SILICOSIS AND LUNG CANCER: PRELIMINARY RESULTS FROM THE CALIFORNIA SILICOSIS REGISTRY

DAVID F. GOLDSMITH • James J. Beaumont • Susan Lutzenhiser • Marc B. Schenker

Division of Occupational and Environmental Medicine
Department of Internal Medicine, University of California—IEHR
Davis, CA 95616, USA

ABSTRACT

Exposure to silica (SiO_2) causes silicosis and silicotuberculosis; now there is new concern about its carcinogenicity (see IARC Monograph on Silica, 1987). The California Silicosis Registry was created to examine the mortality of silicotics (individuals with high SiO_2 exposures) among state Workers' Compensation Appeals Board claimants. The authors used proportionate mortality ratios (PMRs) to assess the risks among 212 while male silicotics who filed claims between 1945 and 1963 and were followed until 1984. The PMRs (and 95% confidence intervals [$CI_{95\%}$]) indicated that silicotics had excesses of cancer of the lung (PMR=2.22; $CI_{95\%}$=1.30, 3.37), tuberculosis (PMR=9.75; $CI_{95\%}$=6.58, 13.92), and nonmalignant respiratory diseases (PMR=4.18; $CI_{95\%}$=3.10, 5.51). Removing tuberculosis deaths from the analysis produced a lung cancer PMR of 2.53. There was no excess risk for gastrointestinal or lymphatic cancers. These preliminary findings from the Registry suggest that silicotics in California have a significant respiratory cancer risk. This risk is consistent with findings from many international studies and strongly suggests that silicosis acts as a precursor lesion for lung cancer.

BACKGROUND

Since the 1930s there has been unsubstantiated conjecture that silicosis predisposes to cancer of many sites. It is established that silica exposure causes silicosis, silicotuberculosis, cor pulmonale, and perhaps nephritis. However, that silica may be a carcinogen or that silicosis may increase the risk of bronchogenic cancer (Goldsmith et al., 1982; Goldsmith et al., 1986; IARC, 1987) has been seriously considered only in the past seven years and challenges a great deal of expert medical opinion (see Heppleston, 1985; Selikoff, 1978; Ziskind et al., 1976).

The following is a summary of the scientific evidence of silica's carcinogenicity and the relationship between silicosis and respiratory cancer:

1. Very recent evidence shows that silica produces mutations and premalignant hyperplasia *in vivo* (Hesterberg et al.; 1986, Gibson et al., 1986; Saffiotti, 1986).

2. Since 1980 silica (as Min-U-Sil) has been shown to be a pulmonary carcinogen in five lifetime rat studies using both intratracheal and inhalation methods (Holland et al., 1983; Groth et al., 1986; Dagle et al., 1986; Wagner et al., 1980; Muhle et al., 1989). Muhle et al.'s research on rats shows that quartz is a carcinogen at a level of 1 mg/m^3. Although the tumorigenic results were not replicated in hamsters (Holland et al., 1983; Saffiotti, 1986), this is the first time that pulmonary tumors were induced using inhalation (Dagle et al., 1986; Muhle et al., 1989; Holland et al., 1986), paralleling the human route of exposure.

3. Workers in dusty trades with known high exposure to crystalline silica, including sandblasting, firebrick manufacture, ceramics, granite and stone work, and tunneling have statistically significant excess mortality from lung cancer (reviewed in Goldsmith et al., 1986; IARC, 1987; Lynge et al., 1986). Smoking was not controlled in most of the studies, however its lack of adjustment cannot completely explain the high lung cancer risk ratios (Axelson, 1978, Fletcher and Ades, 1984). By way of contrast, Goldsmith and Guidotti (1986) presented evidence that smoking may be synergistic with silica exposure in the risk of lung cancer.

4. Paralleling the lymphatic malignancies induced by silica in animals (Wagner et al., 1980), there are several studies indicating an elevated risk in humans (Brown et al., 1986; Kurppa et al., 1986; Redmond et al., 1981; Mirer et al., 1986). In addition there are several studies indicating excess mortality from stomach cancer among workers in which silica exposure predominated (reviewed by Greenberg, 1986).

5. Similar to the observations of pulmonary tumors adjacent to silicotic nodules in rats, lung cancer excesses have been reported consistently in studies of silicotics (reviewed by Goldsmith et al., 1988). The risk measures range from 1.4 to 5.9 and have been reported from Sweden (Westerholm, 1980), Ontario (Finkelstein

et al., 1982, 1987), Switzerland (Schuler and Ruttner, 1986), Austria (Neuberger et al., 1986), Finland (Gudbergsson et al., 1984; Kurppa et al., 1986), Italy (Forastiere et al., 1986; Rubino et al., 1985; Zambon et al., 1986), U.S. (Steenland and Beaumont, 1986), and Japan (Chiyotani, 1984).

EXPERIMENTAL DESIGN AND METHODS

Background of This Study

In 1986 and 1989 we received funding from the California Thoracic Society and the Centers for Disease Control, respectively, to create the California Silicosis Registry. Its purpose is to provide a registry of all claims for silicosis (and claims for other occupational pulmonary disease) within California, and to provide a basis for testing the association between silicosis and cancer. This paper will describe the proportional mortality ratio (PMR) findings from a partial and preliminary examination of the registry.

Methods

Patients having claims for silicosis diagnosed in California who were state residents from January 1, 1946 to December 31, 1980 are being identified. We are using the files of the California Workers' Compensation Appeals Board (WCAB). The following data are being extracted from the archived records of WCAB: name, address, sex, Social Security number, date of hirth, name and address of primary physician, date of claim, type of injury alleged, and employer's name and address. There are three types of controls being selected (excluding fatal injuries): one, matched for age (± 2 years), year of claim, region and sex; second, the next noncase in the files after a lung disease claim is found; the third control is a random selection of one claim from every 12 boxes of files (approximately 1 per 400 sample). These cases of silicosis and controls constitute the California Silicosis Registry.

All subjects are being traced up to December 31, 1984 to determine their vital status. Using California Department of Motor Vehicles (DMV) records, tracing is now being carried out to determine last known address if alive. Deceased subjects are being identified and information extracted from the California Vital Statistics Section of the Department of Health Services.

We used a proportionate mortality ratio (PMR) analysis program developed by Maizlish (1986) to provide a preliminary assessment of mortality between silicosis and respiratory disease claims whose death certificates (up to 1984) could be abstracted from California vital records. Expected values are from U.S. white male rates according to the 8th revision of the International Classification of Diseases. The major advantage is that this approach uses all the deaths obtained in the registry to date and provides a useful indication of any excesses relevant to the hypotheses under evaluation in this study.

RESULTS

This paper will examine only those data from the San Francisco district in a preliminary follow-up. All claims listing either silicosis, silicotuberculosis, anthracosilicosis, pneumoconiosis, dust diseases of the lung, or any lung illness (not accidents) are being extracted from the files of WCAB.

Table I shows the number of WCAB files examined, the number of lung disease claims found and the proportion of cases found per 1,000 records. These preliminary results indicate that about 5 of every 1,000 files reviewed contains a WCAB claim for occupational respiratory disease. As of May, 1988, over 130,000 individual files had been reviewed, and nearly 700 pneumoconiosis claims (plus controls) have been extracted. For this study we focused only on white males because fewer than 5% of the deaths occurred among nonwhites or females.

Tables II and III presents PMRs for white male cases dying from nonmalignant and malignant diseases, respectively. As expected, the cases have a striking excess mortality from tuberculosis (TB), a frequent complication of silicosis (PMR = 9.75; 95% CI = 6.58, 13.92). There is a significant deficit of mortality for all circulatory diseases, PMR = 0.60; 95% CI = 0.47, 0.75. Nonmalignant respiratory disease mortality showed the expected pattern with claimants having a clear excess PMR of 4.18; 95% CI = 3.10, 5.51. Cirrhosis of the liver showed a nonsignificant PMR of 1.39. Accidental deaths among lung disease claimants had a borderline significant deficit PMR of 0.42, and there was no excess mortality for suicide.

Table III indicates that the silicosis claimants have a PMR of 1.07 for all malignant neoplasms. In contrast to the recent findings of Finkelstein et al. (1987), there was no excess of cancer of the gastrointestinal tract among cases (PMR = 0.91). An excess risk for lymphopoeitic cancers was not born out among these pneumoconiotics, PMR = 0.90. There was also a PMR of 2.32 for pancreatic cancer (based on only 5 deaths).

Malignant neoplasms of the respiratory system were significantly elevated for lung disease claimants (PMR = 2.16; 95% CI = 1.37, 3.24). For cancer of the trachea, bronchus and lung, the pneumoconiotics had a PMR of 2.22; 95% CI = 1.39, 3.37. Removing the deaths from tuberculosis, produced a PMR of 2.53 for pulmonary cancer among silicotics.

DISCUSSION

In this preliminary PMR analysis (with the known weaknesses of PMR data acknowledged), respiratory disease claims showed an expected striking excess risk for TB and nonmalignant pulmonary disease mortality. In addition, we demonstrated a significant doubling of respiratory system cancer among claims for occupational lung disease (cases). Because we could not adjust for smoking, this finding can only be considered preliminary. However, these findings support the association between silicosis and lung cancer mortality risk described by Goldsmith et al. (1988), and the consistency of this association suggests that silicosis may act as a "precursor lesion" in the risk of pulmonary cancer (Goldsmith et al., 1983). The nature of the association will become clearer as the research on the California Silicosis Registry progresses.

Table I

Number of Files Examined, Number and Proportion of Claims for Lung Disease Found from the San Francisco Office of WCAB, 1945 to 1965

Years of claim	# Files Reviewed	Claims found	Proportion/1,000
1945-49*	27,242	174	6.4
1951-55	33,321	122	3.7
1956-60	21,931	112	5.1
1962-65	18,776	57	3.0
TOTAL	101,270	465	4.6

* 1950 and 1961 are missing from current files

Table II

PMR Findings from the California Silicosis Registry: Claims of Pneumoconiosis from 1945 to 1963 Followed until 1984 (Nonmalignant Diseases Among White Males; N = 171)

CAUSE OF DEATH	OBS	EXP	PMR	95% CON INT
Tuberculosis	30	3.1	9.75	6.58, 13.92
All Circulatory Diseases	71	119.2	0.60	0.47, 0.75
All Respiratory Diseases	50	12.0	4.18	3.10, 5.51
Cirrhosis of Liver	5	3.6	1.39	0.44, 3.20
All Accidents	4	9.5	0.42	0.11, 1.07
Suicide	0	3.4	000	--- ---

Table III

PMR Findings from the California Silicosis Registry: Claims of Pneumoconiosis from 1945 to 1963 Followed until 1984 (Malignant Neoplasms Among White Males; N = 41)

CAUSE OF DEATH	OBS	EXP	PMR	95% CON INT
All Malignant Neoplasms (MN)	41	38.4	1.07	0.77, 1.45
MN of Digestive Tract	12	13.2	0.91	0.47, 1.59
MN of Pancreas	5	2.2	2.32	0.74, 5.42
MN of Respiratory System	23	10.6	2.16	1.37, 3.24
MN of Lung	22	9.9	2.22	1.39, 3.37
MN of Lymphopoietic System	3	3.3	0.90	0.18, 2.65

CONCLUSION

This preliminary assessment of the proportionate mortality risk for silicosis claims has confirmed the finding of an elevated risk for pulmonary cancer. Because this finding is preliminary and because it only represents a minority of cases expected to be in the registry when finished, some caution is needed in drawing definitive conclusions. Spoecifically, adjustment for smoking is needed, and industry-specific risks should be calculated in order to see if the risk differs according to whether there is confounding from asbestos (in construction and shipbuilding), from pyrolosis products and metal fumes (in metallurgical industries), or from radon (in mining).

In the United States there are over 3,000,000 workers exposed to silica (Frazier and Sundin, 1986) and over 100,000 patients suffering from silicosis (Wegman, 1983). In spite of the limitations of this study, several activities can and should now be undertaken:

1. Physicians who now care for silicosis patients must become aware of the consistent findings of excess lung cancer risk and transmit this information to their patients.
2. Occupational health agencies, including NIOSH, OSHA, and other public health agencies, should reexamine the current standards for silica (0.1 mg/m^3 TWA) in order to factor in the consequences of its being labelled as a probable human carcinogen by IARC (1987).
3. Additional research should now be undertaken among silica-exposed workers in order to prevent new cases of fibrotic lung disease, and to assess their risk for cancer in the absence of silicosis.

BIBLIOGRAPHY

Axelson, O. (1978) Aspects of confounding in occupational health epidemiology. Scan. J. Work Environ. Health 4:85-88.

Brown, D.P. et al. (1986) Retrospective cohort mortality study of underground gold mine workers. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer; Controversy in Occupational Medicine*. Praeger, New York, pp. 335-350.

Chiyotani, K. (1984) Excess risk of lung cancer deaths in hospitalized pneumoconiotic patients. In Proceedings of the VI International Conference on Pneumoconiosis, Bochum, 1983. ILO, Geneva, pp. 228-236.

Dagle, G.E. et al. (1986) Chronic inhalation exposure of rats to quartz. In Goldsmith, D.F., et al. (eds.), *Silica, Silicosis, and Cancer; Controversy in Occupational Medicine*. Praeger, New York, pp. 255-266.

Finkelstein, M. et al. (1982) Mortality among miners receiving workmen's compensation for silicosis in Ontario: 1940-1975. *J. Occup Med.* 24:66-67.

Finkelstein, M. et al. (1987) Mortality among workers receiving compensation awards for silicosis in Ontario: 1940-1985. *Br. J. Ind. Med.* 44:588-594.

Fletcher, A.C. and Ades, A. (1984) Lung cancer mortality in a cohort of English foundry workers. *Scan. J. Work Env. Health* 10:7-16.

Forastiere, F. et al. (1986) Silica, silicosis and lung cancer among ceramic workers: A case-referent study. *Am. J. Ind. Med.* 10:363-370.

Frazier, T.M. and Sundin, D.S. (1986) Industrial demographics and population at risk for silica exposures. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 3-9.

Gibson, E.S. et al. (1986) Industrial mutagenicity testing: Assessing silica's role in lung cancer among foundry workers. In Goldsmith, D.F. et al.

(eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*, Praeger, New York, pp. 167-176.

Goldsmith, D.F., et al. (1982) Does occupational exposure to silica cause lung cancer? *Am. J. Ind. Med.* 3:423-440.

Goldsmith, D.F., et al. (1988) Silicosis and lung cancer: methologic contrasts between epidemiologic mortality and autopsy studies. Submitted to American Journal of Industrial Medicine.

Goldsmith, D.F. and Guidotti, T.L. (1986) Combined silica exposure and cigarette smoking: A likely synergistic effect. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 451-460.

Goldsmith, D.F. et al. (eds). (1986) *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 536.

Greenberg, M. (1986) Silica, silicosis, and cancer in the United Kingdom. In Goldsmith et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*, Praeger, New York, pp. 423-435.

Groth, D.H. et al. (1986) Lung tumors in rats treated with quartz and other minerals by intratracheal instillation. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine* Praeger, New York, pp. 243-254.

Gudbergsson, H. et al. (1984) An association between silicosis and lung cancer. A register approach. In Proceedings of the VI International Conference on Pneumoconiosis, Bochum, 1983. ILO, Geneva, pp. 212-216.

Heppleston, A.G. (1985) Silica, pneumoconiosis, and carcinoma of the lung. *Am. J. Ind. Med.* 7:285-294.

Hesterberg, T. et al. (1986) Mineral fibers and nonfibrous silica induce morphological transformation of mammalian cells in culture. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 177-190.

Holland, L.M. et al. (1983) Pulmonary effects of shale dusts in experimental animals. Chapter 30 in Wagner, W.L. et al. (eds.), *Health Issues Related to Metal and Nonmetal Mining*. Butterworth Publishers, Boston, pp. 485-496.

IARC (1987) International Agency for Research on Cancer (IARC) Evaluation of the Carcinogenic Risk to Silica and Some Silicates, monograph #43, Lyon.

Kurppa, K. et al. (1986) Lung cancer among silicotics in Finland. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 311-320.

Lynge, E. et al. (1986) Silica dust and lung cancer: Results from the Nordic occupational mortality and cancer incidence registers. *J. Natl. Cancer Inst.* 77:883-889.

Maizlish, N. (1986) A micro computer program for proportional mortality analysis National Farm Workers Health Group. Keene, CA.

Mirer, F. et al. (1986) Dust measurements and cancer mortality a ferrous foundry. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 29-44.

Muhle, H., Takenaka, S., Mohr, U., Dasenbrock, C., Mermelstein, R. Lung tumor induction upon long-term low level inhalation of crystalline silica. *Am. J. Ind. Med.* 1989:343-346.

Neuberger, M. et al. (1986) The Viennese dusty worker study. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 415-422.

Redmond, C. et al. (1981) Long-term mortality experience of steelworkers. DHHS (NIOSH) Pub. No. 81-120, U.S. Department of Health and Human Services. PHS, NIOSH, DSHEFS, Cincinnati, OH.

Rubino, et al. (1985) Epidemiologic study of the mortality of a cohort of silicotics in Piedmont (Italy). Presented at Silice, Silicosi, e Cancro Conference, Padova, Italy, May 10.

Saffiotti, U. (1986) The pathology induced by silica in relation to fibrogenesis and carcinogenesis. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 287-307.

Selikoff, I.J. (1978) Carcinogenic potential of silica compounds. In Bendz, G. and Lindquist, I. (eds.), *Biochemistry of Silicon and Related Problems*. Plenum Press, New York, pp. 311-336.

Sluis-Cremer, G.K. (1986) Silica exposure and silicosis in Witwatersrand gold miners in South Africa. In Goldsmith, D.F. et al. (eds.), *Silica Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 67-70.

Steenland, K. and Beaumont, J.J. (1986) A proportionate mortality study of granite cutters. *Am. J. Ind. Med.* 9:189-201.

Wagner, M.M.F. et al. (1980) Silica-induced malignant histiocytic lymphoma: Incidence linked with strain of rat and type of silica. *Br. J. Cancer* 41:908-917.

Wegman, D.H. (1983) Respiratory Disorders, Chapter 18. In Levy, B.S. and Wegman, D.H. (eds.), *Occupational Health*. Little Brown and Company, Boston.

Westerholm, P. (1980) Silicosis-observation of a case resister. *Scan. J. Work Environ. Health* [Suppl. 2] 6:1-86.

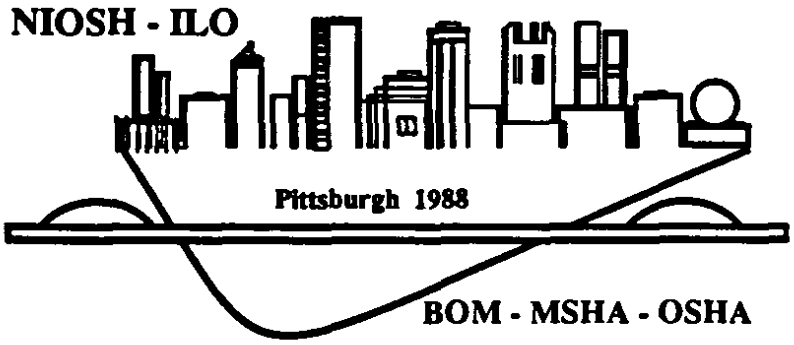
Zambon, P. et al. (1986). A mortality study of workers compensated for silicosis during 1959 to 1963 in the Veneto region of Italy. In Goldsmith, D.F. et al. (eds.), *Silica, Silicosis, and Cancer: Controversy in Occupational Medicine*. Praeger, New York, pp. 367-374.

Ziskind, M. et al. (1976) Silicosis. *Am. Rev. Resp. Dis.* 113:643-655.

Supported by grants from the California Thoracic Society and the Centers for Disease Control, NIOSH.

Proceedings of the VIIth International Pneumoconioses Conference | *Part*
Transactions de la VIIe Conférence Internationale sur les Pneumoconioses | *Tome*
Transaciones de la VIIa Conferencia Internacional sobre las Neumoconiosis | *Parte*

I



Pittsburgh, Pennsylvania, USA—August 23–26, 1988
Pittsburgh, Pennsylvanie, Etats-Unis—23–26 aout 1988
Pittsburgh, Pennsylvania EE. UU—23–26 de agosto de 1988

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CDC
CENTERS FOR DISEASE CONTROL

Sponsors

International Labour Office (ILO)
National Institute for Occupational Safety and Health (NIOSH)
Mine Safety and Health Administration (MSHA)
Occupational Safety and Health Administration (OSHA)
Bureau of Mines (BOM)

September 1990

DISCLAIMER

Sponsorship of this conference and these proceedings by the sponsoring organizations does not constitute endorsement of the views expressed or recommendation for the use of any commercial product, commodity, or service mentioned.

The opinions and conclusions expressed herein are those of the authors and not the sponsoring organizations.

DHHS (NIOSH) Publication No. 90-108 Part I