ORIGINAL ARTICLE

Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers

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ABSTRACT

Objectives Studies of workers in two US cohorts of asbestos textile workers exposed to chrysotile (North Carolina (NC) and South Carolina (SC)) found increasing risk of lung cancer mortality with cumulative fibre exposure. However, the risk appeared to increase more steeply in SC, possibly due to differences in study methods. The authors conducted pooled analyses of the cohorts and investigated the exposure-disease relationship using uniform cohort inclusion criteria and statistical methods.

Methods Workers were included after 30 days of employment in a production job during qualifying years, and vital status ascertained through 2003 (2001 for SC). Poisson regression was used to estimate the exposure-response relationship between asbestos and lung cancer, using both exponential and linear relative rate models adjusted for age, sex, race, birth cohort and decade of follow-up.

Results The cohort included 6136 workers, contributing 218 631 person-years of observation and 3356 deaths. Cumulative exposures at the four study facilities varied considerably. The pooled relative rate for lung cancer, comparing 100 f-yr/ml to 0 f-yr/ml, was 1.11 (95% CI 1.06 to 1.16) for the combined cohort, with different effects in the NC cohort (RR=1.10, 95% CI 1.03 to 1.16) and the SC cohort (RR=1.67, 95% CI 1.44 to 1.93).

Conclusions Increased rates of lung cancer were significantly associated with cumulative fibre exposure overall and in both the Carolina asbestos-textile cohorts. Previously reported differences in exposure-response between the cohorts do not appear to be related to inclusion criteria or analytical methods.

What this paper adds

- Previous analyses of asbestos textile worker cohorts have shown substantial differences in dose-response relationships between asbestos and lung cancer, possibly due to differences in analytical methods or worker inclusion criteria.
- Increased rates of lung cancer were significantly associated with cumulative fibre exposure overall and in both cohorts. Previously reported differences in exposure-response slopes do not appear to be related to differences in inclusion criteria or analytical methods.

INTRODUCTION

Chrysotile asbestos, a known human carcinogen,[1 2] is the predominant form of asbestos used worldwide, and the only form used in the USA since 2002.[3 4] Consistent evidence that chrysotile is a cause of lung cancer, mesothelioma and other respiratory diseases has contributed to its declining use in some countries over the past decade; however, it is estimated that 125 million workers continue to be exposed.[5 6]

While the amphibole forms of asbestos have been banned from most countries, there is controversy about whether chrysotile should be banned as well.[7 8] Initial controversy centred on doubts about whether chrysotile alone increased the risk of cancer, or whether associations between chrysotile exposure and cancer reported in epidemiological studies were due to confounding by amphibole asbestos. With additional evidence that chrysotile asbestos alone is associated with lung cancer and mesothelioma,[9–12] the controversy has turned to the level of risk associated with exposures to chrysotile in contemporary work settings.[7] Studies using quantitative estimates of exposure contribute important evidence to this debate.

Quantitative estimates of exposure to chrysotile, based on phase contrast microscopy (PCM) and transmission electron microscopy, have been used to study the relationship between chrysotile and lung cancer risk in asbestos textile workers in North Carolina (NC) and South Carolina (SC), USA.[11–17] Previous studies of the two cohorts have shown elevated risks of death due to asbestosis and lung cancer compared with the general population, as well as positive exposure-response relationships for asbestos.[11 12] The risk of both asbestosis and lung cancer appeared to increase more steeply with increasing cumulative asbestos exposure in the SC cohort compared with the NC cohort. Possible explanations for the difference include the use of different statistical models and different inclusion criteria for the two cohorts. As part of the ongoing investigation of the relation between chrysotile asbestos and lung disease in these workers, we report the results of a pooled analysis of textile workers from the NC and SC cohorts, using estimates of PCM fibre exposure derived from industrial hygiene measurements and job exposure matrices.

METHODS

Study sites and population

This study includes workers from three asbestos textile mills in NC and one in SC, which have been

studied and described previously.[11–21] Here we identify the NC plants by the numbers used in previous publications that describe them in more detail.[12 21] All plants used raw asbestos fibres to produce yarn and woven materials using processes typical of the textile industry at the time.[12] Asbestos products were produced by the SC plant from 1909 to 1977, by NC plant 1 (NC1) from before 1925 to 1970, by NC plant 3 (NC3) from before 1925 to 1987 and by NC plant 4 (NC4) from about 1942 to sometime after 1994. A fourth NC plant that did not use raw asbestos fibres lacked adequate information for exposure assessment and was not included in this study.

Throughout the periods of asbestos textile production, the vast majority of all the asbestos used was raw chrysotile. Chrysotile fibres used in SC were obtained from Quebec, British Columbia and Zimbabwe; fibres used in NC were obtained mostly from Canada (~90%), with smaller amounts from the USA, South Africa and occasionally Russia and Australia.[18 19] Small amounts of crocidolite yarn were also used in the SC plant (1950s–1975) and some amosite was used in NC3 (1963–1976) in an insulation operation involving a small number of workers.

Detailed methods of cohort enumeration and vital status ascertainment have been described previously for both cohorts.[11–13 20] Occupational histories for workers in the SC plant, first recorded in 1930, included detailed department and job information, including beginning and ending dates. Occupational histories for workers in the NC plants were obtained from several sources, including employers' personnel records, records microfilmed by the USA Public Health Service during the 1960s and records of a state occupational health programme.[12] Originally, the SC cohort included workers after 30 days of employment in either production or non-production jobs during the years 1940–1965 and the NC cohort included workers after 1 day of employment during the years 1950–1973. In the present study, workers were included in the combined cohort after 30 days of employment in a production job during the qualifying years of the individual cohorts (1940–1965 for SC, 1950–1973 for NC).

Vital status was ascertained through 2001 for SC workers and through 2003 for NC workers. A variety of methods were used to trace former workers and the mortality of the SC cohort was ascertained previously through 1975 and 1990.[11–13 20] Cause-of-death information was obtained from the National Death Index for deaths occurring after 1979 and from state records for deaths before that year. Workers who were observed alive after 1979 and had no subsequent death indication were assumed to be alive at the end of the study, while those with no death indication and a last observation before 1979 were treated as lost to follow-up as of the date last observed. The latter group could have been alive or deceased in a state where we did not search: exhaustive searches of all states are cost and time prohibitive. Eventually 449 workers (7%) were lost to follow-up (265 from SC and 184 from NC). Procedures involving human subjects were approved by the Institutional Review Board of the University of North Carolina, Chapel Hill.

Exposure assessment

Chrysotile exposure concentrations were estimated independently for each cohort using job exposure matrices based on detailed employment histories and industrial hygiene sampling measurements.[13 15 18 21] Quantitative exposure estimates for NC were based on 3578 industrial hygiene measurements taken between 1935 and 1986, and estimates for SC were based on 5952 industrial hygiene measurements taken between 1930 and 1975. Air samples collected before 1965 used the impinger method, while later samples were collected on membrane filters and analysed by PCM. Samples taken by both methods from 1965 to 1971 were used to derive impinger-membrane conversions to express impinger results (millions of particles per cubic foot of air) as concentrations of fibres >5 μm in length per ml of air (f/ml), as measured by PCM.[18 21]

Multivariable models were used to estimate mean fibre exposure levels for plants, departments, jobs and time periods, and exposures were linked to workers' occupational histories.[12 18 21] Cumulative exposures were estimated in fibre-years/ml (f-yr/ml) as the product of fibre concentration and duration of employment in each job, summed across all jobs held.

Data analysis

The mortality of the cohort was compared with that of the general population using the National Institute for Occupational Safety and Health modified life table method to estimate standardised mortality ratios (SMRs) and 95% CIs adjusted for age, race, sex and calendar year.[22 23] Person-time at risk was accrued from date of entry into the cohort until: the date last observed for workers lost to follow-up before 1979, date of death, or end of follow-up. Deaths were coded by underlying cause and national mortality rates were used to generate expected numbers of deaths. State-specific rates were used for additional comparisons.

Exposure-response analyses

We employed Poisson regression to estimate the exposure-response relationship between asbestos and lung cancer, using ungrouped observations to retain the ability to include continuous or categorical variables in the analyses.[24 25] We used both exponential and linear relative rate models[26] as in previous analyses of the NC and SC cohorts, respectively.[11 12] Deaths with any mention of lung cancer on the death certificate were included in exposure-response analyses. Cumulative exposure was modelled as a continuous variable. Initial covariates in the models were based on previous exposure-response analyses of SC and NC cohorts and included sex, age (<60, 60–69, 70–79, 80 years), calendar time (<1970, 1970–1979, 1980–1989, ≥1990), race (white, other/unknown) and birth cohort (<1915, 1915–1934, ≥1935). Cohort (NC, SC) and plant (NC1, NC3, NC4, SC) were assessed separately as effect modifiers (but not as confounders because neither was associated with lung cancer).

Covariates were assessed as confounders using a 10% change-in-estimate method[27] and as effect measure modifiers using likelihood ratio tests. Akaike's information criterion was used to compare models for fit (lag periods of 0, 5, 10, 20 and 30 years). Statistical analyses were performed using SAS V 9.2 and Stata V 10.1.

RESULTS

The combined cohort included 6136 workers, contributing 218 630.8 person-years of observation and 3356 deaths. Men contributed 129 846.4 person-years at risk, compared with 88 784.4 person-years for women. SC workers, similar in number to NC workers, contributed more person-years (53.9%) and were more likely to be white and younger at initial employment (table 1).

Cumulative exposures at the study facilities varied considerably (figure 1). Mean exposures in NC1 and NC4 were similar to each other, but 525% and 429% higher, respectively, than mean exposure in the SC plant.

Table 1 Characteristics of a combined cohort of 6136 chrysotile asbestos textile workers from plants located in North Carolina and South Carolina (1940–2003)

Characteristics	NC1 (N=151)	NC3 (N=2475)	NC4 (N=456)	NC (N=3082)	SC (N=3054)	Combined (N=6136)
Men (%)	99 (65.6)	1498 (60.5)	329 (72.2)	1926 (62.5)	1791 (58.6)	3717 (60.6)
White race (%)	108 (71.5)	1442 (58.3)	393 (86.2)	1943 (63.0)	2485 (81.4)	4428 (72.2)
Unknown race	20 (13.3)	561 (22.7)	10 (2.2)	591 (19.2)		591 (9.6)
Mean (range) age at first employment	29.7 (17–71)	27.0 (10–63)	28.3 (15–59)	27.3 (10–71)	25.4 (13–64)	26.3 (10–71)
Mean (range) age at entry, years	33.9 (18–71)	27.9 (16–73)	28.9 (17–64)	28.3 (16–73)	26.2 (13–64)	27.3 (13–73)
Mean (range) duration of employment, years	9.8 (<1–40.6)	3.7 (<1–47.2)	6.8 (<1–38.7)	4.4 (<1–47.2)	7.0 (<1–49.9)	5.7 (<1–49.9)
Mean (range) person-years at risk	26.0 (<1–53.9)	32.5 (<1–53.9)	35.9 (<1–53.9)	32.7 (<1–53.9)	38.6 (<1–61.9)	35.6 (<1–61.9)
Total person-years at risk (% total person-time)	3932.8 (1.8%)	80 428.0 (36.8%)	16 381.0 (7.5%)	100 742.2 (46.1%)	117 888.6 (53.9%)	218 630.8
Mean (range) cumulative exposure, All workers, fibre-years/ml	174.5 (<1–1297)	62.4 (<1–2944)	147.5 (<1-1271)	80.4 (<1–2944)	28.2 (<1–700)	54.4 (<1–2943)
Mean (range) cumulative exposure, Cases, fibre-years/ml	58.9 (5–234)	119 (<1–2839)	296 (12–793)	147.1 (<1–2839)	51.8 (<1–370)	93.8 (<1–2839)
Median cumulative exposure, fibre-years/ml	81.2	8.4	57.6	12.9	5.5	8.2
Lung cancer cases (%)	6 (4.0)	126 (5.1)	27 (5.9)	159 (5.2)	202 (6.6)	361 (5.9)

Combined, combined North Carolina and South Carolina cohorts; NC1, NC3, NC4, North Carolina plants 1, 3, 4; NC, combined North Carolina plants (NC1, NC3, NC4); SC, South Carolina;.

Cohort mortality

For the combined cohort, the workers' mortality from all causes (SMR 1.40, 95% CI 1.35 to 1.45) and all cancers (SMR 1.31, 95% CI 1.22 to 1.40) was higher than expected relative to the national population. Among specific cancers, mortality for lung cancer (SMR 1.90, 95% CI 1.70 to 2.11) was significantly higher than expected (online supplementary tables 1 and 2). Death rates for other major cause of death categories, including cardiovascular diseases, digestive diseases and non-malignant respiratory diseases were also elevated, as in previous mortality studies of the two cohorts.[11 12] Deaths from mesothelioma were higher than expected (SMR 8.61, 95% CI 1.78 to 25.17), although the SMR estimate was based on only three deaths from this cause. However, the International Classification of Disease (ICD) codes were not available for mesothelioma before 1999; therefore, deaths from mesothelioma prior to 1999 are likely to have been classified as deaths from cancer of the pleura (2 deaths, SMR 4.77, 95% CI 0.58 to 17.22) or cancer at "Other respiratory sites" (5 deaths, SMR 3.92, 95% CI 1.27 to 9.14). We observed similar results using SMRs based on expected numbers of deaths generated using state-specific rates.

Exposure-response

Results from regression models of cumulative asbestos and lung cancer deaths are reported in table 2. None of the initial covariates were identified as effect modifiers. After assessment for confounding, models included age, sex, race, calendar year and birth cohort.

Using pooled data from all plants in Poisson regression analyses, the rate ratio (RR) for lung cancer mortality increased approximately 10% per 100 f-yr/ml (RR=1.10, 95% CI 1.05 to 1.15 for 0 year lag), regardless of the lag period and the linear excess relative rate (ERR) increased approximately 26% per 100 f-yr/ml (ERR=0.26) for exposures lagged 10 years. Cumulative exposure with a 10 year lag period was used in subsequent models, as the model fit was slightly better than for other models. For all combined and stratified models, model fit was better for exponential than for linear models. The association between asbestos and lung cancer mortality was less strong in NC workers (RR=1.10, 95% CI 1.03 to 1.16) than in SC workers (RR=1.67, 95% CI 1.44 to 1.93) (p value for likelihood ratio test for interaction is <0.0001). In a sensitivity analysis omitting each NC plant, the estimates were not changed substantially.

Stratifying Poisson models by plant resulted in apparently heterogeneous estimates (table 2), although only the estimates from NC3 and SC (representing 37% and 54% of total person-years, respectively) reached statistical significance. A likelihood ratio test comparing a fully adjusted model with an interaction model also suggested heterogeneity across plants (p value=0.0001).

DISCUSSION

We conducted a pooled analysis of two cohorts of asbestos textile workers to estimate the overall association of lung cancer risk with cumulative exposure and evaluate differences in previously published risk estimates. The pooled cohort, consisting of eligible workers from four asbestos textile plants in North Carolina and South Carolina, USA, had higher than expected mortality from all causes and all cancers, particularly lung cancer, relative to national populations. Pooled and separate exposure-response estimates showed a statistically significant increase in lung cancer mortality with exposure to chrysotile asbestos. The relative rate for lung cancer, comparing 100 f-yr/ml with 0 f-yr/ml, was 1.11 (95% CI 1.06 to 1.16) for the combined cohort, with different effects in the SC cohort (RR=1.67, 95% CI 1.44 to 1.93) and the NC cohort (RR=1.10, 95% CI 1.03 to 1.16), and further variation among the three NC plants.

One of our objectives in conducting a pooled analysis was to investigate whether observed differences in exposure-response slope between SC and NC asbestos textile worker cohorts was due to differences in study methods. For example, the recently reported exposure-response estimate for NC workers with RR per 100 f-yr/ml=1.106 was derived from a log-linear model including workers with at least 1 day of employment and only production jobs. The most recent exposure-response analysis of the SC cohort[11] included workers with 30 days of employment in either production or non-production jobs and estimated an

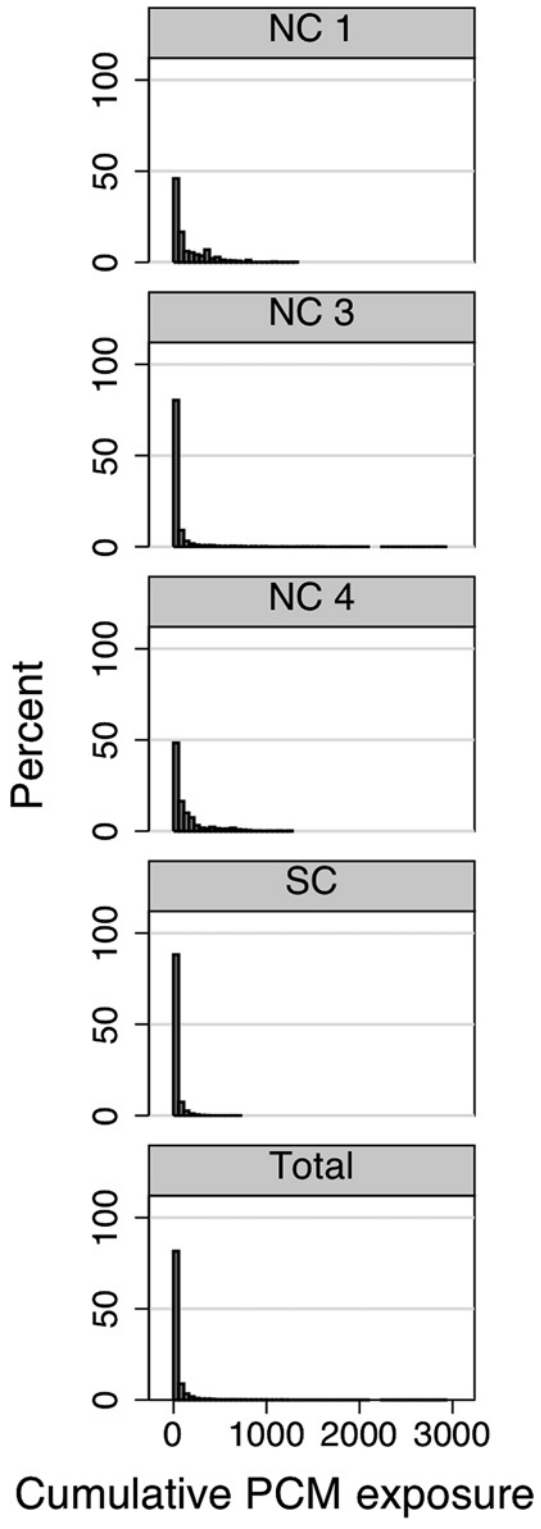

Figure 1 Plant-specific distributions of (log) cumulative exposure (fibre-years/ml) for four asbestos textile plants in North Carolina (NC1, NC3, NC4) and South Carolina (SC). PCM, phase contrast microscopy.

excess RR of 0.0198 per f-yr/ml using a linear excess relative rate model; a previous analysis based on follow-up through 1990 of only male and white female workers reported a log relative rate of 0.00721 f-yr/ml.[28] While not directly comparable, the previously published estimates suggest a roughly sevenfold difference in the log relative rate for the two cohorts. This difference is compatible with our estimates, in which the rate per unit of exposure is approximately six times greater for the SC cohort based on the multiplicative model. The difference is larger with the linear excess relative rate model: approximately 19 times higher per f-yr/ml for SC. These results obtained using identical analytical methods and inclusion criteria for all the plants are consistent with heterogeneity between groups that may preclude a summary estimate that is representative of the true risks associated with the individual cohorts.

The airborne fibre-size distribution across operations in the NC and SC textile plants are similar[15]; therefore, a given cumulative fibre exposure is likely to have the same effect on lung cancer risk in both cohorts. However, there are differences between the cohorts that could help to explain the different estimates of exposure-response effect. These have been identified elsewhere[12 15 21] and relate primarily to differences in quality of available data for the two cohorts. Occupational histories for NC workers were not as complete as those for the SC workers, and the SC plant had 5952 industrial hygiene measurements compared with 3578 measurements for the three NC plants combined. Furthermore, details of process and engineering control changes over the study period were available for the SC plant, while this level of detail was missing for the NC plants. All of these factors point to less precision in the exposure estimates for the NC plants, increasing the probability of measurement error. The number of incomplete occupational and exposure histories for the NC plants may have increased exposure misclassification between NC workers, which could have attenuated an exposure-response association.[12 29] NC1 and NC 4 had the highest proportions of incomplete data, and the observed exposure distributions for those are consistent with missing work history information. For example, both distributions of cumulative exposure are highly skewed to the right, suggesting that workers with shorter periods of employment may not have been enumerated, although they were eligible.

Another difference between the two cohorts was the implementation in 1935 of a surveillance programme (the Dusty Trades Program) in NC that removed workers from exposure if they developed x-ray changes attributable to dust exposure.[12] This could result in systematically lower cumulative exposures for workers at higher risk of lung cancer to the extent that increasing risks of both x-ray changes and lung cancer are associated with increasing dust exposure. Examination of chest x-ray films of 69 workers discharged from the NC plants in the 1930s confirmed a high prevalence (62%) of pneumoconiosis,[19] which is associated with increased risk of lung cancer.[30–32] The examined workers represented less than half of 150 workers who had been discharged from the NC plants 15 months before the Public Health Service conducted an engineering and medical study of these plants.[19] The higher SMR observed previously for pneumoconiosis in SC compared with NC (4.81 vs 3.48, respectively)[11 12] despite higher dust levels in NC is also consistent with selective removal or attrition of high-risk workers. Failure to identify and enumerate similar workers who were dismissed or voluntarily left the industry is a form of health-related selection that would result in an attenuated effect of the exposure-response relationship if removal of highly exposed workers were differential with respect to susceptibility to lung cancer. Further investigation into the possibility that informative workers were missed is warranted.

The flatter exposure-response slope observed for the NC cohort appears to have had a disproportionate effect on the pooled estimate, most likely because the highest exposures occurred in the NC plants. Fourteen per cent of the NC person-time (compared with 3% for SC) was above 125 f-yr/ml

Table 2 Results from Poisson regression analyses of cumulative asbestos exposure and lung cancer deaths among 6136 chrysotile asbestos textile workers from plants located in North Carolina and South Carolina (1940–2003)

	Exponential rate model			Excess relative rate model		
Model*	Coefficient† CE/100	Rate ratio (95% CI)	AIC	Coefficient CE/100	Rate ratio (95% CI)	AIC
(1) Pooled data						
0-year lag	0.093	1.10 (1.05–1.15)	4711.24	0.24	1.24 (1.11–1.43)	5416.4
5-year lag	0.096	1.10 (1.05–1.15)	4710.77	0.25	1.25 (1.11–1.44)	5415.8
10-year lag	0.098	1.10 (1.06–1.15)	4710.61	0.26	1.26 (1.12–1.46)	5415.7
20-year lag	0.106	1.11 (1.06–1.17)	4711.40	0.25	1.25 (1.10–1.46)	5418.4
(2) Separate models (by cohort)						
NC	0.092	1.10 (1.03–1.16)	2020.53	0.12	1.12 (1.02–1.30)	2327.1
SC	0.510	1.67 (1.44–1.93)	2656.96	2.35	3.35 (2.38–4.77)	3039.5
(3) Separate models (by plant)						
NC1	−0.90	0.41 (0.12–1.34)	76.52	−0.08	0.92 (ND‡)	115.3
NC3	0.13	1.14 (1.07–1.22)	1608.43	0.28	1.28 (ND‡)	1849.3
NC4	0.06	1.06 (0.93–1.21)	335.16	0.11	1.11 (ND‡)	383.8
SC	0.51	1.67 (1.44–1.93)	2656.96	2.35	3.35 (2.38–4.77)	3039.5

*All models adjusted for race (white, other/unknown), gender, age (<60, 60–69, 70–79, ≥80), calendar time (<1970, 1970–1979, 1980–1989, 1990), and birth cohort (<1915, 1915–1934, 1935). Models 2 and 3 use exposure lagged 10 years.
†Coefficient of model (cumulative exposure/100), expressed as fibre-years/ml.
‡Not determined (ND) due to instability of the model.
AIC, Akaike's information criterion; CE, cumulative exposure; NC1, NC3, NC4, North Carolina plants 1, 3, 4; NC, combined North Carolina plants (NC1, NC3, NC4); SC, South Carolina;.

cumulative exposure, and 10% (compared with 1% for SC) was above 200 f-yr/ml. Exposure-response graphs in a previous paper on the SC cohort suggested a plateau of predicted lung cancer mortality at cumulative exposures of approximately 125 f-yr/ml.[11] The results of a population-based case-control study in Sweden[33] are also compatible with greater unit risk at low cumulative exposure levels, although direct comparisons are hampered by differences in study design and methods. If lung cancer risk indeed reaches a plateau above a certain exposure level, it is plausible that the effect estimate from the NC cohort is sampled from the flatter portion of the curve. Thus, the difference in exposure distributions could be a non-methodological source of heterogeneity that contributes to differences in effect estimates between the cohorts.

While the SC plant and NC 3 used small amounts of amphibole asbestos in specific operations during part of the study period, there is no indication of general exposure to amphiboles. In the SC plant, crocidolite was never processed into a yarn from raw fibre. From the 1950s until approximately 1975, crocidolite yarn was received and woven into a tape on a single loom or braided into packing. The total quantity of crocidolite ever processed was approximately 2000 pounds compared with 6–7 million pounds of chrysotile annually.[18] Additionally, transmission electron microscopy analyses of historical airborne dust samples found no crocidolite fibres in SC and only a few amosite fibres associated with the insulation operation where that type of fibre was used in the NC plant. NC workers who had been employed in the insulation area were identified, but none died of lung cancer or mesothelioma. It therefore appears very unlikely that exposure to amphiboles had a significant effect on cancer mortality in either plant.

This study had other limitations characteristic of investigations of historical occupational cohorts. Approximately 7% of the cohort was lost to follow-up and we were unable to establish causes for about 5% of known deaths. The proportions of workers lost or missing cause-of-death information are sufficiently low that they are unlikely to have significantly biased the association of exposure and lung cancer for the cohorts separately or after pooling. The quality of cause-of-death coding on death certificates is also known to be variable, but we obtained information for most deaths through the National Death Index Plus service, which has been shown to improve the consistency of coding for comparative mortality analyses[34] and have no reason to suspect systematic differences in coding quality between the states where deaths occurred.

In summary, analysis of the combined asbestos textile cohorts with common methods yielded a statistically significant increase in lung cancer mortality with exposure to asbestos. While the results are consistent with findings from previous independent analyses of the cohorts, from a methodological perspective, the strong heterogeneity between cohorts underscores the potential differences between them and suggests a single estimate of effect may not be possible.[35] The differences in exposure-response estimates from previous studies of the NC and SC cohorts do not appear to be related to inclusion criteria or analytical methods. Potential explanations for the apparent heterogeneity include differences in data quality, the healthy worker survivor effect and differences in exposure distributions or the biological effects of low versus high exposures.

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Competing interests None.

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