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Harvey Checkoway

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Methodological Considerations Relevant to Epidemiology Studies of Silica and Lung Cancer

Harvey Checkoway

Department of Environmental Health, University of Washington, Box 357234, Seattle, Washington 98195

The relation between occupational silica exposure and lung cancer has been addressed in numerous epidemiologic studies, especially during the past decade. Despite the considerable attention given to this topic, no scientific consensus has been reached regarding the potential carcinogenicity of silica in humans. The principal reasons for uncertainty are inadequacies of exposure assessment and incomplete control of confounding from other workplace agents and from cigarette smoking. This article is a review of the biases that have hindered the interpretation of epidemiologic research on silica and lung cancer. Exposure assessment is discussed in terms of the completeness and validity of exposure quantification for silica and other potentially relevant workplace exposures. The advantages and limitations of inferring exposure levels from radiographic evidence of pulmonary fibrosis are also considered. Confounding bias, from cigarette smoking and workplace exposures other than silica (e.g., radon), is examined in reference to the magnitude of effect estimate distortion that is likely to occur in epidemiologic research. Emphasis is also placed on the need to distinguish confounding from effect modification, manifested as synergy between silica and other exposures. Published studies of South African gold miners, Vermont granite workers, and California diatomaceous earth workers are used to illustrate these methodological issues. CHECKOWAY, H.: METHODOLOGICAL CONSIDERATIONS RELEVANT TO EPIDEMIOLOGY STUDIES OF SILICA AND LUNG CANCER. APPL. OCCUP. ENVIRON. HYG. 10(12):1049–1055; 1995.

Considerable attention has been given to a possible causal association between crystalline silica exposure and lung cancer.[1] The experimental and epidemiological literature bearing on the potential carcinogenicity of silica continues to grow, although this remains a controversial topic.[2–4] McDonald's[5] comprehensive review of recent epidemiologic literature underscores some important areas of uncertainty of current understanding, including: potential selection and confounding biases in cohort studies composed of compensated silicosis patients; the lack of adequate control of confounding from cigarette smoking and from cooccurring occupational exposures; and differences in fibrogenic and perhaps carcinogenic potency that may exist among the various silica polymorphs.

This article offers a general overview of some important methodological considerations that affect the interpretation of the epidemiologic findings. In particular, three general issues will be discussed: (1) the quality of exposure assessment; (2) control of confounding from other workplace agents and from cigarette smoking; and (3) pulmonary fibrosis as an indicator of exposure or as a lung cancer precursor. These issues will be illustrated with data from three published studies of Vermont granite workers,[6] South African gold miners,[7] and California diatomaceous earth mining and processing workers.[8]

Study Descriptions and Main Findings

The studies of Vermont granite workers, South African gold miners, and California diatomaceous earth workers were selected for review because each illustrates one or more of the significant methodological shortcomings of the silica and lung cancer literature. Brief summaries of study design and results, exposure assessment methods, and control of confounding follow.

Vermont Granite Workers Study

The study of Vermont granite shed and quarry workers[6] was a historical follow-up of 5414 workers employed between 1950 and 1982. Exposure to quartz was of principal concern. Exposure concentrations were significantly reduced after 1940 as a result of improved dust control. Apparently there were inadequate occupational hygiene measurement data for a direct quantitation of exposures. Instead, work assignment (shed or quarry), employment duration, and time period of employment were used as surrogate indicators of silica doses. Information on cigarette smoking was obtained from medical records or from proxy respondents (relatives or co-workers), and was only reported for a subset of the lung cancer cases (84 of 118).

Predictably, large mortality excesses of silicosis [standardized mortality ratio (SMR) = 6.36] and tuberculosis (SMR = 5.86) were found in the cohort when comparisons were made against national rates. A small relative excess of lung cancer mortality (SMR = 1.16) was observed for the entire cohort. Stratification by employment type revealed a lung cancer excess among granite shed (SMR = 1.27) but not among quarry workers (SMR = 0.82). A strong differential in silicosis mortality risk was also observed by employment type, with a much larger effect seen for shed workers (SMR = 7.73) than quarry workers (SMR = 1.95). Further analyses were performed according to date of hire, a surrogate for exposure intensity, and duration of employment. The largest relative lung cancer excess was detected for long-term (≥30 years) shed workers employed before 1940, during time periods ≥40 since first exposure (SMR = 1.81). The silicosis results were interpreted

by the investigators as being related to heavy exposures received before dust reductions in 1940. However, the lung cancer findings were regarded as equivocal because of potential confounding by cigarette smoking; all of the cases for whom smoking data were available were classified as having been smokers. Data relating to silicosis for a subset of lung cancer deaths indicated a higher prevalence of radiographically determined fibrosis in those hired before 1930 (68%) than in cases hired between 1930 and 1939 (26%). The difference in silicosis prevalence was interpreted as a probable reflection of the generally more intense exposures that occurred before 1930.

South African Gold Miners Study

The second study considered was a case–control study of lung cancer nested within a cohort of South African gold miners.[7] Cases and controls were former white workers who had spent at least 80 percent of their mining employment in silica-containing mines, and had autopsy material available for pathological assessment of silicosis. The time interval during which cases and controls died is not stated explicitly in the article, although it might be inferred from information provided that this was 1975 to the late 1980s, excluding 1979 through 1983, during which cases and controls were identified for a previous study in this work force.[9] A minimum of 1000 shifts in a silica-exposed environment were required of both cases and controls for inclusion into the study. Miners who had worked for more than 1 year in an asbestos mine or as boilermakers were excluded. Cumulative exposure was estimated by combining dust measurement data made during a 1966 survey[10] with information on the numbers of shifts worked. Classification of the presence and severity of silicosis of the parenchyma, pleura, and hilar glands was accomplished using data from postmortem pathological examinations. Data on cases' and controls' smoking habits, obtained from the files of an occupational disease medical bureau, included details on amounts and durations of cigarettes or tobacco equivalents (pipe and cigar) smoked.

The study results were largely negative, as neither silicosis nor cumulative exposure was consistently related to lung cancer. The requirement that both cases and controls had a minimum number of exposed shifts may have diminished the likelihood of observing a difference of cumulative exposure (i.e., overmatching), although there were no evident differences with regard to exposure intensity. There were, however, several isolated findings suggestive of modest associations. One of these was a positive, yet irregular, pattern of dose-response for lung cancer among workers with pleural silicosis (obtained by rearranging data from Table 5 in the published report).

California Diatomaceous Earth Workers Study

Diatomaceous earth is the mineral derived from the deposited skeletal remains of diatoms. The main commercial uses of diatomaceous earth are as a filtration aid for water, foods, and beverages, and as filler in construction materials, paints, and insulation. Exposures to amorphous (noncrystalline) silica and quartz occur in open-pit mining of the ore, and cristobalite exposure represents the main hazard when the raw material is calcined in a kiln. The study evaluated the mortality experience during the period from 1942 to 1987 of approximately 3000 workers who had been employed for at least 12 months cumulative service at one of two California plants.[8] The main study cohort included 2570 white males (533 Hispanic and 2017 non-Hispanic). This total excludes a small group of workers (104) known to have worked in areas where asbestos was mixed with diatomaceous earth. Dose–response analyses were performed with respect to two exposure indices: duration of employment in dust-exposed jobs, and estimated cumulative exposure to crystalline silica. The crystalline silica index was a scaled exposure metric that combined information on exposure intensity differences between jobs and over time, percentages of crystalline silica in the various product mixes, plant production records, and secular patterns of the use and effectiveness of respirators. The investigators reported that the available occupational hygiene data for dust were too incomplete for pre-1950 years of employment for direct quantitation of cumulative exposures. Information on cigarette smoking, which had been obtained since the early 1960s from the industry's medical surveillance program, permitted a distinction between ever and never smokers for 43 percent of the cohort.

In comparison with rates for U.S. white males, the main cohort of diatomaceous earth workers experienced excesses of lung cancer (SMR = 1.43) and nonmalignant respiratory diseases (NMRD) other than pneumonia and infectious diseases (SMR = 2.59). Reasonably strong relative risk gradients for lung cancer and NMRD were detected from internal analyses with respect to duration of dust exposure and the crystalline silica index. The relative risks, allowing for a 15-year latency, comparing the highest and lowest categories of crystalline silica exposure, were 2.74 for lung cancer and 2.71 for NMRD. However, the lung cancer relative risk gradient with respect to the crystalline silica index was not materially different from the trend observed for the less specific exposure variable, duration of dust exposure. Several approaches were used to assess possible confounding by smoking, and in no instance did smoking appear to be a plausible explanation for the observed effect on lung cancer risk.

Sources of Bias

Bias in epidemiologic research is often categorized into three main types: selection bias, information bias, and confounding. This categorization of bias is not mutually exclusive, as a specific manifestation of bias may share properties of more than one type. Selection biases, and hence related confounding, are most prominent in the follow-up studies of compensated silicosis patients.[5] Selection bias may also arise from the process of cohort definition. For example, occupational cohorts typically are defined as workers actively employed as of some date or during some specified time interval. Such cohorts therefore represent "survivor" populations that necessarily exclude workers who previously had left the industry, possibly because of exposure-induced impaired health. In such instances it would be expected that subsequent mortality risks among these survivors would be lower than among all workers who might have been enumerated had sufficient data been available. For example, the Vermont granite workers cohort[6] was composed of persons employed during the period from 1950 to 1982, and thus conceivably may have underestimated occupational disease risks due to an inability to enumerate workers whose periods of employment ended during earlier years when

silica exposures were probably higher. The problem of studying survivor cohorts is by no means unique to studies of silica and lung cancer.

The more common forms of epidemiologic bias that come into play in studies of silica and lung cancer are information bias, in the form of exposure misclassification, and confounding. Before considering these topics in the context of the silica and lung cancer literature, it may be useful to review briefly some general aspects of bias.

It is well known that errors in exposure assessment, due to instrument error, incorrect imputation of exposures when data are missing, or errors in data extrapolation, produce biased study results. Unless there are indications to the contrary, it is most reasonable to assume that exposure assignment errors occur to the same extent among persons with and without disease; this is customarily referred to as nondifferential exposure misclassification. The effect of nondifferential misclassification is usually to bias the results such that the observed effect is attenuated from the true association, so-called "bias toward the null."[11] It is also possible to have unusual, extreme configurations of misclassification that cause bias to be away from the null.[12]

Confounding variables are factors, either measured or unmeasured in a particular study, that are related to exposure and are independent risk factors for the disease of interest. In most occupational epidemiology studies, potential confounding from age, gender, race, and calendar time period are controlled in the study design or in the data analysis. Confounding from cigarette smoking is of obvious concern in any occupational study of lung cancer. This is clearly justified in view of the major causative role of smoking on lung cancer risk. However, reviewers of epidemiologic research often fail to appreciate two less obvious facets about the likelihood and extent of confounding by smoking. First, as mentioned previously, a confounder must be associated with the exposure under evaluation, in addition to being a cause of disease in its own right. Thus, an observed excess of lung cancer or of any other smoking-related disease in an occupational cohort would only be artifactual if exposed workers smoked more than the nonexposed reference group. At times, disease rate comparisons between occupational cohorts and the general population may suffer from confounding bias because of differences in smoking habits. On the other hand, internal comparisons made within a cohort, such as in dose–response estimation, are more appropriate and should be less prone to confounding. Moreover, there is empirical evidence supporting the lack of association between smoking and levels of occupational exposures.[13,14]

The second point regarding confounding is that it should not be confused with effect modification, which is the variation of an exposure's effect on disease risk across categories of a third variable.[15] To illustrate, consider the data in Table 1 from a hypothetical cohort study of disease risk in relation to an exposure variable and smoking. The right-most columns ("Total") present crude data without regard to smoking status, whereas the left and center columns display risks related to exposure among smokers and nonsmokers, respectively. It is evident that smoking is a confounder in this example, as smoking is related to exposure (75% among exposed are smokers versus 25% in nonexposed), and that smoking is an independent risk factor for disease (among the nonexposed the relative risk associated with smoking is 5.0). Thus, the crude relative risk estimated for the effect of exposure (3.88), ignoring confounding by smoking, is exaggerated. It is also evident from these fictitious data that the exposure variable is not in its own right a risk factor for disease; the relative risk associated with exposure among nonsmokers is 1.00. However, this does not mean that exposure can be regarded as completely unrelated to risk, as there is a clear effect (relative risk of 2.00) among smokers. Thus, the proper interpretation of these data is that the exposure under study is not an independent risk factor for disease, but it does confer an elevated risk among smokers. This is an example of effect modification in which the effect modifier, in this case smoking, alters the effect of exposure. Recognition of the possibility of effect modification, and distinguishing it from confounding, are important considerations in the interpretation of the epidemiologic literature on silica and lung cancer. For example, a statement such as "all lung cancer cases were known to be smokers" does not by itself rule out the possibility that silica may have contributed to risk of lung cancer, but only among smokers. Smoking may, in fact, be a necessary precondition for the carcinogenicity of many occupational and environmental agents.

TABLE 1. Hypothetical Example Illustrating Confounding and Effect Modification by Smoking

	Smokers		Nonsmokers		Total	
	Cases	Workers	Cases	Workers	Cases	Workers
Exposed	30	3000	1	1000	31	4000
Nonexposed	5	1000	3	3000	8	4000
Relative Risk		2.00		1.00		3.88

Proportion of smokers among exposed = $^{3000}/_{4000} = 0.75$.
Proportion of smokers among nonexposed = $^{1000}/_{4000} = 0.25$.
Relative risk due to smoking (among nonexposed) = $^{5/1000}/_{3/3000} = 5.0$.

Exposure Assessment

In terms of methods and scope, the exposure assessments performed in the three studies reviewed are fairly representative of those in many epidemiologic studies of silica and lung cancer. The studies of Vermont granite workers and California diatomaceous earth workers were both limited by missing exposure measurement data spanning all relevant time periods, especially during the earliest years of operation when exposure levels were highest. Unfortunately, data limitations of this type are the rule rather than the exception in historical occupational cohort and case–control studies.

Exposure assessment in the three studies varied, depending on the types of data available (Table 2). Of the three, the South African gold miners study included the most direct quantitation of cumulative exposure, although the analysis involved categorization by quartiles of cumulative exposure. A more statistically rigorous quantification of the dose–response relation for lung cancer among South African gold miners appears in a subsequent article,[16] which also provides a more explicit description of the methods of exposure assessment. Dust exposures in the range of 0.05 to 0.84 mg/m^3 were detected in the mines, and these levels were assumed to have remained constant since the 1930s. The exposure values were determined from an occupational hygiene survey conducted in

TABLE 2. Exposure Assessment in Three Studies of Occupational Silica Exposure and Lung Cancer

Study (Reference)	Exposure Data
Vermont granite workers[6]	Duration of employment in shed or quarry; year of hire
South African gold miners[7]	Cumulative dust index (shifts × weighting factor); chest radiographs
California diatomaceous earth workers[8]	Semiquantitative index of crystalline silica exposure

1966 [10]; thus, one may question whether the assumption of unchanged exposure levels is supportable. In the diatomaceous earth workers cohort study, the investigators were unwilling to generate direct quantitative exposure estimates, citing missing data for early years of employment and uncertainties of converting between exposure units (mppcf to milligrams/cubic meter) as the principal difficulties. Exposure classification in the Vermont granite study relied on even simpler parameters: time period and duration of employment, and job assignment.

Differences in the types of available data for exposure assessment in the three studies restrict comparisons of validity. The assessment used in the Vermont granite study was the simplest, and in one respect, namely the lack of measurement error, might be considered the most valid. This is because date of hire, work assignment, and employment duration are undoubtedly less error prone than the exposure metrics used in the gold miners and diatomaceous earth workers studies. The assessments in the latter two studies involved various assumptions regarding temporal changes (or the lack thereof) in exposure intensity, and in the case of the diatomaceous earth study, the percentages of crystalline silica in the dust and the effectiveness of respirator use. The possibility that assumptions incorporated into exposure modeling may have introduced misclassification is illustrated with data from the diatomaceous earth workers study in which the relative risk trend for lung cancer mortality with respect to duration of dust exposure, allowing for a 15-year latency, was slightly stronger than the corresponding trend for the constructed crystalline silica index. The prior expectation was that a stronger association would be observed for the most specific exposure metric, the crystalline silica index, provided that an association does indeed exist. An alternative, yet speculative, explanation is that other components of diatomaceous earth dust (e.g., amorphous silica) may be etiologically relevant.

Exposure misclassification may have biased the South African gold miner study results, although the cumulative exposure index was highly predictive of all three forms of silicosis. Relating estimates of silica exposure with silicosis is an indirect, practical method to determine exposure assessment validity.[17]

There is little debate about the importance of a valid and, where possible, quantitative exposure assessment to examine dose–response associations. The relative bias caused by misclassification will be most pronounced in studies where the anticipated effects are small, as the results can change from slightly positive to null. Masking or seriously attenuating true effects of large magnitude (e.g., relative risks of 3 or more) is much less likely to occur unless the misclassification is so severe that exposure classification approaches random assignment. These three studies typify some of the problems of data interpretation that arise as a result of incomplete or nonspecific exposure data. Unfortunately, most epidemiologic studies of silica and lung cancer suffer from inadequate exposure information, and the consequence is that causal inference and the ability to determine scientifically based permissible workplace exposure levels are severely limited.

Control of Confounding

Confounding factors in studies of silica and lung cancer that warrant greatest attention are other workplace agents, such as radon in underground mines or polycyclic aromatic hydrocarbons in foundries, and cigarette smoking. Less easily determined confounders include previous and subsequent employment in hazardous industries, diet, and residential exposures (e.g., air pollution). Data on smoking or previous employment can be obtained in some studies, whereas information on nonoccupational risk factors other than smoking is ordinarily not available. Certainly, cigarette smoking is the most prominent nonoccupational candidate confounder. Evidence of an increasing dose–response gradient between silica and lung cancer would strengthen support for a causal relation for obvious reasons. A dose–response trend also would argue against an interpretation that the observed association is merely an artifact of confounding, as there would need to be a direct correspondence between levels of exposure and the confounder for confounding to be the sole or primary explanation of effect. Furthermore, as discussed previously, when considering the possibility of confounding, one should maintain a clear distinction between confounding and effect modification between causative factors.

Control of confounding can be accomplished in a variety of ways. Available data on smoking from the three studies are summarized in Table 3. The most desirable situation occurs when data on the confounder (e.g., smoking) are available for study subjects, in which case separate analyses can be performed by confounder level. Stratified analysis also permits examination of synergistic effects between silica exposure and the potential confounder(s). The level of detail on smoking habits tends to be minimal in most occupational epidemiology studies, and usually only allows broad designations of ever versus never smoked, or categorization of current, former, and never smokers. Information is much less often available for amounts smoked and changes in smoking habits over time, including periods of cessation. The South African gold miner study was an exception in that there was considerable detail on smoking history. Nonetheless, crude stratifications by smoking status are generally adequate to control most confounding.

There are situations where data on confounders are incomplete, but the missing data are not randomly distributed in the cohort by exposure level. For example, in the diatomaceous earth worker study[8] data on smoking were initially recorded during the 1960s, well after the period when exposures were maximal. This created a situation where the evaluation of confounding using the available smoking information was limited to workers employed during the most recent time periods. Nonrandom missing data will also limit the ability to explore effect modification by the presumed confounder.

In the absence of direct information on workers' smoking

TABLE 3. Smoking Data from Three Studies of Occupational Silica Exposure and Lung Cancer

Study (Reference)	Available Smoking Data	Finding
Vermont granite workers[6]	Only for cases (84 out of 118)	All 84 were smokers
South African gold miners[7]	Detailed data for cases and controls	Small excess risks among nonsmokers
California diatomaceous earth workers[8]	Available for 43% of the cohort	Minimal change on exposure-response

habits, one might adopt indirect methods of control, such as hypothetical calculations of the extent of correlation between the confounder and silica exposure that would be needed to produce a spurious excess or exposure–response gradient.[18] Inspection of risks for smoking-related diseases other than lung cancer is another indirect method for assessing the likelihood of bias.[19] In the diatomaceous earth workers study, both methods of indirect assessment of confounding were applied, as well as an inspection of the relation between smoking prevalence and exposure for the subset of workers whose smoking histories could be determined. By all three methods, the extent of potential confounding bias from smoking was judged to be minimal.

Past exposures to radon (and probably arsenic) in the South African gold mines have occurred, although effects of these exposures were not addressed in the case–control study. In contrast, in a recent cohort study among Sardinian metals miners,[20] the relative contributions of measured silica and radon levels were examined, leading to the conclusion that any lung cancer excess was more probably related to radon than silica. In the California diatomaceous earth worker study, potential confounding from the limited use of asbestos in certain work areas was addressed by eliminating from the main study cohort workers with known asbestos exposures. There remains a possibility of some residual confounding from asbestos from undocumented exposures in jobs where asbestos was handled (e.g., kiln insulation and repair). However, it is unlikely that asbestos was sufficiently widespread or so strongly correlated with silica exposure levels as to account for the observed exposure–response trends.

The Role of Pulmonary Fibrosis

Evidence of pulmonary fibrosis, usually detected radiographically, may be a useful marker of exposure in situations where occupational hygiene data are sparse. Fibrotic responses to silica may also increase susceptibility to lung cancer. By definition, silicosis is the characteristic exposure-related disease; thus, detection of pronounced pulmonary fibrosis should identify the most heavily exposed workers. There is considerable interest in determining whether pulmonary fibrosis is an intermediate in lung carcinogenesis. Follow-up studies of lung cancer risks among workers with asbestosis[21] and of patients with idiopathic pulmonary fibrosis[22] suggest that the fibrotic process may contribute uniquely to lung carcinogenesis, although the underlying pathogenetic mechanisms remain to be elucidated.

There are some epidemiologic reasons why caution should be exercised when the presence or severity of silicosis is used as the exposure index. First, in order for silicosis to be a valid marker of exposure, the dose–response relation for silica and silicosis should be similar to that for silica and lung cancer. At a minimum, the two dose–response curves should have the same shape (e.g., linear). As reviewed by Hughes,[23] there is a remarkable paucity of information on the shape and magnitude of the dose–response relation for silicosis, despite its long history as a recognized occupational health hazard. A second requirement is that the initial appearance and subsequent changes in severity of fibrosis should be recorded and treated as a time-related variable, in the same manner that cumulative exposure to silica should be analyzed in dose–response estimation. Maintaining the time dependency of fibrotic occurrence and progression is necessary to minimize misclassification bias. For example, if there is only radiographic information from workers' final X-rays, then all person-time and cases would be assigned to that final category in the analysis. For workers whose final radiographs were positive, this method would create an undercounting of person-time spent in earlier (lower) fibrosis categories, with the net effect being biased disease rate estimates.

Missing or poor-quality radiographs and the logistical difficulties of conducting postemployment radiographic surveys to assess fibrotic progression can further hinder the use of fibrosis data. There can also be difficulties with the interpretation of pathology data on fibrosis. In the South African gold miners study, for example, pathological evidence obtained at autopsy indicated the ultimate extent of fibrosis, although this information could not be used to infer the onset and time course of fibrotic changes.

It would be of great scientific and public health benefit to know whether elevated lung cancer risks occur predominantly or solely among persons with pulmonary fibrosis. However, the anticipated high degree of correlation between cumulative silica exposure and silicosis poses a limitation on distinguishing unique effects of exposure and fibrosis. Very large studies will therefore be required to achieve adequate statistical power to address this issue.

Discussion and Recommendations

The question of whether crystalline silica is a human lung carcinogen has not been fully answered. In fact, in some respects, the question is becoming more rather than less complex as new experimental and epidemiologic knowledge accumulates. Toxicity differences in risk among the various silica polymorphs, the possibility of a potentiating requirement for pulmonary fibrosis, and synergy between silica and other agents are notable areas for further investigation. Experimental research will undoubtedly be valuable for revealing mechanisms of toxicity; however, the most relevant information on risk to humans will come from epidemiologic studies. Perhaps it is only realistic to expect that in the immediate future

epidemiologic approaches for studying the health effects of silica will not differ to any great extent from previous work. Poorly characterized exposures and inadequate data on confounding factors are likely to remain problematic. Nonetheless, some recommendations for improving epidemiologic research can be offered.

Improvements in exposure assessment should be given the highest priority. There will be a need for proportionately greater allocations of resources to exposure assessment in the planning and implementation stages of research. Increasingly creative approaches for addressing problems of missing or sparse data should also be attempted. Exposure modeling techniques can assist in quantifying exposures in some instances, although modeling should be done judiciously to avoid unsupported extrapolations. It will also be informative to explore alternatives to direct quantitation of exposures. One strategy is to conduct sensitivity analyses in which a distribution of plausible dose–response curves is generated as the assumptions concerning exposure levels are varied. Simulating past exposure environments to reconstruct historical exposure levels may also be an option in some instances. Improving exposure assessments for other cooccurring agents that may be confounders or synergistic exposures, particularly in underground mine and foundry environments, will likewise be important.

Ultimately, the most reasonable strategy for epidemiologic analysis will be a sequential approach that begins with evaluations of lung cancer risk related to the simplest and least error-prone exposure indices (e.g., job category, exposure duration) and, where data permit, proceeds to quantitative estimation of dose-response for the most specific dose metrics. However, validation of constructed exposure indices may be difficult to achieve in some studies, even when information on pulmonary fibrosis is available. Serial radiographs will probably be most useful for validation, despite their recognized limitations.

Extended follow-up of previously studied cohorts should be encouraged to increase statistical power for examination of etiologic hypotheses. Moreover, follow-up of occupational cohorts through recent time periods, for which exposure data are most complete, should improve the precision of dose–response estimates.

Greater efforts to obtain valid data on smoking are generally warranted, as this information will be important to control confounding and assess synergistic effects. However, in contemplating whether to seek data on smoking, the investigator should balance the costs against anticipated scientific gains. Data collection costs can be sizable, particularly in studies where questionnaires are administered to workers or next-of-kin. Also, care should be taken to avoid collection of data of dubious quality or from unreliable sources. Alternative approaches for control of confounding, especially indirect methods to estimate plausible ranges of bias, are useful options. Indirect assessments of confounding can be valuable, even in cases where smoking data are available; concordance of results from direct and indirect methods of confounding assessment will reinforce confidence in research validity. Perhaps the most important use of data on smoking and other suspected confounders will be to address questions concerning synergistic effects with silica on lung cancer risk. Determination of joint effects of silica and other agents, and a clarification of the role of fibrosis as an intermediate stage or predisposing factor in carcinogenesis, will have important implications for disease prevention, and should therefore be high priority epidemiologic research objectives.

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