Developments in Occupational Cohort Studies

Harvey Checkoway and Ellen A. Eisen

INTRODUCTION

Many occupational health risks were first identified by case-series reports of apparent disease excesses or clusters, often recognized by clinicians. Discoveries of fatal silicosis among underground metal miners (1) and scrotal cancer in young chimney sweeps (2) provide dramatic examples of the importance of case-series reporting in hazard identification. Causal inferences may also be drawn from reviews of routinely collected population statistics that include data on occupation and cause of death. For example, review of mortality and recorded occupational classification in the United Kingdom by Kennaway and Kennaway (3) in the 1920s and 1930s led to the recognition of the association between mineral oil mists and laryngeal cancer. More generally, however, linking the incidence of disease and injury with occupational exposure requires formal epidemiologic study designs, especially in instances where associations are not exceptionally strong and the health outcomes of concern can be caused by multiple factors. In this presentation, we review recent developments in occupational cohort study design applications, with particular emphasis on the increasingly broadened spectrum of health outcomes that can be investigated.

Application of the cohort study design has been instrumental in the identification of numerous occupational hazards and quantification of associated risks. During the past 50 years, occupational cohort studies have been the cornerstone of investigation of chronic fatal diseases. Landmark studies in the United Kingdom of cancer risks in the gas works (4), dyestuff (5), and asbestosis (6) industries made dual contributions of identifying specific occupational carcinogens and advancing the methodology of the historical cohort design.

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MORTALITY STUDIES

Cancer mortality has been the focus of many occupational cohort studies. Because many forms of cancer have high fatality rates and are recorded relatively accurately on death certificates (10), mortality studies are generally suitable for characterizing cancer risks. Linking occupational cohorts with population-based cancer registries can be a valuable adjunct to mortality studies, especially by improving case identification for nonfatal cancers. Diagnostic confirmation and improv-
ing histopathologic classification of death certificate information may also be achieved with registry data. National cancer registries, available in some of the Scandinavian countries, are particularly valuable in this respect because they provide virtually complete cancer ascertainment throughout life, both during and after periods of employment. Cohort studies of Danish stone industry workers (11), Norwegian aluminum smelter workers (12), and Icelandic stone masons (13) are examples where linkage with national cancer registries was performed effectively. Access to population-based incidence data are particularly important when cancers of concern are rare or have low case fatality rates. Illustrative examples are cohort studies of US firefighters (14) and British Columbia sawmill workers (15). In the firefighter study (14), linkage with a regional cancer registry in Washington State identified 24 incident cases, as compared with only two deaths, from bladder cancer. Soft tissue sarcoma and non-Hodgkin’s lymphoma potentially related to dioxin exposures were of prior interest in the sawmill worker study (15). The number of incident cases for each malignancy, identified by linkage with the British Columbia provincial cancer registry, was nearly double that obtained by mortality follow-up (11 versus 6 for soft tissue sarcoma, 63 versus 36 for non-Hodgkin’s lymphoma). However, sole reliance on regional population-based registry data may result in under-ascertainment of incident cases in situations where sizable proportions of the workforce leave the registration area, as occurred in a study of lung cancer among chrome-exposed aerospace workers (16).

Pooling mortality and exposure data from multiple cohorts is a method of increasing statistical precision, which becomes especially important for examining anticipated small increases in risk or associations with rare diseases. Data pooling entails assemblage of the actual health outcome and exposure datasets from multiple cohorts, which differs from meta-analysis (17) that combines published findings. The strategy of data pooling is exemplified by multicountry pooled studies conducted by the International Agency for Research on Cancer of cohorts exposed to dioxin (18), low-dose ionizing radiation (19), and man-made vitreous fibers (20). Distinct advantages to data pooling, relative to meta-analysis, are the opportunities to increase study size and to apply uniform data analysis protocols. However, the advantage in increased statistical precision gained by cohort pooling may be offset if effects localized to specific cohorts become obscured or attenuated. This is most likely to occur when the amount and specificity of exposure data vary substantially across cohorts. These problems can be mitigated to some extent by reporting cohort-specific results along with the pooled analysis data.

Cohort mortality studies typically generate data for numerous health outcomes, in addition to cancer. Mortality findings for some diseases, notably cardiovascular diseases, are especially difficult to interpret because of the healthy worker effect, which is a bias due to preferential selection of relatively healthy persons for employment in many industries (21). (We will discuss the healthy worker effect bias in greater depth in a later section of this presentation.) Nonetheless, mortality studies focusing on cardiovascular diseases have demonstrated etiologic associations with carbon disulfide (22), lead (23), carbon monoxide (24), shift work (25), and temperature extremes (26). Major neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s disease, have also been difficult to investigate in cohort mortality studies despite their important contributions to total mortality. This difficulty is due largely to the variations of death certificate reporting of neurologic disorders (27) and limited detail on specific diseases available in population-based reference rates for these diseases. This problem is illustrated by a multicountry European cohort mortality study of over 33,000 workers exposed to the neurotoxicant styrene (28). In this study, only 30 of a total 2,196 deaths were attributed to central nervous system diseases as underlying cause, and the cause of death data only permitted separate analyses for epilepsy and a nonspecific grouping of “degenerative nervous system diseases” that did not include Alzheimer’s disease.

MORBIDITY STUDIES

Investigations of occupational exposure effects on morbidity, including disease incidence, symptoms, and impaired physiologic function, have traditionally relied on cross-sectional prevalence studies which are particularly vulnerable to selection biases. Increasingly, the cohort design is being applied to investigate morbidity outcomes and to examine changes in health status in relation to changes in exposure. Table 1 lists some morbidity and physiologic parameters that are frequently studied in occupational populations. Health status and exposure measurement intervals in cohort morbidity studies may be as brief as a single day or segments of a work shift for investigations of acute outcomes. Cohort studies in which repeated measurements are obtained on individuals over time are referred to as longitudinal (or repeated measures) studies.
**TABLE 1. Types of outcomes in cohort morbidity studies**

<table>
<thead>
<tr>
<th>Induction period/reversibility</th>
<th>Event (dichotomous)</th>
<th>Change in status (continuous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (days to months)</td>
<td></td>
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<tr>
<td>Reversible</td>
<td>Asthma attack</td>
<td>Cross-shift function (FEV₁)</td>
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<tr>
<td></td>
<td>Tendonitis</td>
<td>Temporary threshold hearing shift</td>
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<tr>
<td></td>
<td>Contact dermatitis</td>
<td></td>
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<tr>
<td>Irreversible</td>
<td>Asthma diagnosis</td>
<td>Annual change in FEV₁</td>
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<td></td>
<td>Spontaneous abortion</td>
<td></td>
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<tr>
<td></td>
<td>Amputation</td>
<td></td>
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<tr>
<td>Long (years)</td>
<td></td>
<td></td>
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<tr>
<td>Reversible</td>
<td>Chronic bronchitis</td>
<td>Sperm count</td>
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<tr>
<td></td>
<td>Endometriosis</td>
<td>Blood pressure</td>
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<tr>
<td></td>
<td>Carpal tunnel syndrome</td>
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<tr>
<td>Irreversible</td>
<td>Silicosis</td>
<td>Noise-induced hearing loss</td>
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<td></td>
<td>Myocardial infarction</td>
<td>Atherosclerosis</td>
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<td></td>
<td>Infertility</td>
<td>Hepatic fibrosis</td>
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</tbody>
</table>

*FEV₁, forced expiratory volume in 1 second.

**Respiratory outcomes**

Longitudinal studies of change in pulmonary function over time have contributed substantially to the understanding of acute and chronic respiratory effects of occupational exposures to dusts and chemicals. Investigations of respiratory impairment among aluminum industry workers illustrate the strategies and advantages of the cohort design, as contrasted with cross-sectional assessments. Employment in the aluminum industry, especially in smelting operations that entail exposures to fluoride gases and particulates, sulfur dioxide, and coal tar pitch volatile compounds, have long been linked with asthma-like conditions from case-series reports and from numerous prevalence studies (29). A cross-sectional study of Norwegian aluminum smelter workers engaged in potroom work (30) revealed increased prevalences of work-related asthmatic symptoms and reduced lung function associated with long-term employment. In an analysis limited to 1,301 newly hired workers in Norwegian aluminum smelters (31), it was found that the incidence of dyspnea or wheeze, which bore an apparent dose-response relation with fluoride exposure, was greatest during the first year of work and stabilized thereafter. A 6-year follow-up of pulmonary function among this cohort demonstrated that accelerated declines in forced expiratory volume in 1 second were associated with particulate exposures in the potroom and with cigarette smoking (32). Longitudinal studies of symptoms and lung function among aluminum smelter workers conducted in British Columbia (33) and Australia (34) have yielded mixed results with respect to duration of employment and exposure levels. Difficulties interpreting the findings of these studies may be attributed to "survivorship" bias, which is preferential out-migration of the most severely affected workers (35) resulting from the follow-up of cohorts of actively employed workers of varying employment durations, rather than inception cohorts of newly hired workers.

The cohort design is also valuable for assessing the clinical course of disease following reduction or removal from exposure. Cohort designs of physiologic status where workers provide their own reference values are appropriate for such investigations. This design is most effective when baseline (pre-exposure) health outcome assessments are made, which serve as reference for subsequent changes in disease occurrence or physiologic function. For example, follow-up studies of asthmatics in the aluminum industry have been conducted over periods of months to years after exposure cessation. Based on findings from symptom questionnaires and spirometry measurements with and without bronchoprovocation challenge testing, evidence has emerged that symptoms and bronchial hyperreactivity tend to diminish with duration of time since exposure, but respiratory impairment may persist in some instances (36–39).

Acute, and possibly reversible, toxic effects may become manifest during a single day or shorter exposure interval. For example, Betchley et al. (40) detected pronounced cross-shift decrements of lung function, accompanied by increased symptom reporting, among forest firefighters. In contrast, considerably weaker associations were found from comparisons made between exposed and nonexposed seasons, suggesting that these respiratory outcomes may be reversible. Cross-shift studies, however, may not be adequate for investigating toxic effects related to short-term peak exposures. Instead, more frequent de-
terminations of exposure levels and health effects made throughout the workday are required (41). This approach has been used in a study of upper respiratory irritation symptoms among workers exposed to sodium borate (42), where symptom status and peak expiratory flow rates were measured hourly throughout the work shift for 4 consecutive days. Other examples include studies of respiratory symptoms and pulmonary peak expiratory flow rates measured in formaldehyde-exposed laboratory personnel (43), and serial peak expiratory flow rates among workers exposed to fuel oil ash (44).

The availability of a nonexposed reference group in longitudinal morbidity studies is a desirable, although not necessary feature. Since 1981, Christiani et al. (45) have studied pulmonary function and respiratory symptoms prospectively every 5 years in a cohort of Chinese cotton textile workers and a comparison group of silk manufacturing workers. Short-term cohort studies may also include nonexposed reference groups, as was done in a cross-shift study of welding fumes and pulmonary function (46). However, in most instances, identifying and following an appropriate reference cohort from an industry or occupation other than the one of interest can pose severe logistic problems. More common designs are those in which exposed subjects serve as their own referents, exposed and nonexposed groups are defined from within the same industry, or comparisons are made with expected values of lung function, specific for age, height, race, and gender, derived from volunteer populations (47).

Reproductive and developmental outcomes

Exposures to numerous occupational agents, including ionizing radiation, lead, mercury, pesticides, anesthetic gases, and organic solvents, have been linked with reduced fertility and adverse reproductive and developmental outcomes (48). Owing to the difficulties of monitoring and detecting common adverse outcomes, such as spontaneous abortion (49), and the rarity of many events of interest (e.g., specific congenital malformations), hospital- and community-based case-control studies have been more commonly applied than cohort studies to investigate occupational associations. Nonetheless, the increasing size of the female workforce, technologic improvements in exposure and health outcome measurement, and the recognition of the potential importance of male-mediated developmental risks (50) have provided rationale for prospective and historical cohort studies.

Recent cohort studies focusing on female workers include investigations of spontaneous abortions, low birth weight, congenital malformations, and reduced fertility among telephone operators who worked with video display terminals (51), nurses exposed to anti-neoplastic drugs (52), dental assistants exposed to nitrous oxide (53) and mercury vapor (54), cosmetologists (55), and workers in the semiconductor industry (56, 57). Data collection in these studies relied primarily on questionnaires eliciting reproductive history data, which in some instances could be corroborated by medical or vital statistics records (51). Two companion studies of women workers in the semiconductor fabrication industry (56, 57) illustrate the methodological and procedural differences between historical and prospective studies. In the historical cohort study (56), reproductive and occupational exposure information was obtained from 891 current and former workers who had had recent pregnancies; elevated risks for spontaneous abortion were observed for exposures to glycol ethers and fluoride compounds. The prospective study (57) involved urine measurements of human chorionic gonadotropin to detect early pregnancy loss among 152 fabrication and 251 nonfabrication reference workers, and contemporaneous assessment of hazardous exposures based on job assignment. Very high rates of spontaneous abortion were found in both groups: 63 percent in fabrication workers and 46 percent in nonfabrication workers. An effect of glycol ethers was inferred from the observation of pregnancy loss in all four women exposed to these chemicals (57).

Determinations of reproductive hazards associated with exposures to male workers can involve obtaining reproductive histories of partners, although reproductive outcome information obtained from men is subject to error (58). Historical cohort studies of male workers that relied on questionnaire responses suggest possible increased risks for reduced fertility in welders (59), spontaneous abortion among wives of copper smelter workers (60), and stillbirth in wives of lead smelter workers (61). Linkage of cohort members with vital statistics records or population-based birth outcome registries, such as for birth defects, is an alternative approach that avoids bias from self-reported data. This method was applied in an historical study of multiple categories of birth outcome in offspring of male sawmill workers in British Columbia (62); evidence was found for dose-response associations of paternal exposures to chlorophenates with congenital defects of the eyes and neural tube.

EXPOSURE ASSESSMENT

Increasingly, epidemiologists have come to appreciate that identifying occupational hazards and estimating risks quantitatively are heavily dependent on the ability to characterize workplace exposures by type and amount. In situations of profound risks, relatively crude exposure indices, such as ever employed or...
duration of employment in a particular industry, have been sufficient for depicting qualitative associations between occupational exposures and disease. However, detailed exposure assessments spanning cohort members’ periods of employment are necessary for quantitative dose-response estimation, which ultimately forms the basis for occupational exposure standards and more broadly applied risk assessments. Examples of exposure assessment applications for mortality and morbidity studies are summarized in table 2.

Reconstruction of historical exposures is necessary for dose estimation in most cohort mortality and cancer incidence studies, as well as in retrospective cohort morbidity studies of other chronic conditions. The requisite data and procedures for historical exposure assessment have been summarized in recent reviews (63, 64). The end product of historical exposure reconstruction is a matrix of exposure levels cross-classified by job and time period that can be linked to workers’ job assignment records (63). Ideally, exposure levels are expressed on a quantitative scale, although the underlying exposure monitoring data may only support ordinal categorization of jobs. Classification of jobs according to process division or similarities of tasks and presumed exposures will be the extent of exposure assessment when exposure data are not adequate for quantitation. For instance, grouping jobs by location in steel industry coke ovens in studies in the United States (65) and China (66) was instrumental in linking lung cancer risk to jobs with the highest emissions levels. Notable examples in which quantitative exposure assessments have advanced knowledge about occupational carcinogens include cohort mortality studies of workers exposed to benzene (67, 68), arsenic (69), machining fluids (70), asbestos (71, 72), and crystalline silica (73, 74).

For several reasons, historical exposure reconstruction probably poses the greatest research challenge in a cohort study. With some exceptions (such as in the nuclear industry), workers’ personal exposures are not monitored throughout their periods of employment. In industrialized countries, routine monitoring, even for known toxic agents, has only been widely adopted in the past 20–30 years (64). Moreover, in most industries, occupational hygiene measurements are made for purposes other than research, often to test whether workplace exposure concentrations are in compliance with governmentally-mandated guidelines. In developing countries, exposure monitoring is both more recent and sporadic (75). As a result, in many instances exposure data spanning relevant years of employment may be incomplete, and available data may not be appropriately representative of workers’ actual exposures. Limited or absent information on changes in process technology, use of protective equipment, and exposure measurement techniques are further complications.

It should be realized that many, if not most, industrial settings have complex environments, comprised of various mixtures of chemicals and physical agents, that may undergo substantial qualitative and quantitative changes over time. Thus, whereas an epidemiologic study may focus on a particular agent (e.g., benzene), exposure data limitations may only permit assessments for a broad category of agents (e.g., sol-

<table>
<thead>
<tr>
<th>Mortality studies</th>
<th>Country</th>
<th>Industry</th>
<th>Health outcome</th>
<th>Agent</th>
<th>Exposure metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 1988 (66)</td>
<td>China</td>
<td>Steel</td>
<td>Lung cancer</td>
<td>Coke oven</td>
<td>Job location, duration employed</td>
</tr>
<tr>
<td>Rinsky et al., 1987 (67)</td>
<td>United States</td>
<td>Rubber</td>
<td>Leukemia</td>
<td>Benzene</td>
<td>Parts per million x years</td>
</tr>
<tr>
<td>Tolbert et al., 1992 (70)</td>
<td>United States</td>
<td>Automobile</td>
<td>Multiple cancer sites</td>
<td>Machining fluids</td>
<td>Years exposed</td>
</tr>
<tr>
<td>Dement et al., 1994 (72)</td>
<td>United States</td>
<td>Asbestos, textile</td>
<td>Lung cancer, asbestosis</td>
<td>Asbestos</td>
<td>Fibers per ml x years</td>
</tr>
<tr>
<td>Ott and Zober, 1996 (67)</td>
<td>Germany</td>
<td>Trichlorophenol</td>
<td>Multiple cancer sites</td>
<td>2,2,7,8-TCDD*</td>
<td>µg/kg body weight</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morbidity studies</th>
<th>Country</th>
<th>Industry</th>
<th>Health outcome</th>
<th>Agent</th>
<th>Exposure metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seppalainen et al., 1993 (64)</td>
<td>Finland</td>
<td>Lead battery</td>
<td>Nerve conduction velocity</td>
<td>Lead</td>
<td>µg/dl blood</td>
</tr>
<tr>
<td>Eisen et al., 1991 (42)</td>
<td>United States</td>
<td>Borate</td>
<td>Respiratory symptoms</td>
<td>Sodium borate</td>
<td>Hourly average mg/m³</td>
</tr>
<tr>
<td>Dimich-Ward et al., 1996 (62)</td>
<td>Canada</td>
<td>Sawmill</td>
<td>Adverse reproductive outcomes</td>
<td>Chlorophenates</td>
<td>Cumulative exposure hours prior to conception, pregnancy</td>
</tr>
</tbody>
</table>

*TCDD, tetrachlorodibenzo-p-dioxin.
vents). Determinations of mutual confounding or interaction among multiple agents within a workplace is a desirable goal in certain cases, but can be complicated when detailed exposure data are limited to a small subset of agents. For example, difficulty isolating specific causative factors was encountered in a multiplant cohort study that was designed to estimate quantitative dose-response relations between formaldehyde and lung cancer, but uncovered stronger qualitative associations with several other chemicals (76).

The features of exposure assessment in occupational cohort studies are largely determined by the health outcomes of interest. Additionally, the presumed nature of the toxic effect (acute, subacute, or chronic) will guide the choice of type of exposure data sought. For example, annual job-specific exposure estimates were cumulated and incorporated into analyses of lung function decrements, spanning years to decades, in granite shed workers (77) and coal miners (78). In contrast, the daily time-weighted average of machining fluids was used in an investigation of cross-shift change of pulmonary function (79), whereas real-time monitoring throughout the work shift was performed to provide continuous estimates of sodium borate dust exposure concentrations in a study of acute episodes of respiratory symptoms (42).

Clinical and biologic monitoring data can be used to infer exposures in situations where workplace environmental data are not available. Radiographic evidence of pulmonary fibrosis, an established consequence of high-dose exposures to some mineral dusts, has been used to identify heavily exposed workers in cohort studies of cancer risks associated with asbestos (80, 81) and silica (82, 83). Tissue concentrations of various toxicants may also be used to estimate current and historical exposures. Blood lead concentration is a convenient marker of recent exposure, and has been used in prospective and historical cohort studies (61, 84). Biomonitoring data can also assist in characterizing exposure profiles when there are exposures to multiple, related agents. For example, blood levels of specific dioxin congeners, combined with data on job assignments and clinical evidence of chloracne, were included in the historical exposure reconstruction supporting mortality and morbidity follow-up studies of workers from a German trichlorophenol manufacturing plant (85–87).

**STUDY BIASES**

Occupational cohort studies are vulnerable to the same types of biases that threaten validity throughout epidemiologic research. Of the many forms and manifestations of study bias, the healthy worker effect stands out as most characteristic of occupational cohort studies. Accordingly, we will devote most attention to healthy worker effect bias. Pertinent aspects of information bias, specifically exposure misclassification, and control of confounding will also be reviewed.

**Healthy worker effect**

Reduced mortality risks compared with external reference populations have been observed in numerous occupational cohort mortality studies (88–90). The healthy worker effect typically is more pronounced for mortality from cardiovascular and other nonmalignant diseases than for cancer (91, 92). There are two widely recognized sources of the healthy worker effect in cohort mortality studies: the initial selection of relatively healthy individuals at time of hire and the survival of the healthiest individuals that permits long-term employment (21). The second aspect, referred to as the healthy worker survivor effect (93), has been attributed to the tendency for the least healthy workers to leave the active workforce. Leaving employment may occur either nondifferentially or differentially with respect to exposure, and may result in biased exposure-response estimates depending on the relation between survival and exposure. A third source of healthy worker effect bias is the tendency for the least healthy workers to transfer from higher to lower exposed jobs within the same workplace, when the exposure is recognized as a contributor to impaired health (94).

As has been pointed out by Hernberg (95) and others (96, 97), the healthy worker effect is due, in part, to the inappropriate choice of the general population (either national or regional) as a reference. Analyses that involve internal reference comparisons, as in dose-response estimation, can minimize but not fully eliminate healthy worker effect bias (98, 99). For this reason, occupational cohort mortality studies increasingly emphasize internal rate comparisons in evaluating causal associations. However, identifying an internal reference group with low or minimal exposure, but that is otherwise similar to more heavily exposed cohort members with regard to potential confounders, can be problematic when exposure levels tend to be uniform across the workforce or exposure data are not sufficiently accurate to delineate exposure levels. The latter situation can occur when exposures are inferred from job titles that may not validly reflect actual exposure concentrations.

In addition to internal comparisons among cohort subgroups, several strategies have been developed to minimize the healthy worker survivor effect in cohort mortality studies. These include exposure lagging (98), restricting analyses to long-term workers among whom survivorship bias is likely to have diminished.
(100), and stratified analyses that adjust for time since hire (101, 102) or active versus inactive employment status (103). Robins (104) has also formulated an analytic strategy to control explicitly for healthy worker effect survivor bias. A comparison of these approaches based on an analysis of data from a cohort study of arsenic exposure and lung cancer indicated some variability in dose-response estimates, but no single method appeared optimal (105). Control of the healthy worker effect survivor bias is a methodological issue that undoubtedly will be developed further.

Healthy worker effect bias has received increasing attention in cohort morbidity studies (94). Direct evidence for a healthy worker survivor effect due to termination of employment of workers with pulmonary impairment or airways reactivity is provided by longitudinal studies of lung function among grain workers (106), coal miners (107, 108), and workers exposed to silica-containing granite dust (109). Healthy worker effect bias due to selective migration by adversely affected workers from more to less heavily exposed jobs is more difficult to detect. However, this phenomenon has been reported in a prospective cohort study of hand-wrist disorders (110) and in a cross-sectional study, analyzed as a retrospective cohort, of occupational asthma in automobile industry machinists (35).

Unless taken into account, healthy worker effect survivor bias can lead to either grossly underestimated or missed causal associations. Prospective cohort morbidity studies, particularly of newly hired workers (inception cohorts) that include repeated measurements of exposure and health outcome, are clearly the optimal choice for minimizing this form of bias. When prospective follow-up is not feasible, historical cohort studies are the alternative, although biased or incomplete ascertainment of past health history may jeopardize validity.

Exposure misclassification

Individual exposure is nearly always performed without knowledge of health outcome in cohort mortality and cancer incidence studies. Consequently, exposure misclassification can be assumed to be nondifferential, which ordinarily, although not always, will result in missed or underestimated exposure-disease associations (111). However, there will be greater opportunity for differential misclassification in morbidity studies because direct participation by study subjects makes it possible that exposure assessment will be performed more thoroughly for persons who manifest or report adverse health effects. The latter situation is hypothetical, but might arise in a disease screening program that combines disease detection with medical follow-up and exposure reduction. It is often difficult or impossible to validate exposure assessments. An alternative approach, used in a longitudinal study of lung function in coal miners (112), was to estimate the amount of exposure measurement error and to perform data analysis adjusted for presumed error.

Sometimes additional information is discovered that permits exposure revisions, that presumably are more valid than previously. A case in point is a cohort mortality study of diatomaceous earth industry workers exposed to crystalline silica. In the original analysis (113), the available historical exposure data were deemed too sparse and lacking in detail for quantitative estimation of cumulative exposures. Instead, exposure-response analyses were based on a qualitative index that incorporated ordinal exposure intensity rankings and duration of exposure. Subsequently, additional dust measurement data for earlier years of the industry were identified and incorporated into a quantitative index, in units of milligrams per cubic meter (114). Additional data on asbestos exposure were also discovered after completion of the original study (115). The additional silica and asbestos data were subsequently included in updated dose-response analyses for nonmalignant respiratory disease and lung cancer (74).

Confounding

The possibility of confounding by nonoccupational risk factors, such as cigarette smoking or environmental air pollution, deserves consideration in occupational epidemiology. Unfortunately, collecting data on important potential confounders, particularly smoking, directly from study subjects is seldom practical in cohort mortality studies. There are some instances where smoking data have been obtained by abstracting data from industry medical records or from personal interviews of workers or their next-of-kin (reviewed in Marsh et al. (116)). Other, less direct approaches have been adopted to assess potential confounding from smoking in mortality studies. One approach is to examine the patterns of all smoking-related diseases as an approximate indication of whether excessive smoking appears to have been pervasive in a workforce (117). Alternatively, it is possible to perform hypothetical adjustments for smoking confounding by specifying the magnitude of association between smoking and exposure and the presumed smoking-related risk for the disease of interest (118). When these indirect methods were applied to assess the possible magnitude of confounding by smoking on the dose-response relation between crystalline silica and lung cancer in diatomaceous earth workers, only minimal confound-
CONFUSING FROM CONCURRENT OCCUPATIONAL EXPOSURES WITHIN THE SAME INDUSTRY, WHICH IS A DISTINCT POSSIBILITY IN COMPLEX ENvironments, MAY ALSO BE VERY IMPORTANT. FOR EXAMPLE, CONFLICTING RESULTS HAVE COME FROM SEVERAL STUDIES THAT ATTEMPTED TO DISTINGUISH THE INDEPENDENT EFFECTS ON LUNG CANCER RISK OF RADON AND SILICA EXPOSURES IN UNDERGROUND MINES (119, 120). MULTIPLE SOURCES OF EXPOSURE TO A SINGLE AGENT, FROM THE WORKPLACE AND NONOCCUPATIONAL SOURCES, CAN CREATE A MUTUAL CONFUNDING CONFIGURATION, AS HAS BEEN DISCUSSED IN THE CONTEXT OF EPIDEMIOLOGIC RESEARCH ON ELECTROMAGNETIC FIELDS (121). IT HAS BEEN SHOWN THAT POORLY MEASURED (MISCLASSIFIED) EXPOSURES TO CONFUNDERS MAY RESULT IN BIASED ESTIMATES OF ADJUSTED ASSOCIATIONS (122, 123). THE RAMIFICATIONS OF MUTUALLY ADJUSTED EFFECT ESTIMATES FOR OCCUPATIONAL AGENTS THAT HAVE BEEN ASSESSED WITH VARYING DEGREES OF ACCURACY HAS NOT RECEIVED ADEQUATE ATTENTION IN OCCUPATIONAL EPIDEMIOLOGY.

There is legitimate concern for potential confounding, particularly in situations where anticipated excess risks are small. Unfortunately, there continue to be many purely speculative criticisms raised that unmeasured confounding, rather than occupational exposures, account for observed associations (124, 125). One source of some of these unfounded criticisms may be a failure to distinguish confounding from effect modification. For example, an observation that “all of the lung cancer cases were smokers” does not necessarily denote confounding, nor does it exonerate workplace exposures as causative factors; instead this observation raises the possibility of synergy between workplace exposure and smoking.

Factors that may be confounders can also be effect modifiers that act synergistically on disease risks. Interactions between cigarette smoking and occupational lung carcinogens, including asbestos, radon, and arsenic, have been identified and analyzed to elucidate disease induction mechanisms (126, 127). Assessments of interactions are also possible from analyses of joint effects of occupational exposures, although there are few instances where this has been reported.

DISCUSSION

We have emphasized the merits of cohort morbidity studies in this review, yet do not want to give the impression that cohort mortality studies are inherently inferior or should be replaced by morbidity studies. Investigations of mortality risks among worker populations have been the fundamental source of occupational carcinogen identification and dose-response estimation. Mortality studies will undoubtedly continue to be an important feature of routine occupational epidemiology practice. Even rudimentary, well-designed and executed cohort mortality studies that do not produce quantitative data on exposure-disease relations can still provide meaningful information about gross patterns of disease excesses that may prompt more focused research using other approaches. Multicenter studies of pooled cohorts with similar exposures, as conducted by the International Agency for Research on Cancer, should be encouraged for investigating rare diseases and anticipated weak associations with relatively common diseases. However, it remains true that mortality studies have generic shortcomings, such as their limited applicability for investigating some important disease categories (e.g., cardiovascular and neurodegenerative diseases).

The application of the cohort design to investigate nonfatal indicators of health impairment is a positive development that should lead to practical disease prevention strategies. It is widely appreciated that prevalence studies, which remain pervasive in occupational epidemiology, can suffer from serious flaws that hinder interpretation. As we have discussed, bias related to the healthy worker survivor effect is an especially prominent limitation of prevalence studies, whereas this bias can be minimized, if not fully circumvented, in longitudinal morbidity studies. Measurement of temporal changes of potential confounders, in addition to changes in exposure and health status, over the course of a longitudinal study is another notable opportunity that has not been exploited routinely but deserves more consideration. In addition, because of increased personal access to cohort members, prospective cohort studies should provide greater opportunities than are ordinarily available in historical studies to verify disease status as a means of minimizing misclassification, thus strengthening causal inference.

Of course, enthusiasm for cohort morbidity follow-up studies should be tempered by a realization of their logistic complexities. Enrollment and follow-up of inception cohorts of newly hired workers is clearly a desirable research plan, from the standpoint of minimizing selection and confounding biases. However, opportunities for identifying sufficiently large inception cohorts in industries of interest are not plentiful. The methodologically less appealing alternative of expanding an initial cross-sectional study, on workers with variable prior health and exposure histories, into a longitudinal study is generally a more feasible option. Depending on the scope of health and
exposure assessment, prospective cohort morbidity studies can require large resources. Moreover, prospective cohort studies will inevitably suffer from attrition of study subjects, for a variety of reasons, including employment termination and loss of willingness to continue participation.

Historical cohort morbidity studies, which present an alternative approach, may be suitable to address certain research questions, provided that past exposure and health data are sufficiently valid and complete. Inasmuch as most industries do not collect and maintain health and exposure data for the purpose of epidemiologic research, historical cohort morbidity studies are not likely to have broad applicability.

Possible effects of occupational exposures on fertility and reproductive outcomes have been difficult to discern from occupational cohort studies. The logistics of conducting prospective surveillance for spontaneous abortion, the most common adverse outcome, are daunting. Moreover, a woman’s choice to become pregnant may influence the type and duration of exposures that are experienced during pregnancy. Questionnaire-based research or studies involving record linkage with medical records and vital statistics databases may be the most practical approaches. Newer methodological strategies to study workplace reproductive hazards in defined occupational cohorts are certainly needed.

All types of occupational cohort studies have benefited greatly from advances in exposure assessment. These advances are not limited to increased specificity and accuracy of measurement techniques, although the importance of these developments to sharpen etiologic research should be acknowledged. The examples of continuous exposure measurements to study acute respiratory toxicity (42) and chemical assay specificity to characterize dioxin exposure biomarkers (85) illustrate some of these technologic enhancements.

In recent years, a theoretical framework for exposure assessment has emerged that increasingly has become highly influential in epidemiologic practice. A central feature of this framework is that reduction of measurement error can be accomplished by adhering to rigorous approaches to exposure data collection and epidemiologic analysis. For example, demonstration that variability of exposure levels among workers with presumably the same jobs and work tasks may equal or exceed variability between workers with dissimilar jobs (128, 129) has motivated refinements of study design and data analysis techniques (130, 131). Exposure and dose modeling to extend mechanistic understanding of epidemiologic associations between occupational exposures and adverse health effects has been a valuable outgrowth of improved exposure assessment methods (132). Progress has been made in exposure and dose modeling in studies of occupational dusts and respiratory impairment (133, 134), and further progress to investigate other associations is anticipated.

Measurement of biomarkers of exposure and as intermediate steps in disease pathogenesis (response) have become established practices in occupational epidemiology. This trend will undoubtedly increase as improved laboratory techniques permit more precise and affordable large-scale applications. Additionally, recent major advances in molecular biology have been instrumental in efforts to explore gene-environment interactions that, theoretically, should identify “susceptible” subgroups within populations (135, 136). Gene-environment investigation in occupational cohort studies should be particularly fruitful when there is a known hazard that exerts a powerful effect on at least some members of the cohort. A good example is a Finnish cohort study of asbestos-exposed workers demonstrating exceptionally elevated pulmonary mesothelioma risks for workers with genetic polymorphisms of glutathione-S-transferase and N-acetyltransferase, indicative of diminished chemical detoxification capacity (137). Prospective studies of inception cohorts are especially well-suited for gene-environment interaction assessments in instances where tissue specimens can be archived. Alternatively, nested case-control and case-cohort designs would be more advantageous than full cohort analyses if genetic assay costs are prohibitive or there are needs for additional data collection on potential confounders. In view of growing public concerns about risks associated with ambient environmental exposures and the desire to protect sensitive members of the population-at-large, characterizations of gene-environment interactions for occupational hazards of low to moderate toxicity should emerge as important future challenges. Large-scale, multicenter occupational cohort studies may be the most practical strategy for this purpose.

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