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Is Silicosis Required for Silica-Associated Lung Cancer?

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Background *Abundant epidemiologic and experimental evidence supports the 1997 International Agency for Research on Cancer classification of crystalline silica as a human lung carcinogen. Nonetheless, there remains uncertainty about whether excessive lung cancer occurs exclusively among workers with silicosis.*
Methods *A review was performed of published occupational epidemiologic literature directly pertinent to the interrelations among silica exposure, silicosis, and lung cancer.*
Results *The association between silica and lung cancer is generally, but not uniformly, stronger among silicotics than nonsilicotics. However, the existing literature is ambiguous due to incomplete or biased ascertainment of silicosis, inadequate exposure assessment, and the inherently strong correlation between silica exposure and silicosis which hinders efforts to disentangle unique contributions to lung cancer risk.*
Conclusions *Until more conclusive epidemiologic findings become available, population-based or individually-based risk assessments should treat silicosis and lung cancer as distinct entities whose cause/effect relations are not necessarily linked.* Am. J. Ind. Med. 37:252–259, 2000. *© 2000 Wiley-Liss, Inc.*

KEY WORDS: silica; silicosis; lung cancer; pneumoconiosis; occupational health

INTRODUCTION

In 1997, the International Agency for Research on Cancer (IARC) classified crystalline silica as a human lung carcinogen, based on sufficient evidence for carcinogenicity from human and animal studies [IARC, 1997]. Among the relatively large body of epidemiologic literature that formed the basis of this classification, was a collection of studies of lung cancer risk among silicotics who experienced collectively a roughly two-fold lung cancer risk [Smith et al., 1995]. However, there remains some question as to whether excessive lung cancer occurs exclusively among workers with silicosis [Weill and McDonald, 1996]. There are several important scientific and public health aspects to the issue of silicosis as a necessary precursor or condition for elevated risk of lung cancer in silica-exposed workers. Further understanding of the role of silicosis in silica-associated lung carcinogenesis would shed light on the underlying biological mechanisms. Moreover, clarification of this question ultimately would be highly influential in occupational standard-setting, designing appropriate medical monitoring programs, and in medico-legal decisions of causation. For example, if it could be established with a reasonable level of certainty that only silicotics experience excess lung cancer, then only lung cancer cases with demonstrable evidence of silicosis would be attributable to silica exposure. This scenario might reflect either a dose–response relation for lung cancer with a presumed exposure threshold below which silicosis does not occur, or a particular susceptibility for silica-related carcinogenesis in persons who develop silicosis. Alternatively, if lung cancer was a potential sequela of silica exposure in the absence of silicosis, then silicosis might best be regarded as a marker of

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heavy exposure, rather than a prerequisite for carcinogenesis or cancer susceptibility factor.

Our premise is that the underlying question: ''Is silicosis required for elevated lung cancer risk?'', is virtually unanswerable from currently available epidemiologic literature, and is unlikely to be addressable in future epidemiologic studies. We review relevant epidemiologic literature bearing on this topic, and indicate how uncertainties in medical techniques for detecting silicosis, accompanied by severe limitations of epidemiologic study design, have impeded attaining a conclusive answer.

UNCERTAINTIES OF SILICOSIS DETECTION

The chest radiograph is the typical method for detecting silicosis in exposed individuals. Standard film-screen chest radiography is inexpensive, widely available, involves relatively low radiation exposure, and for decades has been used routinely in clinical medicine throughout the world to evaluate patients with suspected chest disease, including silicosis and other pneumoconioses. The International Labor Organization system for radiographic analysis [ILO, 1980] is generally used and widely available for epidemiologic research. However, despite many years of experience in the application of chest radiography to the study of the pneumoconioses, and silicosis in particular, there are some significant problems with application of this imaging modality in clinical medicine and epidemiologic studies.

It has been known for some time that, compared to direct microscopic analysis of tissue, routine chest radiographs are relatively insensitive for detecting interstitial lung disease, particularly when the disease is low grade or has a patchy distribution [Epler et al., 1978; Gaensler et al., 1980]. The low sensitivity of standard chest radiography in the setting of even moderate or marked autopsy-confirmed silicosis was shown more recently in South African gold miners [Hnizdo et al., 1993]. The effect of the low sensitivity of standard chest radiography can produce disease misclassification bias in epidemiologic research, i.e., underascertainment of disease status. Moreover, such bias will be differential in instances where the most heavily exposed workers or those with early radiographic evidence of low grade fibrosis preferentially receive intensive medical surveillance. It was thought that the advent of computed tomography, particularly high resolution computed tomography (HRCT), would largely address the problem of low sensitivity of standard radiographic chest imaging for pneumoconiosis [Aberle et al., 1988; Gamsu et al., 1989]. Clearly, HRCT is more sensitive and specific than standard chest radiography for detecting dust-related pleural abnormalities, but the advantages of HRCT for detecting interstitial changes related to pneumoconiosis are less dramatic than originally anticipated [Harkin et al., 1996], and HRCT is substantially more expensive and less feasible for widespread epidemiologic application. The higher radiation dose imparted by HRCT than chest radiography is another significant disadvantage. Most studies comparing HRCT with standard chest radiography in patients with suspected pneumoconiosis have been performed among subjects exposed to asbestos, and most do not incorporate microscopic analyses of tissue as a ''gold-standard.'' The absence of a validated histopathogical gold standard for detecting silicosis by HRCT, especially for early-stage disease, has also been noted [Begin et al., 1991; Talini et al., 1995]. Furthermore, there exist no standardized criteria for HRCT interpretation of changes due to inhalation of dust, analogous to the ILO chest radiograph classification scheme.

There are other problems related to the use of standard chest radiography in the identification of silicosis in epidemiologic studies. Inter-reader and intra-reader variability in the assessment of parenchymal abnormalities can be considerable [Fletcher and Oldham, 1949; Musch et al., 1984; Impivaara et al., 1998], although substantial variability in the interpretation of radiographic images is not unique to chest radiographs of patients with suspected pneumoconioses [Elmore et al., 1994]. Potential contributing factors to such variability include: radiographic quality or technique [Fletcher and Oldham, 1949; Wise and Oldham, 1963; Musch et al., 1985], obesity of subjects [Musch et al., 1985], age of subjects [Ghio et al., 1988; Meyer et al., 1997], cigarette smoking [Dick et al., 1992], gender [Meyer et al., 1997], differences in readers' tendencies [Musch et al., 1984; Meyer et al., 1997], and experience of observers [Fletcher and Oldham, 1949].

Cigarette smoking is a particularly nettlesome issue in the present circumstance. Cigarette smoke, which is the major cause of lung cancer, can also produce microscopically-verified pulmonary fibrosis [Auerbach et al., 1963] with possible low grade changes on chest radiographs [Dick et al., 1992]. Importantly, the prevalence of radiographic silicosis is increased among cigarette smokers who are exposed to silica [Finkelstein, 1994; Rosenman et al., 1996; Hughes et al., 1998]. Distinguishing radiographic opacities, by their shape, due to silica alone from those associated with a combined effect of silica and cigarette smoke may be impossible in many instances. For example, irregular opacities, rather than the rounded nodules characteristic of classical silicosis, are predominant both among smokers [Dick et al., 1992] and in workers exposed to silica in the pottery [Rees et al., 1992] and diatomaceous earth industries [Harber et al., 1998; Hughes et al., 1998]. Therefore, cigarette smoking can be an important confounding or effect modifying variable in epidemiologic studies of silicosis and lung cancer.

In addition to inherent limitations with the technique itself, chest radiography as it has usually been applied in

epidemiologic studies of silicosis and lung cancer, has been problematic. In nearly all studies, radiographic surveillance of workers has ended at the time of termination of employment. However, as cases may develop (or only become radiographically apparent) post-exposure, this can lead to underestimation of silicosis prevalence. Furthermore, the underestimation of silicosis would tend to be biased, because subjects who develop lung cancer (again, a delayed outcome, usually long after employment has ended) are much more likely to have chest imaging, tissue biopsies, and/or an autopsy which can also identify silicosis. The question of the relations among silica exposure, silicosis, and lung cancer would best be addressed if there were serial chest radiographs obtained over a worker's lifetime, rather than at a single (arbitrary) time point, as is usually the case. In the absence of such serial information, accurate ascertainment of date of onset of silicosis is impossible, which confuses the apparent associations between silica exposure, silicosis, and lung cancer.

EPIDEMIOLOGIC STUDIES OF SILICOSIS AND LUNG CANCER

As mentioned earlier, there is ample evidence that lung cancer risk is increased among silicotics. However, as has been noted by McDonald [1995], some of this literature may be biased as a consequence of the failure to define the underlying study bases, as occurs in studies of silicosis compensation registers, and uncontrolled confounding by cigarette smoking. The latter bias can be problematic if smoking exacerbates pulmonary impairment leading to a greater propensity for smokers to become hospitalized or to seek compensation. The potentially synergistic role of silica and smoking on silicosis risk is certainly relevant in this context.

In recognition of these concerns, we have limited our review to the occupational cohort and case–control studies that have examined lung cancer risk in relation both to silica exposure and silicosis. We identified pertinent articles from a MEDLINE search for the years 1985–99, and from publications during that time period that were known to us otherwise. Cohort studies comprised solely of silicotics and case–control studies that only examined associations between silicosis and lung cancer are not included. We identified 17 relevant studies of workers from the following industries: pottery and ceramics [Forastiere et al., 1986; McLaughlin et al., 1992; Meijers et al., 1996; Cherry et al., 1998; Ulm et al., 1999]; quarries and stone [Mastrangelo et al., 1988; Mehnert et al., 1990; Ulm et al., 1999]; refractory brick [Puntoni et al., 1988; Dong et al., 1995]; diatomaceous earth [Checkoway et al., 1999]; gold mining [Hessel et al., 1990; Hnizdo et al., 1997; de Klerk and Musk, 1998]; and various other metals mining [Amandus and Costello, 1991; McLaughlin et al., 1992; Hua et al., 1994; Finkelstein, 1995; Qiao et al., 1997]. Ten of the studies that we reviewed present lung cancer findings on the silica/lung cancer relation separately for silicotics and nonsilicotics (Table I). The other seven studies present data for the associations of lung cancer with silica exposure and with silicosis (i.e., treating silicosis as a proxy exposure variable), but do not provide results for the silica/lung cancer association separately for silicotics and nonsilicotics (Table II).

As can be seen from Table I, the relation between silica and lung cancer is generally stronger in silicotics than in nonsilicotics. Exceptions are the studies of Italian refractory brick workers [Puntoni et al., 1988] which showed roughly equivalent effects, albeit based on very small numbers, and the nested case–control study of South African gold miners [Hessel et al., 1990] which reported no associations for lung cancer with either dust exposure or silicosis. Lung cancer has been reported to be elevated among silicotics compared to nonsilicotics in most studies (Table II), suggesting that silicosis might be a reliable marker for heavy exposure. However, findings from the study of Chinese pottery workers and miners [McLaughlin et al., 1992] were inconsistent, as the associations of silica with lung cancer disagreed with results for silicosis and lung cancer within two of the four industry sectors studied (pottery and iron/copper mines). Recent nested case–control studies among UK pottery workers [Cherry et al., 1998] and German stone and ceramics workers [Ulm et al., 1999] indicate conflicting interpretations regarding the requirement of silicosis for an effect of silica on lung cancer. The UK study [Cherry et al., 1998] detected a strong relation with mean silica exposure; the small, nearly equivalent prevalences of silicosis in cases (6%) and controls (5%) suggests an effect of exposure that is independent of silicosis. The absence of an association between silica and lung cancer in the German study [Ulm et al., 1999], which intentionally excluded silicotics, might lead to the opposite conclusion.

One way to assess the state of existing literature is to consider the most suitable, if idealized, study design that would permit clear conclusions concerning the necessity for silicosis as a precursor of silica-associated lung cancer. Apart from the customary epidemiologic requirements of freedom from or minimal selection, measurement, and confounding biases, a study that could provide a true test of the hypothesis would have the following features: (1) unbiased (blinded) determination of silicosis among lung cancer cases and noncase workers; (2) determination of the times of onset of silicosis to preserve the appropriate temporal relation in the analysis of lung cancer risk (i.e., correct assignment of silicotics' person–time of observation before and after diagnoses of silicosis); (3) equivalent follow-up methods and duration for the subsequent development of lung cancer among silicotics and nonsilicotics; (4) quantitative data on silica exposures; and (5) detailed data on cigarette smoking.

TABLE I. Studies of Lung Cancer: Results Shown Separately for Silicotics and Nonsilicotics

Author (year)	Country	Industry	Study design	Silicosis determination	Silica exposure data	Lung cancer relative risk: Silicotics (lung cancers)	Lung cancer relative risk: Nonsilicotics (lung cancers)	Comments
Forastiere et al. [1986]	Italy	Pottery	Case–control	Compensation claims	Dichotomous	3.9 (25)	1.4 (79)	Population-based study
Mastrangelo et al. [1988]	Italy	Mines, quarries	Case–control	Compensation claims	Duration of exposure	1.9 (50)	0.9 (86)	Hospital-based study, weak trend of lung cancer with exposure duration
Puntoni et al. [1988]	Italy	Refractory brick	Cohort	Compensation claims	Dichotomous	1.7 (6)	2.1 (5)	Only 20 years follow-up
Hessel et al. [1990]	S. Africa	Gold mine	Case–control	Necropsy	Quantitative dust index	0.6 (56)[a]	1.0 (57)[a]	Study nested within cohort
Mehnert et al. [1990]	Germany	Slate quarry	Cohort	Compensation claims	Duration of exposure	1.8 (9)	0.9 (18)	Only 16 years follow-up
Amandus and Costello [1991]	USA	Non-uranium metal mines	Cohort	Radiograph at start of follow-up	Ore type, duration of exposure	1.7 (14)	1.2 (118)	Only 16 years follow-up, heterogeneous results by ore type
Dong et al. [1995]	China	Refractory brick	Cohort	Radiographs (?)	Duration of exposure	2.1 (35)	1.1 (30)	Lung cancer trend with exposure duration; unclear method of silicosis detection
Finkelstein [1995]	Canada	Mines	Cohort	Radiograph	Mine type	2.5 (18)	0.9 (19)	Cancer incidence study
Meijers et al. [1996]	Netherlands	Ceramics	Cohort	Radiographs	Ordinal rankings of intensity	2.2 (10)	0.7 (20)	Weak trend of lung cancer with exposure
Checkoway et al. [1999]	USA	Diatomaceous earth	Cohort	Serial radiographs	Quantitative silica levels	1.6 (4)	1.2 (48)	Exposure–response trend for lung in nonsilicotics; possible under-ascertaiment of silicosis

[a]Estimated from data provided in Hessel et al. [1990] Table 4, comparing highest and lowest exposures in lung cancer cases and controls, by parenchymal silicosis status.

TABLE II. Studies of Silica and Lung Cancer: Results for Associations of Silicosis and Lung Cancer

Author (year)	Country	Industry	Study design	Silicosis determination	Silica exposure data	Lung cancer relative risk		Comments
						Silicotics (lung cancers)	Nonsilicotics (lung cancers)	
McLaughlin et al. [1992]	China	Pottery Tungsten mines Iron/copper mines Tin mines	Case–control	Silicosis registry	Quantitative silica levels	0.5 (8) 0.8 (20) 3.1 (15) 2.0 (37)	1.0 (54) 1.0 (73) 1.0 (59) 1.0 (50)	Study nested within cohorts; inconsistent associations of lung cancer with exposure and silicosis
Hua et al. [1994]	China	Tin mine	Case–control	Medical records	Duration of exposure	2.0 (37)	1.0 (42)	Strong trend of lung cancer risk with years underground exposure
Qiao et al. [1997]	China	Tin mines	Cohort	Radiographs at beginning of follow-up	Duration of employment	1.5 (37)	1.0 (204)	No silica exposure measurements; strong lung cancer trends with radon, arsenic
Hnizdo et al. [1997]	S. Africa	Gold mines	Case–control	Serial radiographs, necropsy	Quantitative dust levels	2.1 (15)[a]	1.0 (63)	Nested study; exposure–response trend persists when controlled for silicosis
de Klerk and Musk [1998]	Australia	Gold mines	Cohort	Compensation claims	Quantitative exposure index	1.6 (60)	1.0 (78)	Weak lung cancer trend with exposure, disappears when controlled for silicosis
Cherry et al. [1998]	UK	Pottery	Case–control	Serial radiographs	Quantitative silica levels	1.1 (3)[b]	1.0 (49)	Study nested within cohort; strong association of lung cancer with average silica concentration
Ulm et al. [1999]	Germany	Stone, ceramics, quarries	Case–control	Serial radiographs	Quantitative silica levels	—[c]	1.0 (247)	Study nested within cohorts; silicotics excluded; no associations of lung cancer with silica

[a]Relative risk for lung cancer associated with silicosis, adjusted for cumulative silica exposure.
[b]Estimated from reported frequencies of silicosis among cases and controls.
[c]Silicotics excluded from cases and controls.

All of the studies listed in Tables I and II are lacking in one or more of our recommended characteristics, or have more fundamental deficiencies, such as potentially uncontrolled confounding by other occupational lung carcinogens (e.g., radon in underground mines). An obvious and pervasive complexity in assessing the separate roles of silica exposure and silicosis in lung cancer is the predictably strong correlation between exposure and silicosis. For example, Hnizdo et al. [1997] had sufficient data on silicosis onset and cumulative exposure, but could not disentangle their unique and interactive contributions. A similar situation occurred in the study of diatomaceous earth workers [Checkoway et al., 1999], despite the observation of an apparently independent effect of cumulative exposure on lung cancer mortality.

Some specific examples will illustrate further the shortcomings of the available literature. Silicosis was identified by compensation claims, rather than by systematic radiographic or other medical surveillance, in studies of Italian pottery workers [Forastiere et al., 1986], Italian miners [Mastrangelo et al., 1988], Italian refractory brick workers [Puntoni et al., 1988], German slate quarry workers [Mehnert et al., 1990], and Australian gold miners [de Klerk and Musk, 1998]. The absence of quantified silica exposure data is a severe limitation affecting most of these investigations [Forastiere et al., 1986; Mastrangelo et al., 1988; Mehnert et al., 1990; Amandus and Costello, 1991; Hua et al., 1994; Finkelstein, 1995; Dong et al., 1995; Meijers et al., 1996; Qiao et al., 1997]. Interestingly, Finkelstein [1995] was able to derive quantitative estimates for radon exposure, and demonstrated that this was a very unlikely explanation for an excess lung cancer risk in silicotics; unfortunately, quantification of silica exposure was not possible. Although several studies were able to estimate the times of onset of silicosis [Finkelstein et al., 1995; Hnizdo et al., 1997; Checkoway et al., 1999], all of the other studies relied on single radiographic or pathological determinations. Identifying silicosis onset times can be particularly challenging when radiographic surveillance is either incomplete in a workforce (e.g., limited to most heavily exposed workers) or irregularly scheduled throughout a plant's history. Equivalent follow-up for silicotics and nonsilicotics was not achieved in the cohort study of diatomaceous earth workers [Checkoway et al., 1999], even though there was evidence of an exposure–response relation for lung cancer with cumulative crystalline silica exposure among workers without radiographic evidence of silicosis. In that study, the duration from hire to final radiograph was substantially shorter in nonsilicotics than silicotics (12 vs. 21 years), which leaves open the possibility of misclassification of silicosis resulting from undetected cases that developed after employment termination, in addition to underdetection of silicosis based on standard radiography.

DISCUSSION AND CONCLUSIONS

The limitations of existing epidemiologic literature that bears on the question at hand suggest that prospects for a conclusive answer are bleak. There may be other occupational cohorts, of which we are unaware, that have been monitored systematically for the occurrence of both silicosis and lung cancer. In order for such cohorts to add meaningful new information, they will need to include very large populations with widely varying silica exposures, spanning levels below those that typically cause silicosis to levels that are clearly linked to silicosis induction. Application of more advanced radiographic imaging procedures for detecting low-grade silicosis might also be beneficial, although this would be very expensive and the yield might be marginal. In the interim, the best information concerning the interrelations of silica exposure, silicosis, and lung cancer may derive from suitably designed experimental animal studies.

We have been critical of chest radiographs, yet they are the mainstay of routine silicosis screening. Radiographs will continue to be valuable components of medical monitoring for the foreseeable future because they are relatively inexpensive, safe in regard to radiation exposure, yield findings that are based on accepted international standards, and, despite limited sensitivity, are reasonably specific when appropriate surveillance programs are conducted. Radiographic data may also serve as reasonably valid, if crude, dose surrogates in epidemiologic studies that do not have adequate industrial hygiene exposure data.

The control of silicosis is clearly a worldwide occupational health priority that has been successful in some industries, at least in the developed countries. However, it is premature to conclude that the elimination of new-onset silicosis cases necessarily implies elimination of an excess lung cancer hazard from silica exposure. Population-based and individual-based risk assessments for silica should, therefore, consider silicosis and lung cancer as separate entities whose cause/effect relations are not necessarily linked.

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