ORIGINAL ARTICLE

Extended follow-up of lung cancer and non-malignant respiratory disease mortality among California diatomaceous earth workers

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ABSTRACT

Objectives Millions of workers worldwide are employed in occupations involving potentiality hazardous exposure to crystalline silica. The diatomaceous earth industry can have particularly high exposures, but there is a lower likelihood of simultaneously occurring confounding exposures. We extended follow-up for diatomaceous earth industry workers previously studied for mortality.

Methods The cohort included 2342 white men who were employed for at least 1 year at a diatomaceous earth plant in Lompoc, California beginning in 1942. Workers' vital status was updated using the National Death Index through 2011, an extension of 19 years from earlier studies. Detailed work history and quantitative air monitoring measurements estimated exposure intensity. Cox proportional hazards modelling estimated HRs and 95% CIs. SMRs were calculated.

Results Elevated mortality was observed by quartile of cumulative crystalline silica exposure for lung cancer (HR=2.03, 95% CI 1.07 to 3.85, highest quartile, unlagged) and non-malignant respiratory disease (NMRD) (HR=3.59, 95% CI 1.94 to 6.67, highest quartile, unlagged), although trends were not statistically significant. Associations were attenuated when adjusted for smoking and asbestos exposure. Mortality from NMRD was significantly increased over the entire follow-up compared to the general population (SMR=1.37, 95% CI 1.17 to 1.60). An increase for lung cancer was confined to the earlier follow-up (SMR=1.29, 95% CI 1.01 to 1.61).

Conclusions The risk of lung cancer and NMRD mortality remained elevated, although generally non-significant, and exposure-response trends with cumulative crystalline silica persisted on extended follow-up of this cohort. The findings support a generally consistently observed aetiological relation between crystalline silica and lung cancer.

What this paper adds

- Tens of millions workers worldwide are exposed to crystalline silica, a classified human lung (category 1) carcinogen. Previous analyses have indicated that occupational exposure limits may be inadequate.
- Study findings on the updated mortality status of a cohort of diatomaceous earth workers of exposure-related elevated risks of lung cancer and non-malignant respiratory disease mortality, although not statistically significant, continue to support aetiological relations of cumulative crystalline silica exposure.
- These findings contribute to reviews of existing occupational exposure standards worldwide.

INTRODUCTION

Crystalline silica is considered a potentially hazardous exposure to an estimated tens of millions workers worldwide.[1] Respiratory exposures to crystalline silica result from drilling, mining and other activities that process silica-containing soil, sand, granite and other minerals in numerous industries. Silicosis, which is a progressive fibrotic lung disease, is an established health effect due to exposure.[2] In 1997, the International Agency for Research on Cancer (IARC) classified crystalline silica as a confirmed human lung (category 1) carcinogen.[3] Subsequently, a pooled analysis of data from 10 cohort studies of silica and lung cancer,[4] including the cohort of diatomaceous earth (DE) workers reported on here, demonstrated an exposure-response relation that was not confined to industries involving underground mining where potential confounding by radon or arsenic may occur. Findings from the pooled analysis supported the IARC determination and suggested that occupational exposure limits may be inadequate.

The DE industry is known to have particularly high exposures and a lower likelihood of simultaneously occurring confounding exposures (eg, radon in underground mines) than in other silica-exposed industries. DE has several commercial applications, including as a filter medium, an absorbent, and as filler material. Created from fossilised diatoms, a type of algae with a hard shell, it is excavated from open pit mines and heated in kilns (calcining). At high temperatures, the final products, typically cristobalite, which can contain 10–60% crystalline silica, is formed.[5] Our original study of California DE workers indicated dose–response relations for lung cancer and non-malignant respiratory disease (NMRD) mortality.[5] Excess lung cancer risk has also been observed in an Icelandic cohort of DE workers.[6]

Similar findings have been observed in other industries with silica exposure, but there continues to be some debate surrounding the strength of the association and consistency of the exposure-response trends.[7] A recent study of roofing granule

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workers found increased risks of NMRD mortality with exposure to respirable crystalline silica, with suggestive but imprecise trends.[8] No association of lung cancer risk was observed with silica exposure in German porcelain production workers[9] and similarly, no evidence was found of increased lung cancer mortality in the Vermont granite workers,[10] although both studies showed increased mortality from silicosis. In contrast, there is a body of evidence supporting elevated mortality from lung cancer and NMRDs in several industries, including those processing stone, such as studies of granite workers in the USA[11] and Finland[12] and among silica and clay brick workers at refractory plants in China[13] and in Italy.[14] A strong exposure-response gradient for cumulative silica exposure and lung cancer risk was observed in Chinese metal mining and pottery factory workers,[15] and strong trends were observed among pottery workers in England for lung cancer and chronic obstructive pulmonary disease (COPD).[16]

We extended the mortality follow-up for a cohort of DE industry workers in Lompoc, California.[5] Earlier analyses of this cohort[17] were among the influential epidemiological studies included as evidence in the IARC classification of silica as a carcinogen. The current study capitalises on the several advantages of this existing cohort, including a quantitative dose-response analysis for exposures and lack of confounding exposures. Extended follow-up thus adds to understanding of aetiological relations.

MATERIALS AND METHODS

Study population

The original study cohort included workers from two DE plants in Lompoc, California and has been described previously.[5 17–19] The larger of the two plants has been in operations since 1902, while the second plant began mining in 1946 and then milling later in 1952.[17] Workers were included in the cohort if they had been employed for at least 1 year cumulatively at either plant and worked for at least 1 day between 1 January 1942 and 31 December 1987. The current analysis was restricted to the larger cohort (N=2343) for which silica exposure assessment was most detailed. Data on asbestos exposure, which might have been a confounder, were also available in the larger cohort.

This cohort was previously studied for cause-specific mortality using searches of the National Death Index (NDI), state driver's license bureaus and a commercial credit bureau. Underlying cause of death was coded according to International Classification of Diseases (ICD) by a trained nosologist using copies of death certificates obtained from state vital statistics offices. The most recent update was in 1994 and the current study ascertained deaths that occurred from 1993 through 2011, the most recent year for which national mortality data are available. This latest search was inclusively completed using NDI and included all cohort members known to be alive or with 'unknown' vital status at the end of the previous follow-up. An ICD code for the underlying cause of death was available directly from the NDI search. All members who were alive at the last follow-up and did not match the NDI files were assumed to be alive as of the end of updated follow-up. The University of Washington Institutional Review Board reviewed and approved this study.

Exposure assessment

As previously described, detailed work history was available through 1994. Quantitative dust exposures were estimated based on several data sources.[20] The estimates were primarily based on measurements from company air monitoring from 1962 to 1988. Data found in the company's archive provided additional measurements for the earlier period, 1948–1962. Measurement methods included particle counts for the earlier measurements and half of the post-1962 measurements, while the rest of the newer measurements were gravimetric quantities of respirable dust (32%) and total dust (17%). Linear regression modelling converted units of millions of particle units per cubic feet to gravimetric units (mg/m^3) by using a subset of samples measured by both methods. Exposures before 1948 were estimated by regression modelling which extrapolated job-specific exposures that accounted for interventions to reduce dust exposures and other changes over time.[5]

Respirable crystalline silica and respirable dust exposure estimates were specific to the 135 jobs across the plants and periods. The estimates for crystalline silica were derived from the percentage silica contained in a given product and the exposure time for a given job to that product. Industry personnel and bulk product measurements assigned the per cent crystalline silica for uncalcined DE (1%), calcined DE (10%) and flux-calcine DE (20%). Job-specific exposure intensities were combined with job duration and summed for cumulative exposures to silica and dust (mg/m^3-years).[5]

As previously described, asbestos exposures were estimated to address two small operations involving chrysotile asbestos in the plants that occurred over the study period.[5 21] For post-1930 exposures, monitoring data and records of quantities of asbestos in mixed products were used to derive the quantitative asbestos estimates. Intensity estimates from 1930 were extrapolated to earlier years to calculate cumulative exposures to asbestos (fibers/mL-years).

Statistical analyses

The National Institute for Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS) mortality programme was used to calculate SMRs and 95% CIs for the

Table 1 Baseline characteristics for cohort of diatomaceous earth industry workers, 1942–2011

Baseline characteristic	N	Per cent
Vital status		
Alive	940	40.1
Dead	1219	52.0
Unknown	183	7.8
Year of birth		
<1920	770	32.9
1920–1929	586	25.0
1930–1939	373	15.9
1940–1949	316	13.5
1950–1959	228	9.7
>1960	69	2.9
Year of hire		
<1940	209	8.9
1940–1949	760	32.5
1950–1959	603	25.7
1960–1969	388	16.6
1970–1979	258	11.0
>1980	124	5.3
Age at hire (median, range)	24.5	15.0–60.5
Duration of employment (median years, range)	5.54	1.00–49.3
Duration of follow-up (median years, range)	38.1	<1–70.0

cohort stratified by 5-year age groups and calendar year.[22] Age-specific, race-specific and calendar year-specific mortality rates for US men were applied to the cohort's person-years distribution to calculate cause-specific expected numbers of deaths. All-cause mortality and specific causes of death were evaluated by the LTAS mortality programme based on the coding of the ICD, revisions 8, 9 and 10. Specific ICD codes by category as presented in this analysis can be found in the documentation for NIOSH LTAS mortality programme.[22]

Cox proportional hazards modelling was applied to assess the associations between cumulative exposures to respirable crystalline silica and mortality from lung cancer and NMRDs. Cumulative exposures were categorised according to the 20th, 40th, 60th and 80th percentile of the distribution of exposure among deaths from each outcome for each analysis. This approach defined the exposure strata with equal numbers of outcomes to maximise statistical power. Risk estimates were adjusted for age at entry, calendar year at entry, ethnicity (Hispanic vs non-Hispanic), where years of follow-up was the time variable. We addressed additional confounding variables by adjusting for asbestos exposure (ever/never) and by estimating confounding bias for smoking by applying the method described by Axelson.[23] Smoking status (ever/never) was available for approximately 50% (N=1171) of the cohort. SAS V.9.3 was used to conduct all descriptive and regression analyses (Cary, North Carolina, USA). Trend analyses were completed using a continuous cumulative measure in units of 5 mg/m^3-years to allow for interpretable estimates in addition to calculating p values.

Table 2 SMRs, by follow-up period

	1942–1992				1993–2011				1942–2011			
Cause	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All causes	749	739.04	1.01	0.94 to 1.09	470	663.79	0.71	0.65 to 0.78	1219	1361.27	0.90	0.85 to 0.95
All cancers	181	172.24	1.05	0.90 to 1.22	124	169.65	0.73	0.61 to 0.87	305	329.89	0.92	0.82 to 1.03
MN buccal and pharynx	4	4.60	0.87	0.24 to 2.22	3	2.63	1.14	0.24 to 3.33	7	7.04	0.99	0.40 to 2.05
MN oesophagus	1	4.26	0.23	0.01 to 1.31	6	5.34	1.12	0.41 to 2.44	7	9.27	0.76	0.30 to 1.56
MN stomach	7	6.78	1.03	0.41 to 2.13	6	3.78	1.59	0.58 to 3.45	13	10.25	1.27	0.67 to 2.17
MN intestine	14	15.46	0.91	0.49 to 1.52	7	13.96	0.50	0.20 to 1.03	21	28.36	0.74	0.46 to 1.13
MN rectum	3	3.98	0.75	0.16 to 2.20	0	2.75	0.00	0.00 to 1.34	3	6.55	0.46	0.09 to 1.34
MN biliary, liver, gall bladder	4	3.93	1.02	0.28 to 2.61	3	5.22	0.57	0.12 to 1.68	7	8.84	0.79	0.32 to 1.63
MN pancreas	10	8.68	1.15	0.55 to 2.12	6	8.73	0.69	0.25 to 1.50	16	16.86	0.95	0.54 to 1.54
MN larynx	4	2.31	1.73	0.47 to 4.43	2	1.59	1.26	0.15 to 4.54	6	3.78	1.59	0.58 to 3.46
MN trachea, bronchus, lung	77	59.87	1.29	1.01 to 1.61	36	54.42	0.66	0.46 to 0.92	113	110.09	1.03	0.85 to 1.23
MN prostate	11	12.58	0.87	0.44 to 1.56	11	19.83	0.55	0.28 to 0.99	22	30.97	0.71	0.45 to 1.08
MN kidney	3	4.32	0.69	0.14 to 2.03	2	4.42	0.45	0.05 to 1.63	5	8.45	0.59	0.19 to 1.38
MN bladder and other urinary	2	4.48	0.45	0.05 to 1.61	7	6.13	1.14	0.46 to 2.35	9	10.28	0.88	0.40 to 1.66
MN skin	2	3.54	0.56	0.07 to 2.04	4	3.96	1.01	0.28 to 2.59	6	7.25	0.83	0.30 to 1.80
MN brain and other nervous	7	5.07	1.38	0.56 to 2.85	5	3.43	1.46	0.47 to 3.41	12	8.23	1.46	0.75 to 2.55
MN lymphatic and haematopoietic	12	16.25	0.74	0.38 to 1.29	13	17.76	0.73	0.39 to 1.25	25	32.87	0.76	0.49 to 1.12
Non-Hodgkin's lymphoma	4	5.85	0.68	0.19 to 1.75	6	7.18	0.84	0.31 to 1.82	10	12.55	0.80	0.38 to 1.47
Hodgkin's disease	1	1.42	0.71	0.02 to 3.94	1	0.32	3.17	0.08 to 17.66	2	1.72	1.17	0.14 to 4.21
Leukaemia	5	6.50	0.77	0.25 to 1.80	4	7.03	0.57	0.16 to 1.46	9	13.09	0.69	0.31 to 1.30
Multiple myeloma	2	2.48	0.81	0.10 to 2.91	2	3.24	0.62	0.07 to 2.23	4	5.51	0.73	0.20 to 1.86
Diabetes mellitus	8	11.44	0.70	0.30 to 1.38	17	17.92	0.95	0.55 to 1.52	25	28.41	0.88	0.57 to 1.30
Ischaemic heart disease	203	243.48	0.83	0.72 to 0.96	112	158.37	0.71	0.58 to 0.85	315	390.92	0.81	0.72 to 0.90
Cerebrovascular disease	34	39.53	0.86	0.60 to 1.20	17	36.94	0.46	0.27 to 0.74	51	74.34	0.69	0.51 to 0.90
Diseases digestive system	21	34.63	0.61	0.38 to 0.93	19	21.32	0.89	0.54 to 1.39	40	54.64	0.73	0.52 to 1.00
Diseases genitourinary system	10	9.53	1.05	0.50 to 1.93	8	15.58	0.51	0.22 to 1.01	18	24.45	0.74	0.44 to 1.16
Diseases of the respiratory system	91	51.22	1.78	1.43 to 2.18	74	73.61	1.01	0.79 to 1.26	165	120.43	1.37	1.17 to 1.60
Acute respiratory infection, except inflation and pneum.	1	0.27	3.67	0.09 to 20.46	0	0.11	0.00	0.00 to 34.46	1	0.37	2.71	0.07 to 15.09
Influenza	1	0.68	1.48	0.04 to 8.24	0	0.28	0.00	0.00 to 13.27	1	0.94	1.07	0.03 to 5.94
Pneumonia	22	16.58	1.33	0.83 to 2.01	14	19.14	0.73	0.40 to 1.23	36	34.34	1.05	0.73 to 1.45
COPD	37	25.35	1.46	1.03 to 2.01	45	40.11	1.12	0.82 to 1.50	82	63.12	1.30	1.03 to 1.61
Asthma	2	1.27	1.58	0.19 to 5.71	0	0.55	0.00	0.00 to 6.72	2	1.76	1.14	0.14 to 4.11
Pneumoconiosis and other respiratory disorders	28	7.08	3.96	2.63 to 5.72	15	13.42	1.12	0.63 to 1.84	43	19.91	2.16	1.56 to 2.91
Tuberculosis	4	4.15	0.96	0.26 to 2.47	0	0.28	0.00	0.00 to 13.10	4	4.38	0.91	0.25 to 2.34
Nervous system disorders	6	8.39	0.71	0.26 to 1.56	12	26.14	0.46	0.24 to 0.80	18	33.75	0.53	0.32 to 0.84
Accidents	49	46.73	1.05	0.78 to 1.39	7	18.98	0.37	0.15 to 0.76	56	64.62	0.87	0.65 to 1.13

Based on rates for US white men, 1940–2011.
COPD, chronic obstructive pulmonary disease; MN, malignant neoplasms.

RESULTS

There were 1219 deaths in the cohort from all causes from 1942 to 2011 (table 1). Earlier follow-up on the cohort identified 749 deaths and the updated NDI search identified 470 deaths between 1993 and 2011. The median follow-up time was 38.1 years. The cohort accumulated a total of 86 561 person-years of observation. For this current analysis, we did not have the resources to update exposure data after 1994. However, approximately 88% of the cohort had ceased working by 1994 and for the remainder, lagging exposure addressed incomplete exposure data to some extent. Overall mean cumulative exposures were as 2.16 mg/m^3-years (STD=3.51) for respirable crystalline silica and 1.44 fibers/mL-years (STD=4.44) for asbestos.[5]

SMRs indicate all-cause mortality was statistically significantly reduced in the cohort compared to the general population of US men (table 2). Mortality from lung cancer during the first follow-up period (1942–1994) was increased in the cohort (SMR=1.29, 95% CI 1.01 to 1.61) but decreased during the second follow-up period (SMR=0.66, 95% CI 0.46 to 0.92). When combined, there was no increased risk over the entire follow-up period (SMR=1.03, 95% CI 0.85 to 1.23). Mortality from NMRDs was significantly increased throughout the entire follow-up period (SMR=1.37, 95% CI 1.17 to 1.60), although the excess was reduced over time. The largest NMRD mortality excess was for pneumoconiosis and other respiratory conditions (SMR=2.16, 95% CI 1.56 to 2.91) and COPD (SMR=1.30, 95% CI 1.03 to 1.61).

Increased risk for mortality from lung cancer was evident for exposure to respirable crystalline silica in unlagged analyses and when exposures were lagged for 10 and 15 years, adjusting for age at entry, calendar year at entry and ethnicity (table 3). Dose-response trends were not statistically significant, although approximately twofold increased risks were observed for the highest categories of cumulative exposures. Notably, when asbestos exposure (ever/never) was added to the model, the estimates were attenuated but the overall increased risk persisted (see online supplementary table S1).

Analyses of NMRD excluded all infectious lung diseases, specifically 38 deaths from acute respiratory infections, influenza and pneumonia (table 4). The results indicate increased risk of mortality from NMRD with exposure to respirable crystalline silica in unlagged and lagged analyses. Similar to lung cancer, risks appeared to increase slightly with increasing lag time and estimates were attenuated when asbestos exposure was included in the models (see online supplementary table S2). Overall dose-response trends were statistically significant with and without this additional exposure. We further stratified into categories of COPD and asthma (n=84) and pneumoconiosis and other respiratory diseases (n=43) to assess trends with respirable crystalline silica exposure. It was evident that the trend of all NMRD mortality per 5 mg/m^3-years exposure to respirable crystalline silica (HR=1.21, 95% CI 1.08 to 1.35, no lag) was influenced more by pneumoconiosis and other respiratory diseases (HR=1.29, 95% CI 1.11 to 1.50) than by COPD and asthma (HR=1.14, 95% CI 0.96). Lagged analyses yielded similar results. However, it is noteworthy that the NMRD category included largely unspecified or other respiratory diseases (>50%).

When the follow-up periods were analysed separately, trends in mortality risk from lung cancer (table 3) and NMRD

Table 3 Lung cancer mortality and exposure to respirable crystalline silica, by follow-up period

	1942–1992			1993–2011			1942–2011			
Cumulative exposure (mg/m^3-years)	Deaths (n)	HR*	95% CI	Deaths (n)	HR*	95% CI	Deaths (n)	HR*	95% CI	Mean (mg/m^3-years)
No lag										
<0.4	15	1.00	referent	8	1.00	referent	23	1.00	referent	0.2
0.4–<0.9	13	1.28	0.61 to 2.70	6	1.22	0.42 to 3.58	19	1.38	0.75 to 2.55	0.6
1.0–<2.6	13	0.70	0.33 to 1.48	12	1.60	0.65 to 3.98	25	1.02	0.58 to 1.80	1.6
2.6–<5.6	16	1.66	0.82 to 3.38	8	2.05	0.75 to 5.63	24	1.89	1.05 to 3.37	3.8
>5.6	20	1.75	0.84 to 3.63	2	1.74	0.35 to 8.63	22	2.03	1.07 to 3.85	10.8
Trend†		1.10	0.94 to 1.27		1.34	0.81 to 2.21		1.13	0.99 to 1.29	
p Value		0.24			0.26			0.08		
10-year lag										
<0.4	19	1.00	referent	9	1.00	referent	28	1.00	referent	0.2
0.4–<0.9	12	1.18	0.57 to 2.44	6	1.11	0.39 to 3.17	18	1.24	0.69 to 2.26	0.6
1.0–<2.6	12	0.66	0.32 to 1.38	11	1.34	0.55 to 3.30	23	0.91	0.52 to 1.59	1.6
2.6–<5.6	14	1.55	0.77 to 3.12	8	1.95	0.72 to 5.23	22	1.77	1.00 to 3.13	3.8
>5.6	20	1.93	0.95 to 3.90	2	1.71	0.35 to 8.47	22	2.14	1.15 to 3.99	10.7
Trend†		1.10	0.94 to 1.28		1.34	0.80 to 2.23		1.14	0.99 to 1.31	
p Value		0.24			0.26			0.08		
15-year lag										
<0.4	20	1.00	referent	9	1.00	referent	29	1.00	referent	0.2
0.4–<0.9	11	1.36	0.65 to 2.84	6	1.17	0.41 to 3.38	17	1.38	0.76 to 2.52	0.6
1.0–<2.6	16	1.09	0.56 to 2.11	11	1.44	0.58 to 3.57	27	1.24	0.73 to 2.10	1.6
2.6–<5.6	12	1.68	0.81 to 3.49	8	2.18	0.80 to 5.94	20	1.98	1.11 to 3.54	3.8
>5.6	18	2.20	1.07 to 4.50	2	1.94	0.39 to 9.73	20	2.36	1.25 to 4.46	10.4
Trend†		1.10	0.94 to 1.29		1.35	0.80 to 2.26		1.14	0.98 to 1.32	
p Value		0.25			0.26			0.08		

*Adjusted for age at entry, calendar year at entry, and ethnicity (Hispanic vs non-Hispanic).
†HR per 5 mg/m^3-years.

Table 4 Non-malignant respiratory disease mortality and exposure to respirable crystalline silica, by follow-up period

Cumulative exposure (mg/m^3-years)	1942–1992			1993–2011			1942–2011			
	Deaths (n)	HR*	95% CI	Deaths (n)	HR*	95% CI	Deaths (n)	HR*	95% CI	Mean (mg/m^3-years)
No Lag										
<0.5	7	1.00	referent	16	1.00	referent	23	1.00	referent	0.2
0.5–<1.4	13	1.96	0.78 to 4.92	13	0.98	0.47 to 2.06	26	1.31	0.75 to 2.31	0.9
1.4–<3.0	8	1.50	0.54 to 4.15	20	2.23	1.14 to 4.37	28	1.93	1.10 to 3.37	2.1
3.0-<6.9	18	4.03	1.66 to 9.74	6	0.93	0.36 to 2.40	24	2.31	1.30 to 4.13	4.4
>6.9	21	4.14	1.67 to 10.27	5	2.64	0.92 to 7.58	26	3.59	1.94 to 6.67	12.4
Trend†		1.16	1.02 to 1.32		1.24	0.87 to 1.77		1.21	1.08 to 1.35	
p Value		0.02			0.23			0.001		
10-year lag										
<0.5	9	1.00	referent	16	1.00	referent	25	1.00	referent	0.2
0.5–<1.4	13	2.03	0.87 to 4.76	14	1.07	0.52 to 2.22	27	1.45	0.84 to 2.51	0.9
1.4–<3.0	7	1.40	0.52 to 3.77	20	2.29	1.17 to 4.49	27	1.97	1.14 to 3.42	2.0
3.0–<6.9	18	4.33	1.91 to 9.84	5	0.82	0.3 to 2.26	23	2.48	1.39 to 4.41	4.4
>6.9	20	4.53	1.91 to 10.72	5	2.89	0.99 to 8.41	25	3.99	2.15 to 7.40	12.2
Trend†		1.18	1.04 to 1.35		1.25	0.88 to 1.78		1.22	1.09 to 1.37	
p Value		0.01			0.22			0.0004		
15-year lag										
<0.5	10	1.00	referent	16	1.00	referent	26	1.00	referent	0.2
0.5–<1.4	15	2.43	1.09 to 5.41	15	1.18	0.58 to 2.43	30	1.67	0.98 to 2.83	0.9
1.4–<3.0	6	1.28	0.46 to 3.54	19	2.25	1.14 to 4.47	25	1.93	1.11 to 3.37	2.1
3.0–<6.9	17	4.45	1.98 to 10.00	5	0.89	0.32 to 2.46	22	2.64	1.48 to 4.72	4.5
>6.9	19	4.86	2.08 to 11.38	5	3.17	1.08 to 9.33	24	4.34	2.33 to 8.08	12.1
Trend†		1.20	1.05 to 1.36		1.25	0.88 to 1.79		1.23	1.10 to 1.38	
p Value		0.008			0.22			0.0003		

*Adjusted for age at entry, calendar year at entry, and ethnicity (Hispanic vs non-Hispanic).
†HR per 5 mg/m^3-years.

(table 4) were similar for silica exposure for the two periods. Overall, the effect estimates were generally lower in magnitude in the recent follow-up period, with the exception of lung cancer mortality and silica. Increased mortality risk was observed for lung cancer and NMRD in the updated follow-up, particularly in the highest silica exposure categories.

To address the uncertainty in the exposure estimates from the earliest years where values were extrapolated, we conducted separate analyses restricted to workers hired after 1950 for whom quantitative exposure assessment for crystalline silica was based on measurements, rather than extrapolation. This subgroup also had minimal asbestos exposure. For lung cancer, the findings were very similar to the increased risks observed overall for higher cumulative exposures to silica, although they were not statistically significant (see online supplementary table S3). For NMRD mortality, however, the results were less comparable (see online supplementary table S4). There were few workers with exposures in the upper categories which made for imprecise estimates. There were similar findings of increased risk of NMRD mortality in the lower exposure categories for silica in the restricted analysis and overall, although they were no longer significant.

The observed smoking distribution across categories of cumulative silica exposure for lung cancer was 0.65, 0.77, 0.72, 0.82 and 0.85 for the unlagged analysis. These distributions were nearly identical for the exposure categories determined for NMRD. To estimate the smoking adjusted effect estimates, we assumed a 10-fold increased risk for each outcome (lung cancer or NMRD) and applied the Axelson[2,3] method for indirect adjustment. For lung cancer, the HR in the highest exposure category would be decreased from 2.03 to 1.60 (see online supplementary table S5). For NMRD, the HR in the highest exposure category would be decreased from 3.59 to 2.82 (see online supplementary table S6). For the 10-year and 15-year lagged analyses, estimates were similarly attenuated when accounting for smoking.

DISCUSSION

Overall mortality risks for lung cancer and NMRD decreased on further follow-up of this cohort of DE industry workers, which may be attributable to a healthy worker effect in more recent years, evidenced by reduced SMRs for all causes, lung cancer and NMRD in the updated follow-up. Reduced SMRs during this time may also be due to younger workers having experienced lower exposures and lower risks with increasing time since exposure. Increasing exposure-response with cumulative crystalline silica exposure for both outcomes persisted, even after adjustment for asbestos exposure and smoking, although observed trends were not statistically significant. Similar non-significant exposure-response gradients observed when analyses were restricted to workers hired since 1950, the subset of the cohort whose crystalline silica exposures were estimated with greatest validity.

Since IARC's 1997 classification of respirable silica as a confirmed human carcinogen (category 1),[2] there have been reports with less consistent results, including an observation of no association with mortality outcomes in two large and well-designed studies of German porcelain production workers[9] and Vermont granite workers.[10] However, potential confounding by smoking was not adequately controlled in those studies. A study which did incorporate detailed smoking information examined a large cohort of 34 018 Chinese workers in metals mines and pottery

factories followed for almost 35 years and found increasing risk of mortality from lung cancer with increasing cumulative exposure to respirable silica.[15] Quartile categories of cumulative exposure to silica were similar to the current study and observed results were similarly consistent with the current findings (HRs (95% CIs), 15-year lag: 1.14 (0.88 to 1.47), 1.59 (1.21 to 2.09), 1.50 (1.12 to 2.00), 1.61 (1.19 to 2.19). A cohort of pottery workers in the UK also showed overall significant excess mortality from lung cancer, but more markedly in an earlier follow-up time period compared to a later follow-up time period.[16] A study of German uranium workers observed a statistically significant increase in mortality from lung cancer in relation to silica dust.[24] For mortality from NMRD, no relation between silica and COPD or other NMRD, except deaths from silicosis or other pneumoconiosis, was observed in the uranium workers.[25] In contrast, another recent study of roofing granule mine and mill workers found exposure to respirable crystalline silica increased risk of NMRD mortality.[8] The cohort of UK pottery workers also showed significantly excess mortality from COPD.[16]

This cohort of DE workers has the advantage of a quantitative dose-response analysis for exposures and extended follow-up time for mortality outcomes. Exposure-response trends for lung cancer and NMRD were attenuated and were not statistically significant when we made relatively conservative adjustments for asbestos exposure and smoking, yet positive gradients persisted. Limitations of the crystalline silica exposure assessment are extrapolation for earlier time periods and uncertainty in conversion factors for dust and respirable fractions. We assume non-differential misclassification from these measurement errors as it was completed without regard to vital status. Cause of death information was obtained from death certificates by an efficient use of resources through the NDI, but there is a possibility of misclassification as they were not validated by medical records or other sources.

We could not fully assess the role of silicosis as a precursor for lung cancer, although radiograph data from the study are only available through the last follow-up in 1994. There is still some debate on the role of silicosis in lung cancer aetiology.[26 27] However, previous analyses of this cohort indicated a dose–response relation between lung cancer and silica among persons with no evidence of radiographic silicosis.[19]

Findings from the updated analyses continue to support aetiological relations of cumulative crystalline silica exposure with lung cancer and NMRD, and thus should contribute to reviews of existing occupational exposure standards worldwide.

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