Uranium Workers Demonstrate Lower Lobe Predominant Irregular Pneumoconiotic Opacities on Chest Radiographs

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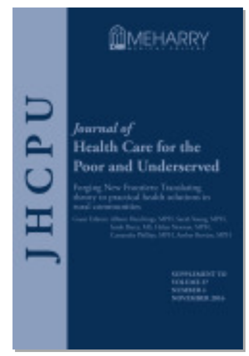

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ORIGINAL PAPER

Uranium Workers Demonstrate Lower Lobe Predominant Irregular Pneumoconiotic Opacities on Chest Radiographs

Elizabeth Kocher, MPH
Kristi J. Rendon
Denece Kesler, MD, MPH
Tawny Wilson Boyce, MS, MPH
Orrin Myers, PhD
Kandace Evans
Linda S. Cook, PhD
Akshay Sood, MD, MPH

Abstract: **Background**. There is a paucity of literature on the chest radiographic findings in uranium workers. **Objective**. To characterize the chest radiographic findings of pneumoconiosis in a New Mexican cohort of uranium workers. **Methods**. The most recent results from chest radiographs were abstracted in this cross-sectional study. **Results**. Radiographs showed small pneumoconiotic opacities of profusion score of ≥ 1/0 in 155/429 (36.1%) uranium workers. The most common shape/size of the primary and secondary opacities was s (90.3%) and t (83.7%) types, respectively. Lower lung zones were the most affected. American Indians were the population group at greatest odds for having profusion score ≥ 1/0 (O.R. 2.65, 95% C.I. 1.61, 4.36). **Conclusions**. Uranium workers' pneumoconiosis is associated with predominantly lower lobe, irregular, and small opacities. Clinical providers and policymakers must consider uranium workers' pneumoconiosis in the differential diagnosis for lower lobe-predominant interstitial lung disease, in the appropriate exposure setting.

Key words: Chest radiographic appearance, uranium workers' pneumoconiosis, profusion score, American Indians.

The uranium industry in the Colorado Plateau of the American Southwest was responsible for the majority of the U.S. uranium production during the Cold War. Many of the earliest mines in this area, known as *dog holes*, were infamous for their lack of ventilation and poor working conditions.[1] Although most uranium mines were shut down by the late 1980s in the U.S., uranium mining continues worldwide with

***ELIZABETH KOCHER**, **KRISTI RENDON**, **DENECE KESLER**, **TAWNY WILSON BOYCE**, **ORRIN MYERS**, **KANDACE EVANS**, and **LINDA COOK** are associated with The University of New Mexico School of Medicine, Internal Medicine, Albuquerque, New Mexico. **AKSHAY SOOD** is the corresponding author and can be reached at The University of New Mexico School of Medicine, 1 University of New Mexico, MSC 10 5550, Albuquerque, NM 87131, USA, Telephone: 505-272-4751, Fax: 505-272-8700, Email:asood@salud.unm.edu.*

documented production in Canada, South Africa and other African countries, and Australia.[2] The uranium industry in the Colorado Plateau has had an adverse health impact on workers, particularly American Indians.[1,3] Elevated standardized mortality ratios were found in Navajo uranium miners for both lung cancer and nonmalignant respiratory diseases.[4] While uranium workers are well studied for their risk of lung cancer development, nonmalignant diseases have not been adequately studied.

There is a paucity of literature on the chest radiographic findings in uranium workers. A prior small survey of underground uranium miners at Ambrosia Lake, New Mexico published in 1984 by Samet *et al.* reported upper lobe rounded opacities, compatible with silicosis, on 12 of 143 (8.4%) participants with chest radiographs available for interpretation, with ≥ 1/0 profusion score for small pneumoconiotic opacities.[5] Our objective was to characterize the most recent radiographic patterns of pneumoconiosis on chest radiographs in a larger population of New Mexican uranium workers, after a longer length of time between uranium work exposure and evaluation, using the database from the University of New Mexico Radiation Exposure Screening and Education Program (RESEP), funded by the Health Resources and Services Administration (HRSA).

Methods

As part of the New Mexico RESEP program, annual surveillance of workers in the surface and underground uranium mines, mills, and transport industry in the state of New Mexico who worked for at least one year between the years of 1952 and 1971, is performed at the Uranium Workers' Clinics at the University of New Mexico, Albuquerque, and the Acoma-Conocito-Laguna Hospital at the Pueblo of Acoma, New Mexico. Uranium workers in the surrounding communities are invited to attend these clinics. The surveillance visit involves a detailed standard questionnaire, physical examination, prebronchodilator spirometry, and posteroanterior chest radiograph. The questionnaire used is based on the American Thoracic Society—Division of Lung Disease (ATS-DLD) questionnaire.[6] Race/ethnicity, smoking status, and mining exposure are self-reported. The chest radiograph is interpreted using the International Labor Organization's (ILO) International Classification of Radiographs of Pneumoconiosis (commonly called B-reads) revised 2000 edition of standard radiographs and the 2011 edition of digital radiographs (derived from the 2000 standard radiographs).[7] All radiographs are read by a licensed physician certified by the National Institute for Occupational Safety and Health (NIOSH) B-reader program as proficient in the classification of chest radiographs for pneumoconiosis using the ILO classification system, reviewing either film screen or digital radiographs, and recording findings in the Centers for Disease Control (CDC) 2.8 chest radiograph classification form.[8] The findings from the most recent chest radiograph obtained on each worker between 2005 and 2015 were abstracted from the form, in this cross-sectional study. Our outcomes included parenchymal abnormalities including both small opacities and large opacities. Small opacities are described by profusion, affected zones of the lung, shape (rounded or regular), and size. In addition, pleural changes and other abnormalities were reviewed.

The profusion of small pneumoconiotic opacities refers to the concentration of small opacities in the affected zones of the lung. The category of profusion *i.e.* 0, 1, 2, or 3 is based on comparisons with the standard radiographs. Profusion is classified into one of 12 ordered subcategories, which are represented from 0/– to 3/+. Category 0 refers to the absence of small opacities or the presence of small opacities that are less profuse than Category 1 and comprises subcategories 0/–, 0/0, and 0/1. Classification of a radiograph using the 12 subcategories scale was performed as follows. The appropriate category is chosen by comparing the subject radiograph with standard radiographs that define the level of profusion characteristic of the centrally placed subcategories 0/0 (for Category 0), 1/1 (for Category 1), 2/2 (for Category 2), and 3/3 (for Category 3). A radiograph that shows profusion which is considered to be similar to that shown on a category 1 standard radiograph is classified as 1/1. Subcategory 1/0 refers to a radiograph with a profusion of small opacities judged to be similar in appearance to that depicted on a category 1 standard radiograph but category 0 was seriously considered as an alternative.

The opacities are recorded by the affected zone. Each lung field is divided into three zones (*i.e.*, upper, middle, and lower) by horizontal lines drawn at approximately one third and two thirds of the vertical distance between the lungs apices and the domes of the diaphragm.

The shape and size of small opacities are recorded. Two kinds of shape are recognized: rounded and irregular. In each case, three sizes are differentiated. For small rounded opacities, the three size ranges are denoted by the letters p, q, and r, and are defined by the appearance of the small opacities of the corresponding standard radiographs. These illustrate p opacities with diameters up to 1.5 mm, q opacities with diameters exceeding about 1.5 mm and up to about 3.0 mm, and r opacities with diameters exceeding about 3 mm and up to about 10 mm. The three size ranges of small irregular opacities are denoted by the letters s, t, and u, and are defined by the appearance of small opacities on the corresponding standard radiographs. These illustrate s opacities with widths up to 1.5 mm, t opacities with widths exceeding about 1.5 mm and up to about 3 mm, and u opacities with widths exceeding about 3 mm and up to about 10 mm. The shape and size of primary opacities (*i.e.* the most predominant opacity type) and secondary opacities (*i.e.* the second most predominant opacity type) are recorded.

A large pneumoconiotic opacity is defined as an opacity having the longest dimension exceeding 10 mm. Three sizes of large opacities are differentiated. Category A is defined as one or multiple large opacities with the sum of the longest dimension not exceeding about 50 mm. Category B includes one or multiple large opacities with the sum of the longest dimension exceeding 50 mm but not exceeding the equivalent area of the right upper lung zone. Category C includes one or multiple large opacities which exceeds the equivalent area of the right upper lung zone.

Pleural abnormalities are divided into pleural plaques (localized pleural thickening), costophrenic angle obliteration, and diffuse pleural thickening. Pleural plaques may be seen on the diaphragm, on the chest wall, and at other sites. Those present on the chest wall are recorded as in-profile or face-on and separately for the right and left sides. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present. Other radiographic abnormalities of importance were also reviewed.

Frequency of abnormal findings was summarized in univariate analysis, using Statistical Analysis Software SAS 9.4 version (Cary, NC). Logistic regression analysis was additionally performed. Institutional Review Board approval was obtained (HRPO 14–058).

Results

Based upon their last surveillance visit, most of the 429 uranium workers studied were either American Indian (38.3%) or Hispanic (30.1%), and almost all were older men (97.2% males and 65.8% males ≥ 65 years of age). Most workers were uranium miners (82.6%), and the rest were millers and transporters in the uranium industry. Most subjects worked underground, either partly or entirely (77.6%; Table 1).

Chest radiographs showed small pneumoconiotic opacities of profusion score of ≥ 1/0 in 155/429 (36.1%) uranium workers, reflecting the preponderance of relatively mild disease. The most common profusion score category of small pneumoconiotic opacities was 1/0, seen in 29.6% of all uranium workers and 81.9% of those with score category of ≥ 1/0; Table 3). Among workers with score category ≥ 1/0, the shape/size of the primary opacity was s type in 90.3%, t type in 6.5%, q type in 2.6%, and p type in 0.6%. The shape/size of the secondary opacity was t type in 83.7%, s type in 13.7%, and q type in 2.6%. Small opacities were most commonly seen in lower lung zones, usually involving multiple zones (Table 2). Large pneumoconiotic opacities were found in only two subjects (one A and one C opacity).

Localized pleural thickening (*i.e.* pleural plaques) was not common among the uranium workers (10.5%). Pleural plaques, when present, were more commonly right-sided, non-calcified, and in-profile in location. Costophrenic angle obliteration (2.8%) and diffuse pleural thickening (2.8%) was rare among these uranium workers (Table 4).

Chest radiographs of 75.3% of these uranium workers demonstrated other abnormalities (Table 5). Among those with other abnormalities, cardiovascular abnormalities were most common, including atherosclerotic aorta (33.7%) and abnormal cardiac shape or size (17.0%). This was followed by skeletal abnormalities, including scoliosis (16.1%) and fractured ribs (13.0%). Thickening of interlobar fissures (16.1%) and significant apical pleural thickening (4.3%) were also noted.

Race/ethnicity was a significant predictor for the radiographic presence of small pneumoconiotic opacities. Compared with non-Hispanic Whites, American Indians had the highest relative odds for having ≥ 1/0 profusion score category of opacities, followed by Hispanics (Table 6). No other subject characteristics, including age and smoking, were strongly associated with pneumoconiotic opacities.

Discussion

A substantial proportion of uranium workers (36.1%) in our study showed radiographically defined pneumoconiotic changes, meeting the threshold of 1/0 profusion score, substantially greater than the 8% described in 1984 by Samet *et al.*[5] A possible explanation for our higher prevalence of radiographic abnormality is that the current study population had a greater length of time between uranium work exposure and evaluation. Those with radiographic pneumoconiotic changes usually had mild disease, predominantly involving lower lobe-predominant, irregular, and small opacities. While pleural changes were not common, cardiovascular and skeletal abnormalities were seen in a significant proportion of uranium workers. American Indian workers were the population group at greatest relative odds for demonstrating small pneumoconiotic opacities.

Table 1.

SUMMARY OF DEMOGRAPHIC AND EXPOSURE CHARACTERISTICS AMONG URANIUM WORKERS (N = 429)

Characteristics	**Frequency (%) or mean ± S.D.**
Male sex	416 (97.2%)
Race/ethnicity	
Non-Hispanic White	131 (30.6%)
Black	4 (0.9%)
Hispanic	129 (30.1%)
American Indian	164 (38.3%)
Age (in years), mean ± SD	69.2 ± 7.8
Smoking status	
Never	142 (33.1%)
Current	66 (15.4%)
Former	221 (51.5%)
Mining experience, lifetime	341 (82.6%)
Location of uranium mining	
Underground	151 (50.5%)
Above ground/Open Pit	67 (22.4%)
Both	81 (27.1%)
Self-reported history of asthma	44 (10.3%)
Self-reported history of chronic lung disease	41 (9.6%)

Table 2.

DISTRIBUTION OF ZONAL INVOLVEMENT OF THE LUNG, AMONG URANIUM WORKERS WITH SMALL PNEUMOCONIOTIC OPACITIES OF PROFUSION SCORE OF ≥ 1/0 (N = 155)[a]

Zonal involvement of the lung	**Frequency of opacities (%)**
Upper right zone	17 (11.0)
Middle right zone	64 (41.3)
Lower right zone	136 (87.7)
Upper left zone	14 (9.0)
Middle left zone	80 (51.6)
Lower left zone	146 (94.2)

[a]98.7% had multiple zones marked and 1.3% had missing data.

Table 3.

DISTRIBUTION OF PROFUSION SCORE OF SMALL PNEUMOCONIOTIC OPACITIES AMONG URANIUM WORKERS (N = 429)

Profusion score category	Frequency (%)
0/0 or 0/–	217 (50.6%)
0/1	57 (13.3%)
1/0	127 (29.6%)
1/1	16 (3.7%)
1/2	4 (0.9%)
2/1	3 (0.7%)
2/2	3 (0.7%)
2/3	2 (0.5%)
>2/3	0 (0%)

Table 4.

DISTRIBUTION OF LOCALIZED PLEURAL THICKENING (I.E. PLEURAL PLAQUES) IN ALL URANIUM WORKERS (N = 429)[a]

Location	Frequency of right-sided pleural plaques only (%)	Frequency of left-sided pleural plaques only (%)	Frequency of bilateral pleural plaques (%)
In-profile	13 (28.9%)	6 (13.3%)	3 (6.7%)
Face-on	1 (2.2%)	3 (6.7%)	3 (6.7%)
Diaphragm	2 (4.4%)	3 (6.7%)	1 (2.2%)
Other site/s	–	–	–

[a]Localized pleural thickening (*i.e.* pleural plaques), found in 45 of 429 (10.5%) uranium workers, and in 23 of 155 (14.8%) of uranium workers with pneumoconiotic opacities of profusion score ≥ 1/0. Calcification was seen in one right-sided in-profile, one left-sided in-profile, two left-sided face-on, two right-sided diaphragmatic and three left-sided diaphragmatic pleural plaques.

Table 5.

DISTRIBUTION OF ANY 'OTHER ABNORMALITIES' FOUND AMONG 323 OF 429 (75.3%) URANIUM WORKERS SCREENED

Symbols	Frequency (%)	Other symbols	Frequency (%)
Atherosclerotic aorta	109 (33.7%)	Eventration of diaphragm	4 (1.2%)
Significant apical pleural thickening	14 (4.3%)	Hiatal hernia	7 (2.2%)
Coalescence of small opacities	3 (0.9%)	Increased bronchovascular markings	12 (3.7%)
Calcified non-pneumoconiotic nodules or nodes	20 (6.2%)	Hyperinflation	3 (0.9%)
Abnormality of cardiac size or shape	55 (17.0%)	Bony chest cage abnormality	4 (1.2%)
Emphysema	17 (5.3%)	Healed non-rib fracture	2 (0.6%)
Fractured ribs	42 (13.0%)	Scoliosis	52 (16.1%)
Enlargement of noncalcified hilar or mediastinal lymph nodes	2 (0.6%)	Vertebral column abnormality	18 (5.6%)
Ill-defined diaphragm border	8 (2.5%)	Lung infiltrate	5 (1.5%)
Ill-defined heart border	7 (2.2%)	Lung nodule	20 (6.2%)
Septal (Kerley) lines	2 (0.6%)	Foreign body	30 (9.3%)
Plate like atelectasis	14 (4.3%)	Postsurgical changes	33 (10.2%)
Parenchymal bands	20 (6.2%)	Anomaly of aorta	13 (4.0%)
Pleural thickening of an interlobar fissure	52 (16.1%)	Other vascular abnormalities	1 (0.3%)

Table 6.

UNADJUSTED ASSOCIATION BETWEEN SUBJECT CHARACTERISTICS AND SMALL PNEUMOCONIOTIC PROFUSION SCORE CATEGORY OF ≥ 1/0, AMONG ALL URANIUM WORKERS (N = 429)

	≥ 1/0 profusion score	
Subject characteristics	**Odds ratio (95% C.I.)**	**p value**
Age ≥ 65 years	1.06 (0.70, 1.62)	0.78
Race/Ethnicity		<.001[a]
Non-Hispanic White	1.00	
Black	2.85 (0.39, 21.05)	
Hispanic	1.28 (0.75, 2.20)	
American Indian	2.65 (1.61, 4.36)	
Mining experience, lifetime	0.93 (0.55, 1.57)	0.78
Smoking status		0.83[a]
Never	1.00	
Current	1.20 (0.66, 2.18)	
Former	1.02 (0.66, 1.59)	
Self-reported history of asthma	1.01 (0.53, 1.93)	0.97
Self-reported history of heart attack	1.03 (0.60, 1.74)	0.93
Self-reported history of chronic lung disease	1.02 (0.52, 1.99)	0.95
Self-reported history of hypertension	0.96 (0.64, 1.45)	0.85

[a]refers to the global p value for the characteristic studied

In addition to nuisance dust, uranium workers are exposed to radiation (including short-lived radon gas progeny), silica, and diesel exhaust. Uranium workers develop chronic bronchitis and emphysema phenotypes of chronic obstructive pulmonary disease, silicosis and other pneumoconiosis, pulmonary fibrosis, and lung cancer.[9,10] Dose-dependent associations between silica dust exposure and decline in FEV_1, decline in FEV_1/FVC ratio, and pathological changes of lung silicosis are described in studies of uranium miners.[9,11] Extrapulmonary cancers involving the stomach and the liver as well as multiple myeloma and non-Hodgkin's lymphoma have also been described in uranium miners.[10,12] While no significant increase in cardiovascular mortality was found in the Wismut cohort of German uranium miners, a statistically insignificant increase for mortality from cerebrovascular diseases with increased radon exposure was reported.[10]

The chest radiographic pattern that we observed in New Mexican uranium workers is most consistent with diffuse interstitial fibrosis. Radiation-induced diffuse interstitial fibrosis in humans was previously thought to occur only as a complication of radiotherapy to the chest. Occupational radiation fibrosis was reported as early as 1931, in case reports associated with alpha emitting radium in dust from florescent paint.[13,14] The predominant injurious agent to the lung in uranium miners is believed to be alpha particles from inhaled radon progeny, decaying in or adjacent to lung tissue.[14] Although silica also probably contributed, the paucity of quartz crystals in the pathological lung specimens from uranium miners suggested silica was not the major pathogen in these cases.[14] In animal studies, the fibrogenic effect of silica in the lung was enhanced by ionizing radiation.[15]

Our results contrast with a smaller study by Samet *et al.* that reports preponderance of upper lobe rounded opacities in New Mexican uranium miners.[5] Our results also contrast with another study of 34 working uranium miners, 15 of whom had radiographic changes of pneumoconiosis; 13 of these 15 miners had bilateral widespread nodular densities and the remaining two had densities characteristic of diffuse interstitial fibrosis.[16] On the other hand, our results support the findings from a 1998 study of 400 uranium miners; 102 (25.5%) of those were considered as possibly having radiographically defined lung fibrosis.[14] The pathological findings reported in lung specimens from a selected group of five uranium miners showed severe and diffuse interstitial fibrosis with honeycombing of the lung, consistent with a pathological lesion known as usual interstitial pneumonitis (UIP).[14] In addition, anthracosilicotic nodules were present in four of the five cases.

Our results are also consistent with a prior study conducted at the Miners' Colfax Medical Center, Raton, New Mexico, using a separate cohort, which demonstrated radiographic pneumoconiosis was more common in American Indians than either Hispanics or non-Hispanic Whites in New Mexico.[1] This study however did not describe the radiographic appearance of pneumoconiosis. A possible explanation for the observed racial/ethnic difference includes a disproportionately greater amount of underground uranium mining exposure in American Indian workers. A genetic basis for uranium workers' pneumoconiosis cannot however be excluded.

The differential diagnoses of lower lobe predominant interstitial lung disease includes idiopathic pulmonary fibrosis that is associated with a UIP pathological pattern, asbestosis and other pneumoconiosis, chronic aspiration pneumonitis, and collagen vascular diseases involving the lung such as rheumatoid lung. To this list, uranium workers' pneumoconiosis should be added, in the right occupational exposure setting. Like asbestosis and unlike UIP, uranium workers' pneumoconiosis is slowly progressive. It can however be differentiated in chest radiographs from asbestosis due to the uncommon presence of radiographic pleural changes. Currently, there exists no specific treatment for uranium workers' pneumoconiosis. Preventive vaccinations, oxygen supplementation, and pulmonary rehabilitation are offered, when applicable. This contrasts with patients with idiopathic pulmonary fibrosis/UIP who may be treated with nintedanib and pirfenidone.[17,18] It is therefore important to differentiate uranium workers' pneumoconiosis from idiopathic pulmonary fibrosis/UIP to avoid unnecessary and expensive treatment.

The strength of our study includes a large number of uranium industry workers with a long length of time between uranium work exposure and evaluation, from the same geographic area. Additional strength includes our use of standard ILO classification, the pertinence of which has been previously demonstrated by studying the correlation between lung anatomic lesion and chest x-ray features.[19] Our study is limited by interpretation by a single B reader; many occupational studies use at least two B readers to account for inter-reader misclassification on presence and profusion of pneumoconiotic opacities. Our study is also limited by selection bias caused by differential loss to follow-up of individuals with pneumoconiosis who receive federal compensation benefits and discontinue follow-up once chest radiographs demonstrate a profusion score of 1/0 (which may partly explain the preponderance of 1/0 profusion category in our database); healthy worker survivor bias that occurs in occupational studies whereby less healthy uranium workers are more likely to reduce their workplace exposures due to employment termination (which may underestimate the prevalence and profusion severity of pneumoconiotic opacities);[20] confounding findings of opacities on the chest radiograph due to alternative diseases such as congestive heart failure; and inadequate quantitative past uranium dust exposure estimation in this study. During the study period, there occurred a shift in chest x-ray technology from film-based to digital imaging but a recent NIOSH study has demonstrated that inter- and intra-reader variability was not affected by this change.[8] Cigarette smokers demonstrate an overall increase of non-specific lung markings on chest radiographs, which has been described as "dirty chest" and explained by the presence of bronchial wall thickening on computed tomography.[21,22] Increasing age may also lead to one- or two-subcategory increase in the profusion of irregular type opacities in individuals without concomitant occupational dust exposures.[22–24] However, the lack of association between smoking status/age and pneumoconiotic changes, as shown in Table 6, argues that smoking and age are unlikely explanations for our findings.

A substantial proportion of uranium workers in our study showed radiographically defined pneumoconiotic changes. Those with radiographic pneumoconiotic changes usually had mild disease, predominantly involving lower lobe-predominant, irregular, and small opacities. Clinical providers caring for patients with lung disease and policymakers involved in provider education and worker compensation must consider uranium workers' pneumoconiosis as an important differential in lower lobe predominant interstitial lung disease, in the appropriate exposure setting.

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