Risk and Significance of Chest Radiograph and Pulmonary Function Abnormalities in an Elderly Cohort of Former Nuclear Weapons Workers

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Objective: To estimate prevalence and risk factors for International Labour Organization radiographic abnormalities, and assess relationship of these abnormalities with spirometry results in former Department of Energy nuclear weapons workers. **Methods:** Participants were offered chest x-ray (CXR) and lung function testing. Three occupational medicine physicians read CXRs. **Results:** Forty-five (5.9%) of 757 screened workers were found to have isolated parenchymal abnormalities on CXR and this rate is higher than that in many Department of Energy studies. Parenchymal and pleural and isolated pleural abnormalities were found in 19 (2.5%) and 37 (4.9%) workers, respectively, and these rates are lower than those in other Department of Energy studies to date. Lung function impairment was associated with radiographic abnormalities. **Conclusions:** This study found an elevated rate of parenchymal abnormalities compared to other DoE populations but the effect of age or other causes could not be ruled out.

Limited data are available on the epidemiology of pneumoconiosis in the Department of Energy (DoE) nuclear weapons workforce. Cross-sectional studies have reported the prevalence of parenchymal abnormalities, on the basis of reviews of chest x-rays (CXRs) according to the International Labour Organization's International Classification System of Radiographs of Pneumoconioses (ILO system), to range from 2.2% in former construction and craft workers to 17.5% in former plutonium workers.[1–3] Abnormalities of the pleura consistent with pneumoconiosis have been reported to range from 11.3% in former nuclear weapons production workers to 19.9% in former construction workers, whereas those involving both parenchyma and pleura range between 3.2% and 3.7% in the same groups of workers.[2–4]

Nuclear weapons workers are at risk for a variety of exposures known to be associated with work-related lung disease. Studies have confirmed exposure to beryllium and ionizing radiation (respirable radionuclides) in former production workers,[3–7] whereas exposures to asbestos and silica have been reported primarily in construction and trade workers from DoE facilities.[2,8,9] High explosives and barium nitrate have been commonly used in the manufacturing of nuclear weapons[10] but data are lacking regarding the degree and potential pulmonary effects of these exposures.

Epidemiological research on the risk factors for lung disease in nuclear weapons industry has shown that beryllium and ionizing radiation are associated with radiographic changes to lung parenchyma[3,5,7] whereas asbestos may be linked to parenchymal and pleural abnormalities in combination or individually.[4] Studies of other industries have also shown parenchymal effects of aluminum powders used commonly in the manufacturing of high explosives[11–13] but population-based data from the nuclear weapons industry are lacking. Also lacking are data on the effect of airborne exposure to barium dusts in this industry, the risk factor that was previously reported to result in at least transient radiographic evidence of parenchymal abnormalities in workers in barium industry.[14]

Radiographic evidence of work-related lung disease has been found to be associated with obstructive airways impairment in former construction and trade workers from across the DoE industry.[9] This finding has important implications for medical surveillance of construction trade workers but DoE sites' production processes and exposures differ dramatically. The association between the radiographic evidence of pneumoconiosis and restrictive airways physiology and the effect of changes in spirometry interpretation standards, based on the lower limit of normal (LLN), on this association have not been studied well, and the implications of this being a geriatric cohort have not been evaluated.

The purpose of this article is to describe the epidemiology and risk factors for and the association of radiographic evidence of parenchymal and pleural abnormalities with spirometry results in a population of former nuclear weapons workers from a single Load, Assembly, and Pack nuclear weapons assembly facility in the Midwest. Between 1949 and mid-1975 this site manufactured, refurbished, and disassembled nuclear weapons under contractual agreement with DoE (formerly Atomic Energy Commission). Exposures to high explosives, beryllium and asbestos but not respirable radionuclides, were common and several tons of high explosives and other nonfissile materials were tested and disposed on-site. The DoE-funded medical surveillance for work-related lung disease at this site was part of the nationwide former DoE workers screening program mandated in 1993 by the U.S. Congress under section 3162 to Public Law 102-484.

MATERIALS AND METHODS

Approval for the study was received from the University of Iowa institutional review board. The details of the needs assessment, identification of the DoE workforce, recruitment of participants, and assessment of exposure potential have been described previously.[15] In short, the contractor's archived employment rosters were used to identify all workers employed on-site between 1948 and 2002. Employment in the DoE was confirmed using contract-specific job codes and job titles supported by information from the local union's seniority log books, radiation-monitoring dosimetry badge records, and lists of workers involved in accidents on DoE lines. Former

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TABLE 1. Exposure Categories and Jobs

Exposure	Beryllium	Asbestos	High Explosives/Barium
Category 0:No exposure, same as background	Administrative, security, storage, medical, power plant, firing site, auto/equipment mechanic, cafeteria, carpenter, custodian	Not assigned	Administrative, security, medical, power plant, cafeteria, carpenter, custodian, auto/equipment mechanic
Category 1:Rare/low indirect or bystander	Production and explosive operator, scientist, engineer, pipefitter, plumber, electrician, laundry	Administrative, security, storage, medical, laundry, custodian, electrician, firing site, production and explosive operator, millwright, tool and die, machinist	Production (assembly), laundry, millwright, tool and die, machinist, inspector, storage
Category 2:Occasional, direct or indirect	Millwright, tool and die, machinist	Power plant, auto/equipment mechanics	Pipefitter, plumber, process engineer, firing site
Category 3:Frequent, direct	Not assigned	Pipefitter, plumber, carpenter,	Production (fabrication) and explosive operator melt operator, scientist

noncontractor workers including food services workers or inspectors, and scale repairmen employed directly by the federal government were allowed to participate in the screenings after confirmation of their DoE employment by other DoE workers or records from the plant.

Workers' contact information was obtained from state driver's license records and major credit bureaus with occasional updates through World Wide Web searches. Workers were contacted primarily by mail, and information about the screenings was distributed throughout the local media and the project's Web site. No minimum duration of employment was required and there were no specific restrictions that would prevent workers' participation in the medical screenings on the basis of age, health status, or geographic location.

Exposure Assessment

Exposure potential to asbestos, high explosives, and barium was assessed using the methods described for beryllium in the previous article.[15] There were no environmental data available for these exposures, and interviews with former production, trade, and health and safety workers were queried by the project's industrial hygienists to refine the qualitative exposure estimates from a job title–based exposure matrix. This matrix (Table 1) ranked jobs into those associated with virtually no exposure or lowest exposure potential at this facility (category 0), those involving rare exposures with potential for bystander or indirect exposure (category 1), those with occasional exposure potential including bystanders or indirectly exposed (category 2), and jobs with frequent exposure potential also including bystanders and indirectly exposed (category 3). Every worker in the screened cohort was subsequently assigned their highest-ever exposure category for all jobs worked on-site for each of the exposures under analysis. Exposure to ionizing radiation was not studied because, according to former workers, most radioactive products were shipped enclosed from other DoE sites, and the risk for work-related lung disease from radionuclides would have been minimal at most except for radon progeny in the underground storage areas.[16,17]

Contractor's wage and salary schedules, matched on job codes and wage information, were used to fill in the missing employment dates for 20 (3.8%) workers used before 1951, before the contractor took over the plant operations from the federal government. For workers with no wage information in the records ($n = 184$; 24.6%), a 1-year term of employment was arbitrarily used from the first available termination date to estimate the earliest hire date on-site.

Screening for Lung Disease and Sensitization to Beryllium

Each worker participating in the screenings signed an informed consent form before being offered CXR, blood testing for effects of exposure to beryllium, and spirometry. Chest x-rays were taken digitally and participant's most recent posteroanterior film was reviewed in hard copy independently, for quality assurance purposes, by three occupational medicine physicians experienced in the ILO system. Workers with a CXR taken within 12 months before the screenings had those films reviewed instead. Readers used the ILO used the ILO (rev. 2000) classification of radiographs[1] and were blinded to worker's age, smoking history, exposure information, and radiologist's and each other's readings. No repeat readings were done to assess the intrareader agreement because of the nature of the program, that is, federally funded surveillance aimed to provide medical testing to all eligible participants with ILO readings used as a part of the medicolegal evidence of work-relatedness of lung disease for workman's compensation purposes. Each of the readers had more than 20 years of experience in ILO interpretation of radiographs for other research projects before the beginning of this study.

Multiple ILO readings were reconciled using the median profusion score, and agreement between the majority ($\geq$2/3) of readers was required to classify the positive pleural reading as consistent with pleural abnormalities. The 12-point ILO system profusion score was compressed, for the risk factor analysis, to seven groups according to Miller et al[18] and the three highest groups, 4, 5, and 6, were combined into one category because of the small number of observations. The groups were distributed as follows: $0/-$ and $0/0 =$ group 0; $0/1 =$ group 1; $1/0 =$ group 2; $1/1 =$ group 3; 1/2 through $3/+ =$ group 4. ILO abnormalities were also expressed as dichotomous outcome (yes/no), with profusion score $\geq 1/0$ used as a cutoff point. Distribution of ILO abnormalities and associations with the independent variables under study was evaluated separately for parenchymal, parenchymal and pleural, and pleural abnormalities.

Sensitization to beryllium was evaluated by blood Beryllium Lymphocyte Proliferation Testing (BeLPT) in accordance with the DoE-approved standard laboratory protocol for BeLPT testing as described previously in the literature.[15,19,20] Sensitization to beryllium carries a risk for progression to chronic beryllium lung disease[21]; therefore, results of BeLPT screenings were included in the analyses to assess the association between confirmed beryllium exposure and radiographic evidence of lung abnormalities. A confirmed abnormal BeLPT result was defined according to current consensus in the literature as two abnormal results or one abnormal and one borderline result from any DoE-approved laboratory.[8,22]

Spirometry was performed according to the American Thoracic Society[23] guidelines by trained personnel, with calibration of testing equipment before each screening day.[24] A reasonable effort was made to obtain at least three acceptable and reproducible results but no test was rejected on the basis of the lack of three tests.[25] The LLN values for forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1/FVC ratio were calculated using formulas suggested by Hankinson et al[26] and on the basis of the results from the Third National Health and Nutrition Examination Survey.

Spirometry results were interpreted according to the American College of Occupational and Environmental Medicine–recommended algorithm for use with LLN values.[27] A decrease in FEV_1/FVC ratio (<LLN) accompanied by a decrease in FEV_1 (<LLN) was interpreted as obstructive airways. A decrease in FEV_1/FVC ratio without decrease in FEV_1 was considered normal physiology but follow-up evaluation for borderline obstruction was recommended. Restrictive impairment was suspected in cases with FEV_1/FVC ratio greater or equal to LLN and FVC < LLN. A decrease below the LLN values in all three parameters was considered a possible mixed obstructive and restrictive airways physiology. All results with FVC, FEV_1, and FEV_1/FVC greater or equal to LLN were considered normal and those that could not be interpreted according to the criteria mentioned earlier were labeled inconclusive and repeat testing was recommended.

Every worker with abnormal results on any of the screening tests was referred for clinical evaluation, but this evaluation was not part of the screening protocol and results of the follow-up care are not available.

Analysis

All analyses were performed using Windows SAS 9.2 statistical software (SAS Institute Inc., Cary, NC)[28] on de-identified data. Workers' age was calculated as of the date of their CXR and never-smokers were defined as participants with less than 20 packs of smoking history during their lifetime. Ex-smokers and current smokers were combined into one category of ever-smokers in the interest of sample size.

Frequencies of ILO abnormalities were calculated for all categorical independent variables under study, and means, standard deviations, and ranges were computed for continuously distributed data, such as age. The Fisher exact test was used to evaluate the hypothesis of no difference in frequencies of dichotomous outcome variables whereas trend in ILO profusion by multicategorical covariates was tested using the Cochran-Armitage test and chi-square test. The Shapiro-Wilk test was applied to test the normality of the continuously distributed data, and difference in medians between those with abnormal ILO readings and those with no abnormalities was compared using the Wilcoxon ranked sum test. The unadjusted association of each of the categorical covariates with parenchymal, pleural, and parenchymal and pleural abnormalities was assessed by crude odds ratios and 95% confidence intervals (CIs), calculated using simple logistic regression methods. Kendall-tau coefficients for categorically ordered variables and Spearman rank correlation coefficients for continuously distributed data were calculated to examine correlation between independent predictors.

Multivariable logistic regression models were tested to assess the association of ILO abnormalities with each of the exposures under study while controlling for potential confounders. Each model was built using forward selection with an entry P value of 0.15, and separate models were generated for parenchymal, pleural, and parenchymal and pleural abnormalities. Cases were defined by positive findings on ILO reading and each type of abnormality was modeled separately; for example, the parenchymal model included all cases with parenchymal abnormalities but no pleural or coincident parenchymal and pleural abnormalities. The rate ratio for parenchymal abnormalities was assessed for each of the exposures under study. Exposure to asbestos was selected as the only risk factor to be modeled in pleural, and parenchymal with pleural abnormalities models on the basis of the literature. All analyses were adjusted for noncollinear confounders and age was chosen as a proxy for the first date of hire. Exposure to barium was strongly correlated with exposure to high explosives ($P < 0.001$) and the latter was chosen as a surrogate for both exposures. Isolated parenchymal and coincident parenchymal and pleural abnormalities were also analyzed in models with ILO profusion score strata defined according to Miller et al[18] and described in the Methods section.

The association of ILO abnormalities with spirometry results was assessed by multivariable logistic modeling. These models were built for relevant categories of spirometry interpretations with specific type of ILO abnormality as the dependent variable, analyzed separately from the other two types and adjusted for nonlinear confounders.

All statistical tests conducted were double-sided and a $P <$ 0.05 was selected as a level of statistical significance in all analyses throughout the study.

RESULTS

A total of 1005 of an estimated 3617 eligible living former DoE workers were screened and received a posteroanterior CXR or had their most recent films submitted for ILO review. Of this total, 757 (75.0%) workers had their films reviewed by all three ILO readers and were included in the study of risk factors. There were 12 (1.2%) workers with unreadable films, 26 (2.6%) with CXR taken more than 12 months before the screenings, and 210 (21.0%) with incomplete set of one or two readings only, and all of those individuals were excluded from the analyses.

The prevalence of radiographic abnormalities and their distribution by variables under study are presented in Table 2. There were 45 (5.9%) workers identified with isolated parenchymal abnormalities, 37 (4.9%) with pleural, and 19 (2.5%) with both parenchymal and pleural. Among those with isolated parenchymal abnormalities, there were 27 workers with profusion score 1/0, 10 with 1/1, 3 with 1/2, 2 with 2/1, and 1 of each in 2/2, 2/3, and 3/2 category. Of those with parenchymal and pleural abnormalities, there were nine workers with profusion score 1/0, five with 1/1, four with 1/2, and one with 2/2. On average, workers with ILO abnormalities were 5 to 6 years older than those with no abnormalities consistent with pneumoconiosis and a statistically significant trend in increasing prevalence with age was noted for all three types of abnormalities. Age was strongly correlated with the first date of hire ($P < 0.001$) and there was a statistically significant association found between earlier hire date and presence of parenchymal abnormalities alone and pleural abnormalities alone. Spirometry results were significantly associated with each type of radiographic abnormalities under study.

Associations With Measures of Exposure and Other Independent Variables Under Study

The results of unadjusted analysis of associations of ILO abnormalities with all the *a priori* selected independent variables are presented in Table 3. Ever working in highest exposure class to asbestos (category 3 exposure) was associated with a statistically significant increase in likelihood of pleural abnormalities on CXR, when compared to employment in jobs with lowest exposure potential–job exposure matrix category 1 exposures. The oldest workers had

TABLE 2. Characteristics of DoE Medically Screened Workforce By Dichotomous ILO Abnormality Categories

Parameter	Parenchymal ($n = 45$)	Parenchymal and Pleural($n = 19$)	Pleural ($n = 37$)	Not Abnormal ($n = 656$)
Age (yrs), *n* (%)				
≤59	3 (2.6)	2 (1.7)	2 (1.7)	114
60–69	9 (4.1)	2 (1.0)	8 (3.7)	208
70–79	20 (7.7)	8 (3.2)	15 (5.9)	240
≥80	13 (12.1)	7 (6.9)	12 (11.3)	94
*P**	0.01	<0.01	<0.01	
Mean (SD), range	74(9); 54–92	75(9); 53–87	75(9); 54–91	69(9); 47–94
P†	<0.01	<0.01	<0.01	
Sex, *n* (%)				
Female	7 (5.0)	1 (1.0)	4 (2.9)	134
Male	38 (6.8)	18 (3.3)	33 (5.9)	522
P‡	0.56	0.15	0.20	
Race, *n* (%)				
white	44 (6.5)	18 (2.8)	37 (5.5)	631
Other	1 (3.8)	1 (3.8)	– (0.0)	25
P‡	1.00	0.53	0.64	
Smoking, *n* (%)				
Never-smoker	11 (5.0)	4 (1.9)	10 (4.5)	210
Ever-smoker	34 (7.1)	15 (3.3)	27 (5.7)	446
P‡	0.32	0.45	0.59	
First date of hire, *n* (%)				
<1/1/1950	4 (14.3)	1 (4.0)	4 (14.3)	24
1/1/1950–12/31/1959	28 (9.3)	12 (4.2)	20 (6.8)	272
1/1/1960–12/31/1969	11 (3.2)	6 (1.8)	13 (3.8)	328
1/1/1970–6/30/1975	1 (4.2)	– (0.0)	– (0.0)	23
Missing	1 (10.0)	– (0.0)	– (0.0)	9
*P**	<0.01	0.66	<0.01	
Beryllium sensitized, n (%)				
No	42 (6.3)	18 (2.8)	34 (5.1)	627
Yes	1 (10.0)	1 (10.0)	– (0.0)	9
Missing	2 (9.1)	– (0.0)	3 (13.0)	20
P‡	0.59	0.33	0.17	
Beryllium exposure, *n* (%)				
Category 0	22 (6.4)	7 (2.1)	17 (5.0)	321
Category 1	19 (6.3)	9 (3.1)	18 (6.0)	281
Category 2	3 (6.7)	3 (6.7)	2 (4.5)	42
Missing	1 (7.7)	– (0.0)	– (0.0)	12
*P**	0.78	0.15	0.92	
Asbestos exposure, *n* (%)				
Category 1	39 (6.5)	15 (2.6)	27 (4.6)	558
Category 2	3 (7.9)	1 (2.8)	2 (5.4)	35
Category 3	2 (3.8)	3 (5.6)	8 (13.6)	51
Missing	1 (7.7)	– (0.0)	– (0.0)	12
*P**	0.67	0.19	0.01	

*Cochran-Armitage test.
†Wilcoxon ranked sum test.
‡Fisher exact test.

statistically significant increase in rates of isolated parenchymal and pleural abnormalities when compared to the youngest group, and abnormal spirometry results were found to be associated with the increased likelihood of all types of ILO abnormalities.

Table 4 presents results of multivariable logistic regression analyses of association of occupational exposures with all types of ILO abnormalities separately and defined as dichotomous outcomes. Each model was adjusted for age, sex, race, and smoking, and none showed a statistically significant association of exposures under study with ILO abnormalities. There was a suggestion of an increased likelihood of coincident parenchymal and pleural and isolated pleural abnormalities with exposure to asbestos, but the results

TABLE 3. Unadjusted Analysis of Predictors of ILO Radiographic Abnormalities

Predictor, *n* (%)	Parenchymal OR (95% CI) (*n* = 45)	Parenchymal and Pleural OR (95% CI) (*n* = 19)	Pleural OR (95% CI) (*n* = 37)
(yrs)			
≤59	1.0	1.0	1.0
60-69	1.64 (0.44–6.19)	0.55 (0.08–3.94)	2.19 (0.46–10.50)
70–79	3.17 (0.92–10.88)	1.90 (0.40–9.09)	3.56 (0.80–15.84)
≥80	5.26 (1.45–18.99)	4.25 (0.86–20.92)	7.28 (1.59–33.33)
Sex			
Female	1.0	1.0	1.0
Male	1.39 (0.61–3.19)	4.62 (0.61–34-92)	2.12 (0.74–6.08)
Race			
White	1.0	1.0	NA
Other	0.57 (0.08–4.33)	1.40 (0.18–10.93)	
Smoking			
Never-smoker	1.0	1.0	1.0
Ever-smoker	1.46 (0.72–2.93)	1.77 (0.58–5.39)	1.27 (0.60–2.68)
Beryllium sensitized			
No	1.0	1.0	NA
Yes	1.66 (0.21-13.40)	3.87 (0.47–32.20)	
Beryllium exposure			
Category 0	1.0	1.0	1.0
Category 1	0.99 (0.52–1.86)	1.47 (0.54–4.00)	1.21 (0.61–2.39)
Category 2	1.04 (0.30–3.63)	3.28 (0.82–13.15)	0.90 (0.20–4.03)
Asbestos exposure			
Category 1	1.0	1.0	1.0
Category 2	1.23 (0.36–4.17)	1.06 (0.14–8.28)	1.18 (0.27–5.17)
Category 3	0.56 (0.13–2.39)	2.19 (0.61–7.81)	3.24 (1.40–7.51)
Explosives exposure			
Category 0	1.0	1.0	1.0
Category 1	0.57 (0.22–1.49)	0.65 (0.12–3.40)	1.13 (0.47–2.71)
Category 2	0.82 (0.23–2.91)	1.86 (0.35–9.86)	0.71 (0.16–3.27)
Category 3	1.0 (0.50–1.99)	1.89 (0.64–5.62)	0.94 (0.43–2.08)
Spirometry			
Normal	1.0	1.0	1.0
Obstructive	3.34 (1.17–9.58)	2.41 (0.27–21.20)	1.85 (0.40–8.55)
Restrictive	1.91 (0.93–3.92)	3.92 (1.26–12.17)	2.64 (1.21–5.74)
Mixed	2.76 (1.04–7.28)	6.62 (1.72–25.49)	3.82 (1.39–10.51)

Abbreviations: NA, not applicable; CI, confidence interval; ILO, International Labour Organization; OR, odds ratio.

were not statistically significant. The algorithm for ILO readings stratified into five major profusion groups according to Miller et al[18] did not converge and no models were built.

Associations With Spirometry Results

Table 5 presents results of multivariable logistic regression analyses of associations of spirometry results, adjusted for age, sex, race, and smoking with ILO abnormalities. The results of these analyses confirmed the unadjusted findings of Table 3, showing associations of lung function abnormalities with radiographic findings.

DISCUSSION

The 5.9% prevalence rate of parenchymal abnormalities in this study is comparable with the 5.4% rate of parenchymal abnormalities found in another population of former DoE production workers from a single nuclear reservation but higher than the 2.2% rate reported in construction and trade workers from three former DoE sites combined.[2,4] Although based on a different protocol, with multiple instead of single ILO readers, this increase is somewhat surprising given the low overall potential for exposure to beryllium, the main hazard evaluated in the pathogenesis of parenchymal disease in this population.[15] Also exposure to inhaled radionuclides would likely have been insignificant for this workforce, as most of the radioactive materials handled on-site were enclosed and ready-to-assemble into the weapon, shipped from other DoE sites. Exposure to asbestos, although widely used at this facility with hundreds of miles of asbestos-fitted steam pipes and all workers potentially exposed to levels above background, was not found to be associated with increase in prevalence of parenchymal abnormalities, and the 4.9% rate of pleural and 2.5% of parenchymal and pleural abnormalities in this study were lower than those in any of the other DoE studies. Direct exposure to high explosives and barium additives, as subsets of this workforce were potentially exposed to a variety of trinitrotoluene-derived high-energy nitrate explosive compounds, was found to be associated with higher prevalence of combined parenchymal and pleural abnormalities but the result was not statistically significant.

TABLE 4. Logistic Regression Models for Exposures as Predictors of ILO Radiographic Abnormalities

Exposure predictor*	Parenchymal OR (95% CI)	Parenchymal and Pleural OR (95% CI)	Pleural OR (95% CI)
Beryllium			
Category 0	1.0	NA	NA
Category 1	0.99 (0.52–1.88)		
Category 2	0.75 (0.21–2.65)		
P	0.90		
Asbestos			
Category 1	1.0	1.0	1.0
Category 2	0.94 (0.27–3.24)	0.67 (0.08–5.30)	0.92 (0.21–4.06)
Category 3	0.38 (0.09–1.65)	1.20 (0.32–4.51)	2.21 (0.92–5.29)
P	0.43	0.89	0.19
Explosives			
Category 0	1.0		
Category 1	0.60 (0.23–1.58)	NA	NA
Category 2	0.70 (0.20–2.51)		
Category 3	1.01 (0.50–2.02)		
P	0.69		

*Controlled for age, sex, race, and smoking.

TABLE 5. Logistic Regression Models for Spirometry Results as Predictors of ILO Radiographic Abnormalities

Spirometry results*	Parenchymal OR (95% CI)	Parenchymal and Pleural OR (95% CI)	Pleural OR (95% CI)
Normal	1.0	1.0	1.0
Obstructive	2.96 (1.01–8.71)	2.03 (0.23–18.27)	1.68 (0.36–7.93)
Restrictive	2.00 (0.96–4.15)	4.14 (1.32–13.01)	2.82 (1.28–6.20)
Mixed	2.35 (0.87–6.39)	1.36 (1.36–22.11)	3.25 (1.16–9.08)
P	0.09	0.05	0.04

*Controlled for age, sex, race, and smoking.

Collapsing exposure categories for any of the exposures under study did not reveal different results.

Previous studies have shown that smoking is a risk factor for pulmonary fibrosis and adds to the risk of development of parenchymal opacities in workers with history of heavy exposure to asbestos.[29,30] Ever-smoking was found to be associated with increased prevalence of all types of ILO abnormalities in this study but the results were not statistically significant. A detailed smoking history was not available for the whole cohort, but restricting the exposure models' analyses to a sample of 407 workers with available pack-year smoking history did not affect the lack of significance. These results most likely lacked significance because of insufficient power, but the suggestion of increased prevalence and risk for all types of ILO abnormalities among ever-smokers adds to the body of evidence on effects of smoking on occupational lung disease.

Other studies of DoE workers have shown a strong age effect, with increase in rates of both parenchymal and pleural abnormalities especially at the upper extreme of age.[2,4] This study also found increase in rates of ILO abnormalities with age ($P < 0.001$) and age was the strongest predictor of all types of ILO abnormalities in every regression analysis with P value consistently below 0.05. Although age has been previously shown to correlate with prevalence of ILO abnormalities in unexposed populations,[31] its strong association with exposure to asbestos ($P < 0.0001$) and beryllium ($P = 0.0329$), as well as that with the first date of hire ($P < 0.001$) in this study makes it difficult to discriminate the effects of age from cumulative exposure.

No medical records were available to assess the rates of ILO abnormalities in those workers who did not participate in the screenings. Nonparticipants may have differed from the screened workers in many characteristics including age, sex, race, smoking, and most importantly date of first hire and exposure potential. In addition, those who enrolled in the screenings may have self-selected themselves on the basis of their health status and concerns about the long-term effect of exposures. As this was a federally funded screening program widely advertised in the media, the screenings were opened to all confirmed former DoE workers without the opportunity to implement the traditional research design.

Exposure potential in this study was assessed on the basis of industrial hygiene estimates and input from former weapons workers with extensive knowledge of site's history and exposures. A misclassification of exposures was possible, especially because those exposures occurred several decades before the study and there were no industrial hygiene records available to quantitatively estimate exposures. The potential for bias was minimized; however, as all of those involved in estimating the exposures were blinded to individual and group screening results. In addition, all uncertainties in exposure categorization were resolved toward the highest exposures in each exposure category and as such a potential misclassification would have biased the results toward the null hypothesis.

Between- and within-reader variability in interpretation of radiographs for pneumoconioses has long been recognized as a potential issue for epidemiological studies.[32–35] The National Institute for Occupational Safety and Health[36] recommends using multiple ILO-trained readers, with median reading as a preferred reconciliatory protocol, to increase accuracy and precision in film classification. This study employed three experienced ILO readers and the agreement between them ranged from moderate to substantial for both parenchymal (simple kappa statistic, $\kappa = 0.57$, 95% CI, 0.47 to 0.67, for reader 1 vs reader 2; $\kappa = 0.67$, 95% CI, 0.59 to 0.76, for reader 1 vs reader 3; and $\kappa = 0.56$, 95% CI, 0.46 to 0.66, for reader 2 vs reader 3), and pleural abnormalities (simple kappa statistic, $\kappa = 0.61$, 95% CI, 0.50 to 0.72, for reader 1 vs reader 2; $\kappa = 0.53$, 95% CI, 0.41 to 0.64 for reader 1 vs reader 3; and $\kappa = 0.56$, 95% CI, 0.43 to 0.69 for reader 2 vs reader 3) expressed as dichotomous outcomes. The agreement in ordinal profusion scoring was substantial between all three readers (weighted kappa statistic, $\kappa = 0.68$, 95% CI, 0.57 to 0.78 for reader 1 vs reader 2; $\kappa = 0.72$, 95% CI, 0.64 to 0.80, for reader 1 vs reader 3; and $\kappa = 0.70$, 95% CI, 0.59 to 0.81 for reader 2 vs reader 3). Although minimal variability between readers is a desirable outcome, it is unknown whether and in what direction this could have biased the prevalence estimates of ILO abnormalities in this study.

A statistically significant association was found in this study between isolated pleural abnormalities and impairment of lung function on spirometry. This finding is consistent with previous findings of studies of asbestos-exposed workers.[18,37–39] Interestingly, however this association remained significant regardless of the spirometry interpretation protocol used. Using different reference values and protocols to interpret spirometry results has been shown to potentially lead to discrepancy in reporting of obstructive and restrictive airways physiology, but LLN is accepted as a more valid method in characterizing spirometric abnormalities compared to the clinically used percentage-predicted fixed cutoff values.[40–43] This study used the currently recommended Third National Health and Nutrition Examination Survey–based equations to calculate the predicted and LLN values for those workers tested with spirometry. The prevalence of obstructive airways was found, as expected, to be statistically significantly lower ($P < 0.001$) when LLN-based protocol was used (5.6%) than the fixed cutoff percentage predicted values protocol (27.9%). Restrictive airways were, however, statistically significantly ($P < 0.001$) more prevalent when LLN criteria were used (26.9%) than the traditional clinical approach (19.0%). It is not clear why such a reverse in trend occurred, but studies have found a marked shift in discordant results between the two protocols with age, in particular in those individuals older than 65 years,[41] and the mean age of participants with parenchymal and pleural abnormalities in this study was 75 years (± 9). In addition, the Third National Health and Nutrition Examination Survey equations have been generated on the basis of the population of individuals 8 to 80 years old and 13% of participants in this study were over this age limit at the time of testing. As age is becoming a growingly important issue in occupational studies, further research is needed into spirometry reference values for older individuals.

In summary, this study found an elevated prevalence of ILO parenchymal abnormalities in the population of former nuclear weapons workers at overall low risk for exposure to beryllium compared with other DoE populations. Work in high explosive, barium fabrication, and melt operations was associated with higher prevalence of combined parenchymal and pleural abnormalities compared to administrative and office jobs, but the result was not statistically significant. Conversely, the rates of ILO coincident parenchymal and pleural and isolated pleural abnormalities were lower than those in other DoE populations, but pipefitters and plumbers had an increase, although statistically nonsignificant, in risk of these abnormalities compared to office personnel. The isolated pleural abnormalities were associated with abnormalities on spirometry. This study also found a substantial agreement between ILO readers in all aspects of film review.

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