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Historical shift in pathological type of progressive massive fibrosis among coal miners in the USA

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Contributors LHTG, CSR and RAC designed the study, with input from LMZ-B, KSA, AFH, MSO, EAS and ELP. SC, DLR, AFH, MSO, LMZ-B and CI acquired the tissue specimens used in the study. JLA, CDC, ADF, FHYG, JM, SS and NIV evaluated the tissue specimens and resolved disagreements in pathology consensus conferences. LHTG, LMZ-B, KSA, CI and RAC facilitated the pathology consensus conferences. LHTG, LMZ-B and KSA contributed to the statistical analyses. LHTG wrote the initial draft of the manuscript. All authors reviewed and edited the manuscript. LHTG is the guarantor for the overall content of the manuscript.

Competing interests LHTG and RAC report preparing independent medical reviews for individuals with occupational lung disease. JLA, CDC and FHYG report pathology consultation for occupational lung disease.

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Abstract

Background—Pneumoconiosis among coal miners in the USA has been resurgent over the past two decades, despite modern dust controls and regulatory standards. Previously published studies have suggested that respirable crystalline silica (RCS) is a contributor to this disease resurgence. However, evidence has been primarily indirect, in the form of radiographic features.

Methods—We obtained lung tissue specimens and data from the National Coal Workers' Autopsy Study. We evaluated specimens for the presence of progressive massive fibrosis (PMF) and used histopathological classifications to type these specimens into coal-type, mixed-type and silica-type PMF. Rates of each were compared by birth cohort. Logistic regression was used to assess demographic and mining characteristics associated with silica-type PMF.

Results—Of 322 cases found to have PMF, study pathologists characterised 138 (43%) as coal-type, 129 (40%) as mixed-type and 55 (17%) as silica-type PMF. Among earlier birth cohorts, coal-type and mixed-type PMF were more common than silica-type PMF, but their rates declined in later birth cohorts. In contrast, the rate of silica-type PMF did not decline in cases from more recent birth cohorts. More recent year of birth was significantly associated with silica-type PMF.

Conclusions—Our findings demonstrate a shift in PMF types among US coal miners, from a predominance of coal- and mixed-type PMF to a more commonly encountered silica-type PMF. These results are further evidence of the prominent role of RCS in the pathogenesis of pneumoconiosis among contemporary US coal miners.

INTRODUCTION

Excessive coal mine dust exposure can lead to coal workers' pneumoconiosis (CWP), including its most severe form, progressive massive fibrosis (PMF). The prevalence of CWP declined after the implementation of a permissible exposure limit for respirable coal mine dust in the USA in 1972. However, the disease has been resurgent over the past two decades¹ despite a continued long-term decline in mean respirable dust levels in US coal mines.^{2,3} In 2005, an analysis of a US surveillance programme for working coal miners identified rapid progression of radiographic pneumoconiosis in 35% of miners with CWP,⁴ an unexpected finding particularly because these coal miners had worked all or nearly all their careers under modern dust regulations. In central Appalachia—a region of the USA which includes parts of Virginia, West Virginia and Kentucky—the prevalence of PMF among long-tenured miners has risen sharply, recently approaching the rate recorded before modern dust regulations were instituted.⁵

One possible cause of the current resurgence of radiographically identified CWP is excessive exposure to respirable crystalline silica (RCS). An earlier study of autopsy cases accessioned

through 1996 found that rates of cases with silicotic nodules had declined among workers whose first decade of coal mine employment had occurred in 1970 or after.⁶ However, analysis of more recent US radiographic surveillance data demonstrated a rise in the prevalence of coal miners with findings associated with simple silicotic lesions beginning in the 1990s, particularly in the central Appalachia disease ‘hotspot’.⁷ A case series of former coal miners with rapidly progressive pneumoconiosis described pathological evidence of accelerated silicosis and mixed-dust lesions, and 11 of the 13 cases had evidence of silicosis.⁸ Moreover, a recently published comparison of 23 contemporary vs 62 historical US coal miners, who differed in the likelihood with which they worked in fully mechanised coal mines, found among contemporary miners: increased silica particle concentration and percentages, increased rates of associated histopathological features of accelerated silicosis such as alveolar proteinosis, and increased rates of PMF with features of silicosis.⁹ The time at which the role of RCS might have become a major factor in the resurgence of pneumoconiosis in coal miners, however, remains unclear.

The US National Institute for Occupational Safety and Health (NIOSH), part of the Centers for Disease Control and Prevention (CDC), operates the National Coal Workers’ Autopsy Study (NCWAS). NCWAS, which was most active from 1970 to 2012, is a programme that offered families of recently deceased coal miners the opportunity to have an autopsy performed to determine the presence and severity of pneumoconiosis for use in workers’ compensation claims and public health research. We undertook the current study to analyse the entirety of available PMF lung tissue specimens from NCWAS to characterise the temporal trends in PMF type by birth cohort to further explore the potential contribution of RCS to resurgent pneumoconiosis in US coal miners.

METHODS

Study population

To be eligible for inclusion in NCWAS, coal miners had to have worked underground for more than 1 day and died after 14 May 1971. All subjects for this study were from the NCWAS dataset, which was reviewed to identify cases originally classified as PMF by NIOSH-contracted pathologists. Those cases were included in this study if the archived lung tissue specimen was adequate for evaluation as determined by review of the associated pathology slides (FHYG, AFH and MSO). The NCWAS dataset included occupational history data. At the time of the original accessioning of each case to NCWAS, the deceased miner’s next of kin submitted a short questionnaire containing basic information relating to coal mine employment, including years of underground and surface coal mining, and states where the subject worked as a coal miner.

Histological definitions and pathological scoring

Brightfield images from H&E-stained lung slides were digitally acquired at 40× magnification using an Olympus VS-120 virtual slide microscope and Olympus VS-ASW V.2.9 software (Olympus Life Science, Tokyo, Japan), and these images were classified using digital microscopy platforms by study pathologists. Pathologists were blinded to all details of the case histories other than prior employment as coal miners and that these miners

were thought to have PMF. Three pathologists (JLA, CDC and SS) evaluated specimens individually; two pairs of pathologists (FHYG/ADF and JM/NIV) submitted joint findings. This approach yielded a total of five separate classifications for all cases.

PMF was defined as a dust-related fibrotic lesion measuring greater than one centimetre in longest dimension with irregular or whorled collagen fibres, with or without necrotic areas, and presence of dust consistent with coal mine dust.⁶ To address the question of the role of RCS in PMF, we developed a classification system characterising three types of PMF lesions based on the proportion of silicotic nodules in the PMF lesions by area in the image(s) reviewed⁹ (figure 1). These were: (1) 'coal'-type PMF defined as having 25% silicotic nodules; (2) 'silica'-type PMF defined as having >75% silicotic nodules and (3) 'mixed'-type PMF having >25% and 75% silicotic nodules. Discordant classifications, defined as disagreement on the presence of a finding of PMF or on the type of PMF, were resolved by video consensus meetings involving all study pathologists. Previous work demonstrated the overall inter-rater weighted Cohen's kappa for all readers was consistent with substantial agreement ($\kappa=0.62$).¹⁰

Data analysis

To determine rates of each PMF type and overall rate of PMF by birth cohort relative to the larger NCWAS population, we excluded NCWAS cases in which there was no determination by a NIOSH pathologist as to whether pneumoconiosis was present. We evaluated rates of observed PMF type and overall rate of PMF by 5 years birth cohorts from 1885 to 1954.

We used SAS (V.9.4; SAS Institute) for all analyses. Categorical variables were compared between groups using Fisher's exact test. We used analysis of variance with post-hoc Tukey's pairwise comparison to compare mean differences in continuous variables across multiple groups. We used Joinpoint (V.4.9.0.0; Statistical Methodology and Applications Branch, Surveillance Research Programme, National Cancer Institute, Bethesda, Maryland, USA) to identify temporal trends relating to rates of PMF type cases relative to the larger NCWAS dataset and to identify any meaningful inflection points in the data. The optimal number of inflection points for each trend was assessed by using the Bayesian Information Criterion, and all models were controlled for serial correlation. To further investigate the potential role of RCS, we used multiple logistic regression to model the odds of silica-type PMF relative to other PMF types (ie, coal-type and mixed-type PMF combined) to assess factors associated with the silica-type PMF. Factors assessed included continuous variables of year of birth, age at death and years of underground coal mining, and the categorical variable of whether the coal miner had ever worked in one of the central Appalachian states of Kentucky, Virginia and West Virginia. A $p<0.05$ was considered significant.

RESULTS

Study population

Of 7200 NCWAS cases accessioned between 1970 and 2012, 6538 had recorded observations as to whether pneumoconiosis was present (online supplemental table 1). Data from four miners born in 1960 or later were censored due to small numbers. The remaining

6534 miners were born between 1885 and 1954 (table 1). Five hundred cases had been classified by NIOSH pathologists as having PMF and, of these, 370 had tissue of sufficient quality available for review. Study pathologists reviewed the available cases, and 322 cases were confirmed to have PMF based on available sections. Mean age at death was 71 years (SD 9 years). Eighty-eight per cent of the study population were identified by next of kin as white. Mean total coal mining tenure was 36.3 years (SD 9.2 years) and most were underground workers, with a mean underground tenure of 34.5 years (SD 10.6 years). Mean surface coal mining tenure was 1.8 years, and only 17 miners had 10 or more years of reported surface coal mining experience. Most coal miners with PMF were reported to have ever worked in Pennsylvania (57.8%) or West Virginia (30.0%).

Histopathological findings

Of the 322 cases found to have PMF, study pathologists characterised 138 (43%) as coal-type PMF, 129 (40%) as mixed-type PMF and 55 (17%) as silica-type PMF. There were no significant differences in age at death, race, total years of coal mining, years of underground coal mining, or years of surface coal mining among those miners in each PMF type group (table 2). There was also no significant difference in the years of reported coal mining work in the states comprising central Appalachia by PMF type. However, year of birth was significantly later among miners with silica-type PMF than among miners with coal-type PMF. Year of death in miners with coal-type PMF was significantly earlier than in miners with mixed-type or silica-type PMF.

Trends in types of PMF

Temporal trends in PMF type were evaluated using birth year as a surrogate for the year in which the miner began working. Figure 2 shows the overall rate of PMF as originally determined by NIOSH pathologists and by study pathologists, as well as the rates of coal-type, mixed-type and silica-type PMF relative to the NCWAS population by 5-year birth cohort categories. Coal-type PMF was most commonly observed in earlier birth cohorts, comprising 5.5% of the NCWAS population born 1885–1889, followed by a significant decline to no identified cases among miners born 1940 and later. The proportion of NCWAS cases with mixed-type PMF increased non-significantly until the 1915–1919 birth cohort, then declined significantly with no cases being identified among miners born 1945 and later. Silica-type PMF was initially the least frequently observed type of PMF, found in 2.1% of NCWAS cases born 1890–1894. The proportion of NCWAS cases with silica-type PMF declined until the 1935–1939 cohort. However, unlike other types of PMF, silica-type PMF could be identified among miners born 1945 and later.

Silica-type PMF

Table 3 summarises the results of logistic regression models of relationships between silica-type PMF and demographic and occupational characteristics. In crude models, later year of birth was significantly associated with increased odds of silica-type PMF compared with the other PMF types. Greater total years of underground mining was associated with lower odds of silica-type PMF. Neither total years of mining nor reported history of mining in the central Appalachian states of Kentucky, Virginia and West Virginia was associated with

increased odds of silica-type PMF in bivariate, or crude, analyses. In the adjusted model, only later year of birth was significantly associated with increased odds of silica-type PMF.

DISCUSSION

In this study, we used a robust approach to characterise the histopathological type of PMF in a large autopsy repository dedicated to evaluating lung disease in coal miners. We observed temporal reductions in rates of coal-type and mixed-type PMF, while silica-type PMF persisted in more recent birth cohorts. Notably, in multivariable analysis, only later year of birth was associated with increased odds of silica-type PMF. These findings confirm multiple PMF types found in coal miners and show that a historical shift in rates of these types has indeed occurred. This historical shift is consistent with the hypothesis that RCS exposure later became an increasingly significant factor in resurgent pneumoconiosis among more recent US coal miners.

Despite regulation aimed at limiting respirable dust exposures in coal mines, a resurgence of advanced pneumoconiosis has occurred in the USA. Some of these advanced pneumoconiosis cases have radiographic progression of unusual rapidity compared with 'classical' CWP.^{4 11} Older case-control studies examining rapid radiographic progression of pneumoconiosis found significant association with higher cumulative quartz (ie, crystalline silica) exposure and exposure to mixed dust with higher quartz content.^{12 13} More recent work using indirect evidence (eg, 'r' opacities on chest radiographs, defined as rounded opacities 3–10 mm in diameter by the International Labour Office classification¹⁴) has found an increased prevalence of silica-associated disease,⁷ and a pathological case series implicated silica and silicates in rapidly progressive pneumoconiosis.⁸ We have previously shown that contemporary US coal miners have evidence of increased silica lung burden and associated histopathological findings of silica exposure compared with historical miners.⁹ By characterising trends in PMF types in a much larger sample of US coal miners in the NCWAS through 2012, the current study underscores and expands these prior findings, first by explicitly demonstrating a temporal decline in typical coal-type PMF, and second by showing the persistence of silica-type PMF.

We suspect shifts in mining practices in the US led to increased silica exposure among coal miners in more recent birth cohorts. Mechanisation of coal extraction using devices such as continuous mining machines became widely adopted in the USA in the 1950s,¹⁵ suggesting that miners born beginning in the 1930s were more likely to have worked their entire careers in highly mechanised operations. Such advances in mining technology, along with more efficient methods to clean and process the mined material, have enabled the profitable extraction of thin seams of coal, even though substantial amounts of the surrounding rock strata are typically also extracted with the coal. This has the potential to generate more RCS dust compared with mining that is better confined to the coal seam itself; and the potential to change exposure risks for workers near the production face, where dust is generated continuously rather than during cyclic unit operations (ie, drilling, blasting, loading) associated with conventional mining methods.

The implementation of federal respirable dust exposure limits in the USA in 1972 may have contributed to the observed decline in the overall PMF rate in the NCWAS cases, since many of the miners in our study would still have been of working age at that time and likely benefitted from dust regulations. However, the persistence of silica-type PMF observed here—as well as findings from previous studies indicating that more contemporary miners have suffered from silica-associated disease^{7 8}—could be related to the indirect manner in which RCS has been regulated in US coal mines. At the time of enactment of modern dust regulations in the USA, there was a theoretical limit of 100 $\mu\text{g}/\text{m}^3$ for RCS. An analysis of respirable dust samples from US underground coal mines from 1982 to 2017 demonstrated that 19% of samples exceeded 100 $\mu\text{g}/\text{m}^3$ for RCS.² Compliance determined by measuring the quartz percentage in dust samples might not be representative of some, perhaps many, exposures. For instance, compliance dust sampling for quartz determination occurs infrequently (ie, generally on a quarterly basis) and, until 2016, such sampling was permitted at a level of production as low as 50% of the average production for a given mine. Furthermore, dust monitoring efforts have not been aimed at mine development activities (including with continuous mining machines), during which the likelihood of RCS exposure may be even greater than during coal production, since many primary openings are driven into rock rather than coal. Considering these factors, it is highly likely that many contemporary US coal miners have been exposed to RCS concentrations exceeding 100 $\mu\text{g}/\text{m}^3$.

Despite studies demonstrating that the resurgence of PMF is clustered in central Appalachia⁴ and that radiographic findings of silicosis are more frequently observed among coal miners in this region,⁷ we did not observe an association between work in a central Appalachian state and likelihood of silica-type PMF in our study. Central Appalachia typically refers to the region comprised of eastern Kentucky, southwestern Virginia, and central and southern West Virginia. The occupational data available for analysis, however, did not allow determination of employment in specific parts of a state. This presents a particularly significant challenge for Kentucky and West Virginia, which each span two distinct coal mining regions. Previous work has demonstrated that respirable dust composition and characteristics differ significantly between mine regions; for example, dust samples from central Appalachia typically have higher percentages of aluminosilicates and silica than those from northern Appalachia, though mines in both regions are located in West Virginia.¹⁶ While there are insufficient data to determine the relative breakdown, it is probable that miners from West Virginia and Kentucky in this study did not solely work in central Appalachia.

Our findings demonstrate that coal mine workers have a broad spectrum of lung histopathology which reflects their exposure to mine dusts of varied composition. Although 'r' opacities on plain chest radiography have been associated with silicosis on postmortem studies,¹⁷ the sensitivity and specificity of this feature for RCS-related disease in the mixed-dust exposures faced by coal mine workers has not been studied. Further investigation correlating pathological findings with chest CT imaging might identify chest imaging features corresponding to the histopathological patterns of disease identified in our study. This could be used to inform future medical surveillance and clinical management of this population.

Our study had several strengths. Most prior studies of PMF have relied on chest imaging, rather than tissue specimens, to assess for the possible contributions of RCS to disease, but this indirect approach cannot confirm the contribution of RCS to observed shifts in PMF severity and prevalence. Using the NCWAS, which has the largest lung tissue repository for coal mine dust lung disease in the USA, and outside of South Africa, the largest for mining-related lung diseases internationally, we were able to histopathologically confirm the presence of PMF and characterise the historical trends in PMF types among coal miners in the USA. We also used a group of expert occupational pulmonary pathologists using digital microscopy platforms to identify and characterise PMF lesions. We were able to leverage their experience to resolve discordant reads. Final consensus was achieved via virtual conference.

Our study had several limitations. It is possible that the observed predominance of coal-type and mixed-type PMF among miners from earlier birth cohorts may have resulted from survivor bias, as NCWAS did not begin accessioning cases until 1971. However, this would not explain the absence of these PMF types among the most recent birth cohorts. Next, due to a decline in the number of cases accessioned to NCWAS in more recent years, there were fewer histologically available cases of PMF with which to characterise PMF type among more recent birth cohorts. Our recent study found relatively few cases of contemporary miners who had undergone surgical lung biopsies, resections, lung transplants or autopsies outside of NCWAS.⁹ We speculate that this reduction in lung tissue samples may be related to widespread use of advanced chest imaging, such as CT, which largely obviates the need to perform surgery or autopsy to diagnose PMF. Also, there were limitations related to characterising each miner's occupational exposures. Since available occupational histories were limited, we were unable to assess specific job duties and cumulative dust exposure. The lack of more detailed occupational histories or exposure data may be why we observed little difference between the crude and adjusted modelling of the odds of silica-type PMF. We also found cases previously characterised as PMF by NIOSH pathologists that study pathologists could not confirm, and we were unable to obtain samples from all NCWAS cases originally characterised as having PMF by NIOSH pathologists. This may have affected the relative proportions of PMF types we observed. Finally, the large number of miners in the study who worked in the states of Pennsylvania and West Virginia may represent referral bias given NCWAS's location in northern West Virginia, rather than being representative of the overall mining population.

CONCLUSION

Our study demonstrates a significant shift in PMF types in US coal miners which provides further evidence that excessive exposure to RCS is important in the pathogenesis of resurgent severe pneumoconiosis in contemporary miners. Our findings underscore the importance of controlling RCS to prevent disease among modern US coal miners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

No data are available.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Previously published studies have suggested that respirable crystalline silica (RCS) is a contributor to the resurgence of pneumoconiosis in the USA, but the evidence for this has been primarily indirect and in the form of radiographic features.

WHAT THIS STUDY ADDS

- We found evidence of the prominent role of RCS in the pathogenesis of pneumoconiosis among contemporary US coal miners.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The findings of this study underscore the importance of controlling RCS to prevent disease among coal miners.

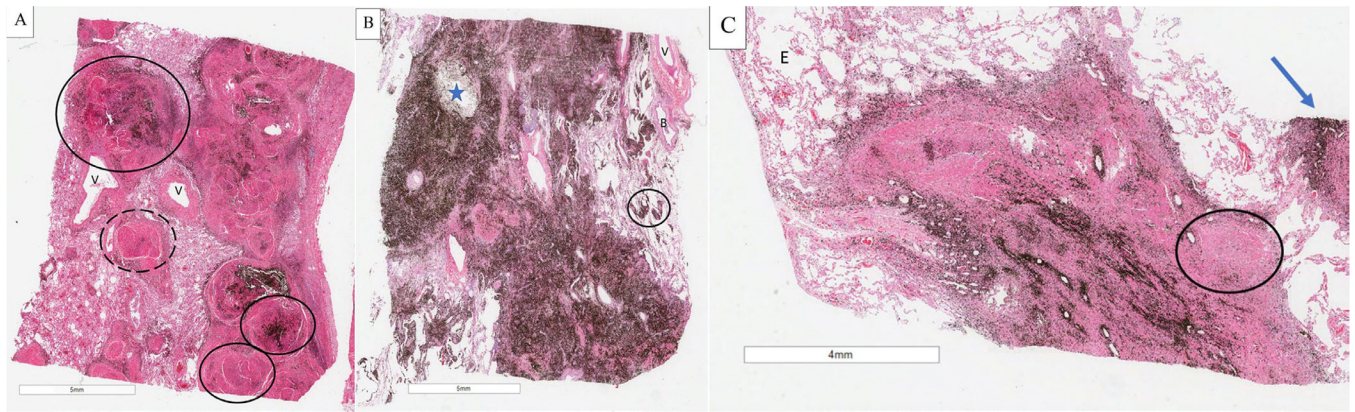


Figure 1.

Representative examples of silica, coal and mixed types of PMF, (H&E stains). (A) Silica-type PMF (>75% silicotic nodules). This lesion of silica-type PMF, extending from the upper portion of the section to bottom-right quadrant, consists of a conglomeration of rounded silicotic nodules (solid black circles) admixed with a moderate degree of black coal pigment. Black coal pigment is present, but to a lesser extent than is visible in the coal or mixed-type PMF lesions. This silica-type lesion is transected at top and bottom of the section, indicating that the actual lesion is larger than is visible on this slide. Also evident are silicotic nodules (< 10 mm in greatest linear dimension) in the surrounding lung tissue (dotted black circle). The remainder of the lung parenchyma shows scattered coal macules. V=vessel. (B) Coal-type PMF lesion (< 25% silicotic nodules). In contrast to the silica-type PMF, this lesion consists of dense coal deposits associated with underlying fibrosis resulting in a large lesion measuring greater than 10 mm in greatest linear dimension. There is focal necrosis with cavitation typified by the cystic appearing space partially filled with degenerating material (blue star). No significant silicotic nodules are identified within this lesion. The surrounding lung parenchyma shows abundant coal macules (example in black circle) and nodules associated with centriacinar emphysema. V=vessel, B=bronchiole. (C) Mixed-type PMF (>25% and < 75% silicotic nodules). The mixed type of PMF shows both silicotic nodules (example in black circle) and dense coal deposits resulting in a lesion greater than 10 mm in greatest linear dimension. The silicotic nodule component consists of rounded to elongated parallel collagen fibres. This lesion was partially transected at bottom of the section, indicating that this lesion is larger than is visible on this single slide. To the right of the PMF lesion, there is a portion of a coal nodule (blue arrow). The remainder of the lung parenchyma shows emphysematous changes (E=area of emphysema). PMF, progressive massive fibrosis.

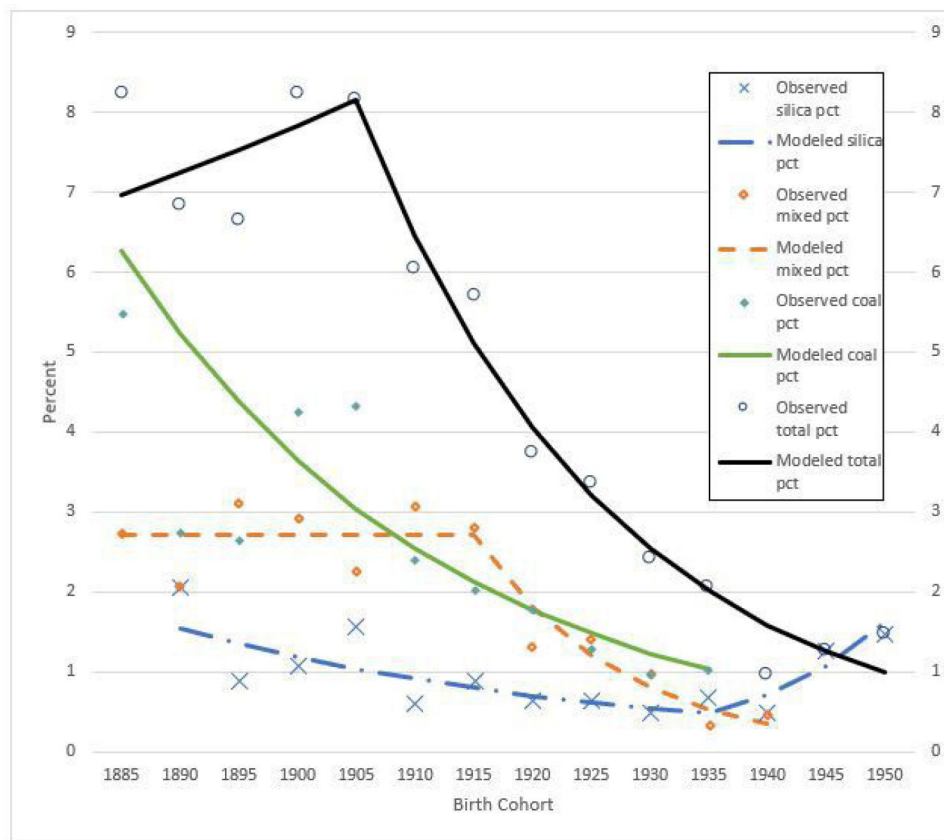


Figure 2.

Rates of PMF and PMF types relative to NCWAS population by 5-year birth cohort.

Best-fit trend lines for PMF types do not include periods in which no cases of that type were identified (eg, coal-type PMF for 1940–1944 birth cohort). NCWAS, National Coal Workers' Autopsy Study; PMF, progressive massive fibrosis.

Table 1

Demographic and mining characteristics of cases

N	322
White (n, %)	284 (88.2)
Age at death (years) (mean, SD)	71.2 (9.0)
Year of birth (median, IQR)	1914 (1906–1920)
Year of death (median, IQR)	1984 (1978–1992)
Coal mine experience (n, %)	
Underground only	259 (80.4)
Underground and surface	56 (17.4)
Incomplete data	7 (2.2)
Total years of coal mining (mean, SD) *	36.3 (9.2)
Years of underground coal mining [†]	34.5 (10.6)
Years of surface coal mining [†]	1.8 (5.9)
Ever smoker (n, %)	201 (62.4)
States worked [‡]	
Central Appalachia	130 (42.4)
West Virginia	90 (30.0)
Virginia	29 (9.0)
Kentucky	11 (3.4)
Rest of USA	209 (64.9)
Pennsylvania	186 (57.8)
Ohio	13 (4.0)
Other states [§]	10 (3.1)
Unknown/incomplete	2 (0.6)

* Data for n=319 subjects due to incomplete information.

[†] Data for n=315 subjects due to incomplete information.

[‡] Subject ever had any coal mine employment listed in these states; sum of percentages exceeds 100% because miners may have worked in multiple states.

[§] Other states were Illinois, Alabama, Utah, Colorado and Wyoming.

Table 2

Demographic and mining characteristics of cases by type of PMF

	Coal type	Mixed type	Silica type	P value
n	138	129	55	
White (n, %)	118 (86.1)	117 (90.7)	49 (89.1)	NS
Age at death (years) (mean, SD)	70.8 (8.6)	72.2 (8.5)	70.1 (10.6)	NS
Year of birth (mean, SD)	1912 (11)	1914 (10)	1917 (15)	0.025
Year of death (mean, SD)	1984 (8)	1986 (9)	1988 (10.4)	0.005
Coal mine experience (n, %)				NS
Underground only	111 (83.5)	107 (83.4)	41 (75.9)	
Underground and surface	22 (16.5)	21 (16.4)	13 (24.1)	
Total years of coal mining (mean, SD)	36.4 (8.5)	36.7 (9.4)	34.9 (10.3)	NS
Years of underground coal mining	35.1 (9.3)	35.1 (10.8)	31.6 (12.4)	NS
Years of surface coal mining	1.3 (4.8)	1.6 (6.1)	3.3 (7.8)	NS
Work in central Appalachia	60 (43.5%)	40 (31.0%)	22 (17.1%)	NS

NS, not significant; PMF, progressive massive fibrosis.

Table 3

Odds of silica-type PMF versus non-silica- type (ie, mixed-type or coal-type) PMF

	Crude			Adjusted*		
	OR	95% CI		OR	95% CI	
Year of birth [†]	1.18	1.04	1.34	1.22	1.02	1.45
Age at death	0.98	0.95	1.02	1.02	0.98	1.07
Years of underground coal mining	0.97	0.95	1.00	0.98	0.95	1.01
Region worked						
Central Appalachia [‡]	1.11	0.62	2.02	0.98	0.52	1.86
Rest of USA	Ref			Ref		

* Adjusted ORs and CIs are derived from a multivariate logistic regression model that includes all covariates listed in the table.

[†] Every 5 years after 1885.

[‡] Central Appalachia includes Kentucky, Virginia and West Virginia.

PMF, progressive massive fibrosis.