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A New Way to Look at Old Questions of Silica Carcinogenicity

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Although results from some epidemiologic studies indicate an association between silicosis and lung cancer, other investigations have not confirmed these findings. The discrepancies may be related to methodologic problems. These include the lack of autopsy confirmation for the presence of silicosis or of information on the histologic lung cancer type, and unavailable or uncertain estimates of exposures to silica and to known carcinogens that may interact with silica or silicosis. This study will be designed to avoid the above weaknesses and reconcile observations in humans with results from animal studies, which show a carcinogenic effect for silica. We have formulated a series of testable hypotheses based on plausible mechanisms of carcinogenesis. These hypotheses suggest that silica interacts with known carcinogens (e.g., radon or cigarette smoke), and that only specific types of lung cancer are associated with silica or silicosis: (1) if silica or silicosis of lung parenchyma causes proliferation of adjacent epithelial cells previously damaged by known carcinogens (e.g., radon or cigarette smoke), then the percentage of peripheral adenocarcinomas will be increased; and (2) if silicosis of hilar lymph nodes increases residence time of known carcinogens such as radon and cigarette smoke, then the percentage of centrally located squamous and small cell carcinomas will be increased. To test these hypotheses, we plan to compare the histologic type and location of lung cancers in subjects with silicosis to the histologic type and location of lung cancer in subjects without silicosis. Access has been obtained to an autopsy archive comprising 30,000 cases, including some 5000 lung cancers among former East German uranium miners. Information on smoking habits is available for those who died after 1971, and detailed employment histories for all decedents have been computerized. Increasingly detailed records of radon and dust levels underground, from the late 1950s onward, provide an opportunity to develop job-exposure matrices that may enable estimation of individuals' exposures to these and other agents. The efficiency of these procedures and of the proposed laboratory analyses is being tested by sampling 250 autopsy cases based on year of birth, year of death, type of employment in uranium mining (underground, surface, none), gender, and pathologic diagnosis (primary lung cancer, no cancer). This should generate an informative distribution of exposures to radon and to dust and will permit refinement of provisional power estimates. The population and data identified are suitable in principle for testing the research hypotheses. Results from the current pilot study will determine whether the longer-term work plan is feasible in practice.

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After several decades of research, the International Agency for Research on Cancer (IARC) concluded in 1987 that there was "limited" evidence for the carcinogenicity of crystalline silica to humans,[1] but the issue remains controversial.[2–10] Some epidemiologic studies have suggested that silicosis is weakly associated with lung cancer.[1–4] A recent study of lung cancer in several industries found inconsistent results regarding increased lung cancer risk with either exposure to silica or with silicosis.[10]

A major problem with the epidemiological data is the difficulty of accounting for the effects of simultaneous exposures to other known or suspected carcinogens (such as tobacco smoke, radon progeny, asbestos, and polycyclic aromatic hydrocarbons).[11] Furthermore, possible interactions between potential carcinogens have not been explored. Most of the studies lack pathologic confirmation, and thus, have considered all histopathologic types of lung cancer as a single entity.

The evidence from animal studies is more definite but species-specific: silica exposure induces lung cancer in rats, but not in hamsters or mice.[12–22] However, both rats and mice but not hamsters are susceptible to silica-induced pulmonary fibrosis. These studies show that in silica-exposed rats, peripheral adenocarcinomas, particularly the "scar" and bronchioloalveolar variants, are produced most commonly. These tumors are often preceded by precursor lesions such as type II alveolar cell hyperplasia, adenomatoid lesions and, rarely, adenomas. A recent literature review concluded that there was experimental evidence for a carcinogenic effect of silica.[11] Silica exposure without silicosis did not appear to increase lung cancer risk in humans, but it was thought that silicosis was "probably associated" with an increased risk of pulmonary carcinoma. Clarification of the reasons for the ambiguity remains an urgent research question.

Lung tissue material from a large series of autopsies of former uranium miners has been preserved in Germany.[23,24] This

may be a useful new resource. Unique features of this autopsy archive include the large number of cases due to the high autopsy rate, and the availability of detailed work histories and industrial hygiene data. These miners worked in Saxony and Thuringia (German Democratic Republic) after World War II. In the uranium mines, they were exposed to a range of doses of radon, as well as crystalline silica from the mine dust. The uranium mines were under total Soviet control during the early years (1946–1953). No industrial hygiene measures were used in this period, so that exposures to radon progeny and to silica were extremely high. Control was transferred to a joint Soviet-East German company (Wismut SDAG) in 1954. Radiation protection and dust suppression measures were introduced after that, and levels of exposure are known to have declined subsequently.[25]

Study Aim

The aim of the proposed research is to investigate possible mechanisms of lung cancer in humans exposed to silica. If the results support one or more of the postulated mechanisms for silica-induced carcinogenesis, then such human (as opposed to animal model) evidence would support interpretation of the disputed epidemiological data as implicating silica as a human carcinogen. Conversely, if analyses with adequate statistical power do not support the postulated mechanisms, then this would justify a more cautious and critical approach to the existing equivocal epidemiological data. The new insights into disease mechanisms sought in this study would thus contribute to a more scientific appraisal of an important occupational and environmental public health issue.

Study Objectives

The specific objectives for this study are to test the following two hypotheses: (1) inhaled silica or parenchymal silicosis induces proliferation of pulmonary epithelial cells, and thus increases the risk of lung cancer; and (2) silicosis of hilar lymph nodes impedes clearance of known carcinogens and thus increases their residence time. Both hypotheses imply that silica or its fibrotic sequelae interacts with known carcinogenic agents and that only specific histologic types of lung cancer are associated with exposure to silica or with silicosis.

The rationales for these hypotheses and some predictions that follow from them are as follows. An agent other than silica may cause irreversible damage (mutation) to DNA of pulmonary epithelial cells ("initiation"). Such known carcinogens include cigarette smoke, of course, and in underground miners, also radon progeny.[26–32] It could be that the transformed cells proliferate under the influence of silica (perhaps via parenchymal silicosis), clonally expand, and form a tumor ("promotion"). However, silica or silicosis may by itself also induce an initial proliferation of alveolar cells, possibly mediated by the actions of cytokines. Proliferating cells are more susceptible to DNA mutation during the mitosis by carcinogens such as radon. We would then expect to see premalignant precursor lesions in lungs of miners with parenchymal silicosis (with and without lung cancer). In fact, several of the authors (B.S.D., A.F.H., U.S., V.V.) have observed a few cases of proliferation of type II alveolar cells adjacent to parenchymal silicotic nodules in the lungs of human silicotics. However, the number of such cases has been small, and it has not been possible to determine whether the observation can be interpreted as supporting the hypothesis or whether this was due simply to chance. If silica or silicosis cause lung cancer by inducing proliferation of epithelial cells, then we also predict that there would be an increased proportion of peripheral adenocarcinomas among lung cancer cases from miners with parenchymal silicosis.

TABLE 1. Idealized Representation of the Type of Analyses Envisaged to Answer the Research Questions

	Lung Cancer Type	
Silicosis	Hypothesized Type[A]	All Other Types
Type X[B]	a	b
None	c	d

[A]Hypothesized type = peripherally located, to test the "proliferation" hypothesis; small cell and squamous cell, to test the "impaired clearance" hypothesis (where a,b,c,d are percentages).
[B]Type X = parenchymal, to test the "proliferation" hypothesis; lymph node, to test the "impaired clearance" hypothesis.

An increased prevalence of lung cancer was found in autopsied South African gold miners with silicotic nodules in lymph nodes, rather than in the lung parenchyma alone.[9] This is consistent with the idea that hilar silicosis impedes lymphatic clearance of inhaled carcinogens.[33] The resultant increase in the residence time for such carcinogens in the lung effectively increases the time available for induction of DNA damage and cellular changes that lead to cancer. The percentages of centrally located, small-cell carcinomas, and to a lesser extent, squamous cell carcinomas, are reportedly increased in uranium miners exposed to radon progeny.[34,35] However, studies of these miners do report on the presence or absence and extent of silicotic lesions. Squamous cell carcinomas, and particularly small-cell carcinomas, are also found with increased frequency in cigarette smokers. If these inhaled carcinogens have an increased chance of acting on the lungs of those with hilar silicosis, then one would expect preferential damage to central airways (the classic site of damage). Thus, if our second hypothesis is valid, then we predict that lymph node silicosis will be associated with a preponderance of small-cell and squamous cell (as distinct from other types of) lung cancers.

The crux of the questions we are seeking to answer in this research involves comparisons as noted in the idealized Table 1. We will compare the number of the hypothesized type of lung cancer (e.g., adenocarcinomas) to that of all other histologic types in silicotic miners (e.g., a:b) as contrasted with the same ratio in miners without silicosis (e.g., c:d). Specifically, is (a:b) significantly higher than (c:d)? At first glance, this simplified presentation of the problem suggests that no exposure data are necessary to answer the research questions, since convincing evidence that (a:b) is indeed greater than (c:d) would be consistent with the hypothesis; and, assuming sufficient statistical power, failure to demonstrate that (a:b) is greater than (c:d) would be interpretable as a negation of the hypothesis. However, although it is true that the presence of pathologically confirmed silicosis implies relatively high exposure to silica, the converse does not follow; not all high exposures to silica dust result in silicosis. Therefore, it is possible that, even if high exposures to silica dust (as distinct

from fibrosis resulting from such exposures) are truly associated with higher proportions of a particular histological type of lung cancer, as predicted by the hypothesis, a test of the difference between (a:b) and (c:d) may give a null result—if the exposures to silica of cases with no silicosis among those sampled were, on average, not much lower than those experienced by the silicotics. This is why it will be necessary to stratify the kind of analysis implied by Table 1 into at least two, but preferably more, contrasting levels of exposure to silica dust.

Similar considerations lead to the conclusion that it will also be necessary to have information about levels of exposure to various carcinogens, in particular to tobacco smoke, radon progeny and arsenic, since it is possible that such exposures may themselves affect the ratios (a:b) and (c:d). However, the (approximately quantifiable) presence of exposures to known carcinogens is an essential element in this particular study. These are not "nuisance variables" or "confounders" in the sense that those terms are usually employed, since the possible interactions between such carcinogens and inhaled silica dust (or silicotic lesions) are central to both research hypotheses. Note, however, that even if there are high correlations in that data sampled between exposures to silica dust and various known carcinogens (such as radon progeny or tobacco smoke), analyses like those suggested above could still be usefully interpreted.

Recent *in vitro* studies have suggested that silica can bind to the phosphate backbone of the DNA molecule, placing oxygen radicals close to DNA.[36] It has been hypothesized that these free radicals then act irreversibly to damage DNA. Contact of silica particles with DNA *in vivo* is likely to occur at sites of DNA unwinding during replication and, therefore, to damage transcribed genes as seen with chemical carcinogens. It has also been shown that silica can cause chromosomal aberrations in cultured mammalian cells.[37] Thus, it is possible that silica may also directly initiate the carcinogenic process. Further studies using the same postmortem material may provide new information on this postulated mechanism.

Materials and Methods

Available Material

The autopsy archive comprises approximately 1.5 million histologic slides and 35,000 autopsies from the period of 1957–1992. Approximately 5000 of these autopsies are from underground uranium miners who died of lung cancer. Reportedly, 97 percent of all underground miners were autopsied (the autopsy rate in the former East German state was about 90 percent compared with the U.S. rate of less than 10–15 percent).

Detailed work histories on former Wismut employees, abstracted from personnel records, have been entered on a computerized data base. These include a chronological listing of all jobs held during employment at Wismut, dates worked for each of these, and days worked underground. Smoking history information is also available for some miners. A job-exposure matrix has been produced recently to estimate workers' exposures to ionizing radiation. A similar exposure matrix, referring specifically to silica dust, is currently being developed, and we anticipate that this will allow us to classify the cases into at least broad "high" and "low" exposure groups.

Study Design

Testing the predictions arising from the two research hypotheses requires examination of appropriate material from the lungs of miners with and without lung cancer and with and without silicosis. We intend to characterize the exposures to tobacco smoke, ionizing radiation, and respirable silica dust at least as dichotomies (high/low or none/some), but possibly in a larger number of mutually exclusive ordered categories. The basic (minimum) design for the study will therefore approximate to a factorial arrangement involving at least two, but possibly more, levels of exposures to silica dust and to ionizing radiation. Smoking habits and exposures to other possible occupational carcinogens are unlikely to be represented equally in such silica and radiation-exposure-defined groups. Data regarding these additional factors will therefore be treated as concomitant variables in the analyses of results.

We plan to sample cases from the computerized autopsy archive within strata defined by: (1) presence or absence of lung cancer; (2) defined ranges of dates of birth (to generate material from persons likely to have been first employed during calendar periods known to differ systematically with respect to radiation and dust levels); (3) dates of death (to control the distribution of ages of death and thus, indirectly, likely duration of exposure) starting after 1971 in order to guarantee access to smoking information; and (4) main occupation (underground, surface, other).

Measures of Response

The response variables in the analyses of results will be based on pathologic analyses, including tumor location, histologic type of lung cancer classified according to the World Health Organization classification schema, presence and type of premalignant precursors, and presence, extent, and sites of silicosis. This slide review will preserve the major asset of the archive *in toto* for any additional future studies. Some whole lung specimens from silicotic miners may also be available. These may be used to assess the presence, location, and extent of premalignant precursors. If the above hypotheses are confirmed, additional laboratory studies will be conducted to explore mechanisms in a subset of cases.

Pilot Study

We are currently pursuing a pilot study with the objectives of: (1) testing all laboratory, data retrieval, and exposure assessment methods that are under consideration for the main study; (2) assessing the efficiency of the sampling strategy outlined above, with respect to generating the contrasting exposure groups required to answer the research questions; and (3) determining the size of the samples necessary to discriminate, with sufficient statistical power and significance, between the research hypotheses and their null alternatives.

We are identifying at least 250 deceased individuals from the autopsy archive record books using criteria (1), (2), and (3), described above as envisaged for the main study. Histologic slides for the sampled subjects will be extracted and used for the trial of contemplated laboratory methods. Copies of the corresponding autopsy protocols will also be sought, and searches will be conducted for the identified individuals' smoking habits, occupational histories, and exposures.

Discussion

The proposed research will be a retrospective autopsy study, with many of the difficulties inherent in such investigations. We plan to examine only a sample of the potentially available material, and we are restricted to studying slides taken at the time of autopsy, by criteria, and for purposes unconnected with our objectives. Clearly, this is not an ideal situation, and it could generate biases in the material available for study. A further possible difficulty is that the number of cases exemplifying different types of lung cancer may be limited. The total number of cases that would need to be sampled to achieve adequate statistical power could be unrealistically large. It is likely also that the number of individuals with combinations of high silica but low radiation (and, conversely, low silica and high radiation) exposures will be smaller than those with high (or low) exposures to both agents. Determination of an optimal sampling strategy from the archive, to achieve desired distributions of exposures among the cases to be studied, is therefore a critical issue. Some miners' occupational histories may indicate significant exposures to other occupational carcinogens. This might affect cell type and thus complicate analysis of the data. The pilot study now in progress was designed in a way that will allow us to consider these potential difficulties in detail, and to assess at least approximately their implications quantitatively.

If research of the kind envisaged proves to be feasible, then this will provide a unique opportunity to study the role of silica and silicosis in lung cancer using definitive (i.e., tissue) diagnoses. Precise grading of the extent, severity, and location of silicotic lesions in the presence of lung cancer, and determination of the types and locations of such cancers, is possible only in the kind of detailed pathologic analyses planned. Since the archive encompasses a very high proportion of the deaths that occurred in the regions of Germany in question during a defined calendar period, this investigation should suffer less from the selection biases common in most hospital-based autopsy studies.

Mechanisms of human carcinogenesis are difficult to assess, and often represent complex interactions between various genetic and environmental factors. This is true for all studies of humans (as opposed to many animal studies in which only a single exposure is assessed). Some of the epidemiologic evidence suggests that silica functions as a cocarcinogen rather than as a carcinogen *per se*. The plans outlined above will allow us to investigate pathogenesis in a population with reasonably defined exposure histories to known carcinogens (radon, tobacco smoke) and a suspected carcinogen or cocarcinogen *(silica)*.

Conclusion

The planned mechanistic study may allow us to differentiate between the effect of high silica exposure in the absence of silicosis on one hand, and the presence of silicosis itself on the other. The population of cases that we have chosen to study will allow us also to explore, quite specifically, possible interactions between a suspected carcinogen and established carcinogens. Thus, this research will complement both previous epidemiologic studies and laboratory investigations using animal models. In principle, this population and the data are suitable for testing the research hypotheses. The pilot study will determine whether a longer-term study is feasible in practice. We believe that a cautious approach, implied by our decision to first pursue a fairly elaborate pilot study, has many advantages.

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