unrecognized occupational carcinogens among the large number of agents in the occupational environment; another is the narrower one of evaluating and characterizing risks due to specific suspect or recognized carcinogens, such as formaldehyde, benzene, or asbestos. These functions generally can best be accomplished through different types of study design. Although there certainly are exceptions to this generalization, the best design for examining the occupational environment to discover occupational hazards is the community-based case–control study, while the best design for evaluating and characterizing specific hazards is the industry-based cohort study. Until the late 1970s there were very few community-based case–control studies on occupational cancer; nearly all were industrial-based cohort studies. The balance has been somewhat redressed since then, but cohort studies continue to substantially outnumber case–control studies in occupational cancer epidemiology (*17*).

Industry-based Studies

A major methodological problem in occupational cancer epidemiology, as in other areas of epidemiology, is exposure assessment. In an industry-based study, it is sometimes possible to obtain quite high-quality historic exposure information and to use this in assessing and characterizing hazards. Notable examples from the past decade include studies on formaldehyde (*18*) and mineral fibers (*19*). In some historic examples, such as in certain cohorts of asbestos workers, there were no available quantitative data on exposure levels, but the industrial process was thought to be so simple that only one substance was thought to be worth considering as an explanation for the excess risk of the entire cohort (*20*). Such reasoning may be acceptable in a few industries, the extractive industries, for example, but most industrial processes entail diverse mixtures of exposures. Where the circumstances are favorable for a historic cohort study (namely, existence of historic lists of workers with their job history information; existence of data or semiquantitative information on exposure circumstances; willingness of company and/or union officials to cooperate with investigators; ability to trace the health outcomes of the workers; a large enough work force to have reasonable statistical power), such a study can and has provided precious information. While many of these studies have been useful, a significant number have not, either because of small sample size or poor quality exposure data. A dilemma facing investigators who contemplate carrying out cohort studies is that the sample size is usually not controllable; that is, the number of workers in the plant is fixed. Sometimes multiple similar plants can be identified and enrolled and pooled to enhance the statistical power of the study, but not always. Another important determinant of study power is the quality of the exposure assessment. In part, the success at characterizing past exposures will depend on the skill and resources of the investigating team. Ingenious methods have been brought to bear by industrial hygienists working with epidemiologists to evaluate historic exposures to specific substances in various cohorts (*21,22*). A related determinant of the quality of exposure data in an industry-based cohort study is whether the company has had a good tradition of industrial hygiene, including the nature and quality of past exposure measurements.

Community-based Studies

Although many of the known human carcinogens are related to occupational exposures, the vast majority of occupational exposures have not been evaluated for human carcinogenic potential. Also, as argued above, it cannot be assumed that most occupational carcinogens have been discovered. There have not been systematic and sensitive approaches to discovering occupational carcinogens (*23*).

Although industry-based cohort studies have some advantages over community-based case–control studies in evaluating and characterizing risk due to specific substances, community-based studies have the unique advantage of being able to monitor a wide spectrum of occupational circumstances. This deserves particular attention because it has been less successfully addressed than the problem of evaluating specific hazards through industry-based studies. It was long thought that this monitoring function could be accomplished by fairly crude methods such as analysis of occupations mentioned and coded on death certificates (*24,25*). However, these methods are so crude that they probably

only detect the strongest of risk factors under unusual circumstances (*15,23*), in large part because they rely on the job title as an indication of the occupational exposures a worker experienced. While the analysis of routinely collected data such as the analysis of occupations mentioned and coded on death certificates should be continued and even enhanced, it is important to foster more refined methods.

Case–control studies can overcome some of the limitations of routinely collected data sets, but more often than not the investigators used job titles as the exposure variables. Although this has long been shown to be of dubious validity and value, much of the research on occupational cancer still uses job title as the main epidemiological variable for occupational studies. These kinds of studies are unlikely to give us important new information.

Improving the quality of exposure assessment is difficult. In the past 15 years several methods have been developed (*17,26,27*). One of the more prominent is an approach we developed in Montreal. A brief explanation of this approach prompts some additional recommendations.

In 1979, we undertook in Montreal a large case–control study designed to provide evidence on the associations between hundreds of relatively common occupational exposures and many sites of cancer. Between 1979 and 1986, interviews were carried out with 3730 cancer cases distributed among several cancer sites, and with 533 population controls. Each subject's job history was scrutinized by a team of specially trained chemists and hygienists, who inferred a list of chemical exposures. The data collection involved probing interviews to obtain a detailed description of each of the subject's jobs as well as information on potential confounders and review of each job description by experts in chemistry or hygiene to identify possible chemical exposures. The list of chemicals thus inferred became part of the subject's data file and the basis of subsequent statistical analyses.

The point of departure for the chemical coding methodology was the interview. Interviewers were specially trained and continuously monitored to elicit in-depth descriptions of subjects' lifetime work histories. The completed interview with detailed notes was then given to the team of chemists and hygienists who proceeded to translate the information provided into chemical exposures using an exposure checklist. A code sheet was filled out for each job in a subject's history. An occupational exposure was considered to be any kind of contact found at a higher level in the workplace than in the general environment. To indicate the presence of an exposure, the chemical coder circled that code on the checklist and provided semiquantitative evaluations of concentration of exposure, frequency (proportion of working day exposed), and a measure of confidence in the evaluation. Since much of the estimation involved jobs that are no longer performed today, there was considerable detective work in attempting to describe such chemical environments. Several sources of information were used: the interviewees themselves, bibliographic material, and consultants.

The limiting factor in this kind of research is the paucity of information on exposures in different occupations and industries. It would be useful to have information about the particular exposures in each job of each study subject, but it is doubtful that such individualized information exists for a community-based study sample. What we need is more modest, namely, some generic, information about the type of occupation and industry in which the subject worked, so that exposure circumstances can be inferred with some degree of confidence. For some occupations, the expert coders can draw upon a reasonably extensive technical literature to infer the exposures of a worker in a particular job in a specific era. But for most occupations and industries, the information base is very thin. Few workplaces have ever been subject to industrial hygiene measurements and the ones that have are not representative. In workplaces where exposure measurements have been carried out, only a few substances have been measured. And those measurements that were carried out were only carried out for compliance purposes, not to obtain representative information about exposures at any point in time (*28*). Thus, even if we invest in an exposure assessment study today using as expensive an approach as we used, little basic information is available on substances to which workers are being exposed or have been exposed in the past.

To lay the groundwork for epidemiology in this field, we need large-scale industrial hygiene surveys to provide representative characterizations of occupational environments (*28*). These surveys should be jointly organized by epidemiologists and industrial hygienists. Unfortunately, even if such surveys were carried out today, they would be only marginally useful for current epidemiological studies. Current epidemiological cancer studies focus on exposures that occurred in the past. The results of contemporary hygiene surveys will be most useful in epidemiological studies carried out 10 to 15 years hence. So we must undertake hygiene surveys today that will provide the proper foundation for future epidemiology.

I emphasize the need for hygiene surveys to support epidemiological studies, but this is not the only important use to which such data would be put. A major gap in public health knowledge exists because we cannot adequately quantify and pinpoint how many workers are exposed to various industrial chemicals. Setting priorities and developing programs depends on such elementary information as where and how many people are exposed to toxic agents.

Epidemiological studies of occupational cancer should be based on collaborations between epidemiologists and industrial hygienists, chemists, and engineers. While few would disagree, there are structural impediments that make it difficult for epidemiologists to interact properly with industrial hygienists. Industrial hygienists do not have career paths that would naturally allow them to interact with epidemiologists in universities or in research institutes. In industry-based studies, this is less of a problem, since it often is the company's industrial hygienist who interacts with the epidemiologist. In a community-based study, the industrial hygienist must either be an academic collaborator or an employee in the same institution. One of the few institutions that has an interest in community-based studies and that houses both epidemiologists and industrial hygienists in close quarters is the National Cancer Institute's Occupational Studies Section. In the United States there are a few academic institutions, such as the University of Massachusetts Lowell where such interaction is fostered by the institutional structures, but this is the exception.

Another problem in the relationship between these disciplines is that whereas the logic of epidemiological research usually requires assessment of past environmental exposures without preconceived ideas about what is dangerous, industrial hygienists are trained to think in terms of the present and of substances that have been shown to be toxic. These problems are manageable if recognized and confronted.

Apart from exposure assessment, the second reason for the weakness of most case–control studies is that most have been hopelessly small. Many case–control studies

Table 2. Distribution of the prevalence of exposure to the 294 substances in the Montreal study.

Prevalence,%	Substances, number	Substances, %
<0.1	65	22.1
1–3	73	24.8
3–10	109	37.1
>10	47	16.0
Total	294	100.0

over the past 15 years have had sample sizes in the range of 100 to 500 or even fewer. Because in community-based studies levels of exposure to individual occupational agents are rarely as high as 10% (they are often below 5 or even 1%), studies in this size range are almost useless. Table 2 shows the distribution of lifetime prevalence of occupational exposure to 294 substances in the Montreal study referred to above. These substances were selected because they were thought to be the most prevalent ones. Most of these fell between 1 and 10% in lifetime prevalence.

Table 3 shows the relationships among exposure measurement error, sample size, statistical power, and prevalence of exposure. We compare the statistical power attached to two different sample sizes: 400 cases and 400 controls to represent the size of many studies conducted recently or 1200 cases and 1200 controls to represent what I recommend as a minimum for the future. Comparisons are made under two different assumptions about the potency of the carcinogen (RR = 4 or RR = 2), two different assumptions about lifetime prevalence (10 or 1%), and five different assumptions about the validity of the exposure assessment. The first validity assumption is the unrealizable one of sensitivity = specificity = 100%. The next two represent very good quality assessments such as those based on the expert assessment of the Montreal study. The last two represent the quality of exposure assessment as embodied in conventional approaches such as using job titles as proxies for exposure, or using self-reports of exposure, or using crude job exposure matrices.

Table 3 illustrates the effect of misclassification on study power when the misclassification is of the magnitude of the very good exposure assessments (scenarios II and III) or conventional (scenarios IV and V). If the exposure assessment is perfect (e.g., sensitivity = 100%; specificity = 100%), then a study of 400 cases and 400 controls would be adequate to detect a true relative risk of 4, even at an exposure prevalence of 1%, or a true relative risk of 2 at an exposure prevalence of 10%. But it would not likely detect a true relative risk of 2 at an exposure prevalence of 1%. Under scenarios II through V the potential of such a study size to detect hazards becomes more and more remote, though it remains quite robust if both relative risk and the prevalence are high. With a study size of 2×1200, prospects are much better to detect a 4-fold excess risk and are not bad to detect a 2-fold excess risk. If the exposure assessment is mediocre, it is unlikely that any but the high-risk, high-prevalence exposures can be detected.

The two points I want to emphasize are illustrated in Table 3: *a*) we must improve the quality of exposure assessment, and *b*) we need much bigger sample sizes. The sample size problem is generally solvable, although it may require that an investigator expand the geographic base of the study or extend it in time, and it certainly involves greater costs. The exposure assessment problem is more complex.

Biomarkers in Occupational Cancer Epidemiology

It may seem anachronistic to write an article in the 1990s about the future of cancer research and fail to mention the advances in molecular biology that are widely being touted as the portals to a new way of conducting epidemiological research (*29*). These advances are sometimes called *molecular epidemiology*, a term to avoid because it inappropriately shifts the focus from the object of epidemiological research (a disease and/or a risk factor) to the tools used to accomplish the research.

The most plausible contributions of molecular biology to occupational cancer epidemiology are *a*) to provide an early marker of cancer onset so the lengthy empirical induction period can be shortened, *b*) to provide a marker of exposure to the carcinogen(s), and *c*) to provide a marker of susceptibility to cancer. While each of these contributions is theoretically useful, there are serious limitations to their potential value. Even if early markers of neoplasia are developed, their use in epidemiological studies instead of conventional cancer diagnosis would only be warranted if they substantially shortened the time interval between exposure and onset of neoplasia and if they were used on a universal screening basis; otherwise cancer samples would be biased. This is already a problem in prostate cancer studies because of the increasing nonuniversal, nonrepresentative access to PSA as a screening test. Furthermore, to the extent that it is effective as an early marker of prostate cancer, PSA may reduce 15- to 30-year induction periods by only a few years. Nor are there any other biomarkers on the horizon that would satisfy the conditions needed to make them useful for our purpose. The second plausible contribution of biomarkers, namely markers of exposure, shows somewhat more promise, with candidates such as DNA adducts of various chemicals. But time is also a serious limitation here, since there is no evidence that currently measured DNA adducts have any relationship to occupational exposures experienced many years earlier (*17*). This is in contrast to the research situation on the viral etiology of cancer in which the etiologic agent seems to leave a telltale sign of its presence long ago (*30*). The third plausible contribution of biomarkers, namely markers of susceptibility, has shown some signs of success, but in a sense it is the least interesting from a public health point of view. That is, even if we could earmark a susceptible part of the population, how would that information be used? It is much more acceptable to conceive of public health action geared to the elimination of environmental hazards

Table 3. Power to detect risk under five scenarios of validity of exposure assessment, by two levels of relative risk and two levels of prevalence of exposure, for two sample sizes.

	True		Validity scenarios				
			I	II	III	IV	V
Sample size[a]	Relative risk	Prevalence of exposure, %	Sensitivity = Specificity =	100% 100%	80% 99%	70% 95%	60% 90%	50% 80%
400	4	10		1.00	1.00	1.00	0.98	0.64
	4	1		0.84	0.61	0.28	0.16	0.09
	2	10		0.96	0.88	0.70	0.46	0.20
	2	1		0.31	0.19	0.10	0.08	0.06
1200	4	10		1.00	1.00	1.00	1.00	0.97
	4	1		1.00	0.95	0.58	0.30	0.13
	2	10		1.00	1.00	0.98	0.85	0.40
	2	1		0.63	0.37	0.16	0.10	0.07

[a]Sample sizes represent the number of cases and the number of controls.

than to the selective separation between genetically susceptible individuals and environmental hazards. Since it is likely that susceptibility is agent-specific, it seems that we will still have to identify carcinogens to identify phenotypes or genotypes that carry excess risk. The example of the role of *N*-acetylation as a mediating host factor in benzidine-related bladder carcinogenesis is instructive (*31*). While some studies in Europe suggested that the effect of benzidine on bladder cancer was present only among slow acetylators, the largest study yet, a Chinese study, exhibited the exact opposite pattern. Rather than clarifying the role of benzidine in bladder carcinogenesis, this research has in aggregate left the field somewhat murkier and more open to misinterpretation than it otherwise would be.

My purpose is not to deny the potential value that the use of biomarkers might have in understanding the mechanisms of carcinogenesis. We must, of course, be open-minded about these prospects and welcome any approach to exposure assessment, early detection of disease, or identification of high-susceptibility individuals that would facilitate research into the environmental causes of cancer. But it would be a grave error to succumb to the lure of technology and be side-tracked from the primary task of epidemiology, which is identifying risk factors so they can be eliminated or reduced in the interest of disease prevention. While the techniques of molecular biology have not yet proven themselves to be useful in identifying and eliminating occupational carcinogens, the more conventional epidemiological methods, described above, have proven themselves, and if bolstered by the recommendations made herein, can continue to provide the cornerstone of required research.

Conclusion

To summarize, I make the following points:

- Occupational cancer research remains an important issue in our society. We need community-based studies of occupational cancer to detect previously undiscovered occupational carcinogens, and industry-based studies to characterize and refine the associations found in community-based studies. Because they have been relatively neglected in the past, there is a greater need for community-based studies.
- The two major obstacles to quality research have been inadequate exposure assessment and insufficient sample sizes. Many past studies have suffered from one or both of these flaws and consequently have produced unreliable, mainly negative, results. Research should only be supported if it entails adequate exposure assessment and sufficient sample sizes.
- Quality exposure assessment requires the participation of trained experts (industrial hygienists, chemists, etc.) and requires an adequate information base on the exposures that occur in different workplaces.
- We need structures and career paths that facilitate the participation of exposure experts in epidemiological research.
- We need active large-scale industrial hygiene surveys to better characterize the U.S. workplace. These studies will be useful for epidemiological studies and for public health purposes.
- To be useful, community-based case–control studies should be much larger than in the past, with 1000 as the minimum number of cases and controls.

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