Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers

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ABSTRACT

Objective: To describe mortality among workers exposed to chrysotile asbestos and evaluate the relationship between lung cancer and asbestos fibre exposure.

Methods: Workers employed for at least 1 day between 1 January 1950 and 31 December 1973 in any of four plants in North Carolina, USA that produced asbestos textile products were enumerated. Vital status was ascertained through 31 December 2003. Historical exposures to asbestos fibres were estimated from work histories and 3578 industrial hygiene measurements taken in 1935–1986. Mortality of the cohort was compared with that of the national population via standardised mortality ratios (SMRs). Exposure–response relationships for lung cancer were examined within the cohort using Poisson regression to compute adjusted mortality rate ratios.

Results: Follow-up of 5770 workers included in the cohort resulted in 181 640 person-years of observation, with 2583 deaths from all causes and 277 from lung cancer. Mortality from all causes, all cancers and lung cancer was significant higher than expected, with SMRs of 1.47 for all causes, 1.41 for all cancer and 1.96 (95% CI 1.73 to 2.20) for lung cancer. SMRs for pleural cancer, mesothelioma and pneumoconiosis were also elevated. The risk of lung cancer and asbestosis increased with cumulative fibre exposure (RR 1.102 per 100 fibre-year/ml, 95% CI 1.044 to 1.164, and RR 1.249 per 100 fibre-year/ml, 95% CI 1.186 to 1.316, respectively, for total career exposure).

Conclusions: This study provides further evidence that exposure to chrysotile asbestos in textile manufacturing is associated with increased risk of lung cancer, asbestosis cancer of the pleura and mesothelioma.

What this paper adds

- Asbestos is a known carcinogen and all forms are regulated but there is conflicting evidence about the relative carcinogenicity of the chrysotile form and about whether it causes mesothelioma.
- This paper reports findings on the mortality of a cohort of workers exposed to chrysotile asbestos that has not been studied before.
- The risk of lung cancer increased about 10% per 100 f-y/ml and the increase was statistically significant.
- Increased risks of asbestosis and mesothelioma were also observed.
- These findings do not support suggestions that chrysotile asbestos is safe for us or does not cause mesothelioma.

Asbestos is classified as a known human carcinogen, with both human and animal evidence regarded as sufficient to support that designation.[1–4] There is strong evidence from epidemiological investigations that exposure to asbestos causes asbestosis, lung cancer and pleural and peritoneal mesothelioma.[1 2 5–7]

Asbestos is not a single substance, however, and there is continuing debate about the relative carcinogenicity of the chrysotile and amphibole forms. The challenges of assessing the risks associated with exposure to asbestos are exacerbated by the variability of exposure–response associations between studies of workers using the same form of asbestos in different industries, as well as between studies within industries. This heterogeneity is particularly notable in the asbestos textile industry, where only three worker cohorts have sufficient quantitative exposure data to have been included in recent risk assessments.[8–10]

The objectives of this study were to describe mortality, estimate exposures to asbestos fibres, and characterise the quantitative risk of lung cancer in a historical cohort of asbestos textile workers in North Carolina, USA, that has not been the subject of previous epidemiological investigation. Early research in these plants played a significant part in advancing scientific understanding of health effects and establishing the first threshold limit value (TLV) for asbestos,[11–13] but no long-term studies of mortality or cancer risk in this population have been conducted before.

METHODS

Study setting

This study includes workers at four asbestos textile factories in the Piedmont region of North Carolina: operations began at three plants before 1925, and at the fourth around 1942. Beginning in 1935, all of the plants were subject to medical and industrial hygiene surveillance by the state health department's Dusty Trades Surveillance Program.

A summary description of the plants and their operations is shown in table 1 and further details are given by Dement *et al*.[14] Information concerning production processes and asbestos use was obtained from historical records, which included detailed industrial hygiene studies by the United States Public Health Service (USPHS) in the mid-1930s and between 1964 and 1971 and by the North Carolina Dusty Trades program between 1935 and 1986.

Three of the four plants converted raw asbestos and cotton fibres into yarn and woven materials

Table 1 Description of North Carolina asbestos textile plants

Plant	Location	Process and products	Began production	Ceased production
1	Davidson	Yarn and woven goods from raw fibres	Before 1925	1970*
2	Charlotte	Tapes, belting and friction products from purchased yarns	Before 1925	1971
3	Charlotte	Yarn and woven goods from raw fibres	Before 1925	1987
4	Marshville	Yarn and woven goods from raw fibres	About 1942	After 1994

*Plant closed.

using methods typical of the textile industry at the time. Approximately 90% of the asbestos came from Canada, with smaller amounts from the United States and South Africa, and occasionally from Russia and Australia.[11] According to available records, only chrysotile was used except for a separate operation in plant 3, where a limited amount of amosite was carded, twisted and woven between approximately1963 and 1976. The other plant (plant 2) produced friction products and other finished goods from purchased asbestos yarn and tape. The plants changed names and ownership several times during the study period, but the physical facilities and manufacturing processes remained much the same. Plant 1 closed in 1970 and plant 2 stopped using asbestos in 1971, while the other plants continued production into the 1980s or later (table 1).

Population and vital status ascertainment

The study population included all men and women employed in any of the four plants for at least 1 day between 1 January 1950 and 31 December 1973. Enumeration of eligible workers was begun in the 1980s as part of a study of workers in the "dusty trades" conducted jointly by the University of North Carolina and several government agencies. Asbestos textile workers hired before 1968 were identified from personnel records microfilmed by the USPHS in 1968, while workers hired from 1968 through the end of 1973 were identified from a review of records on site at plants 1–3. Plant 1 had already closed at the time of the site visits, so company records for that plant were not available. No exposure assessment or epidemiological analysis was conducted for asbestos textile workers at this stage.

Collection of data for the current study began with the information obtained earlier for the Dusty Trades project. Only identifying information, plant and dates of first hire and final termination had been abstracted previously, so detailed work histories were sought. Information for the majority of workers was abstracted from original personnel records obtained from plant 3 and from the records microfilmed by the USPHS. These records were scanned, indexed, abstracted and linked to workers enumerated previously. Data were also abstracted from medical records of the Dusty Trades Surveillance Program. Those records provided dates of chest *x* rays with job titles, which allowed missing work history information to be filled in for some workers who continued employment into the 1970s or 1980s. Workers who had been employed in the plants during the study period but not identified in the previous project or by the USPHS were added to the cohort. Information on smoking was available for <15% of the cohort.

The vital status of the cohort was ascertained through 31 December 2003. We utilised records from the Social Security Administration, the National Death Index (NDI), a death audit by a private company, the North Carolina Death Index, North Carolina state archives and an online database (http://www.Ancestry.com) to trace members of the cohort. Information on causes of death was obtained from NDI Plus for deaths in 1979 or later and state vital records offices for earlier deaths. Causes of death, including underlying cause, immediate causes and other significant conditions were coded to the International Classification of Diseases (ICD) in effect at the time of the death. The 9th and 10th revisions of the ICD were used for causes of death obtained from NDI, while deaths before 1979 required revisions 6–8 and were coded manually by a nosologist. Procedures involving human subjects were approved by the Institutional Review Boards of the University of North Carolina, Chapel Hill and the University of Nevada, Reno.

Exposure assessment

In order to estimate individual cumulative exposures, a job-exposure matrix was developed, providing quantitative estimates of average fibre concentrations by plant, department, job and time period. Details of the method used to derive the matrix are presented elsewhere[14] and summarised here. All known industrial hygiene samples (n = 3578) for the plants were collected, covering the time period 1935–1986; 3420 samples were available to estimate exposures for workers in plants 1, 3 and 4. The number of air samples in each plant ranged from 550 to 1883, with 459 air samples prior to 1950, 1674 covering the period 1950–1969, and 1287 samples for the period from 1970 onward.

Air samples before approximately 1964 used the impinger method, while later samples were collected on membrane filters and analysed by phase contrast microscopy (PCM). Using paired samples and samples by both methods during 1964–1971, conversion factors, specific for plant and operation, were derived to express the 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. Both paired and concurrent samples were available for all combinations of plant and operation and final impinger to membrane filter conversions were derived by combining these independent estimates. Impinger to PCM conversion factors ranged from 1.60 to 8.04.

While air samples were available by plant covering the study period, samples were not collected yearly and therefore, mean PCM-equivalent fibre concentrations by plant, department, job and time period were estimated using multivariate mixed models. These models accounted for 64% of the variance in fibre concentrations.

Mean fibre exposure levels derived from fitting the models were linked to workers' occupational histories for assignment of individual cumulative exposure. Work histories were coded using the same categories used for the exposure data. Approximately 27% of the work history records available for exposure–response analysis were missing details of jobs held within departments. For these records, estimates of fibre exposure were assigned as predicted department means derived by re-fitting the models to estimate mean exposure by plant, department and time period. There were very few work history entries before the first air samples were collected in 1935, and for these jobs exposure levels were assigned using estimates for 1935, which reflected exposures prior to widespread implementation of dust controls. Jobs in insulation processes where

Table 2 Descriptive data for workers employed in four North Carolina asbestos textile plants, 1950–1973 and followed through 2003

			Person-years
All workers (no, %)	5770	100	181640
Men	3975	68.9	121681
Women	1795	31.1	59949
White race	4061	70.4	135218.51
Other or unknown race	1709	29.6	46421.91
Hired before 1950	747	13.0	23857
Hired 1950 or later	5023	87.0	157784
Years of observation (mean, range)	31.48	<0.1–54	–
Age last observed (mean, range)	60	18–96	–
Years employed (mean, range)	3.5	<0.1–47.5	–
Deceased (cause unknown for 70 workers)	2583	44.8	–
Alive	2820	48.9	–
Unknown	367	6.3	–
Workers included in exposure–response analysis* (no, %)	3803	100	124029
Men	2419	63.6	78473
Women	1384	36.4	47236
White race	2265	59.6	79551
Other or unknown race	1538	40.4	46158
Hired before 1950	467	12.3	16088
Hired 1950 or later	3336	87.7	109621
Employed <30 days	711	18.7	20632
Employed at least 30 days	3092	81.3	105077
Years of observation (mean, range)	32.0	<0.1–54	–
Age last observed (mean, range)	60	18–95	–
Years employed (mean, range)	2.9	<0.1–46.8	–
Cumulative exposure, f-y/ml (mean, range)	17.1	<0.1–2943.4	–
Deceased	1681	49.5	–
Alive	1882	44.2	–
Unknown	241	6.3	–

*Never employed in plant 2, work history complete to department level, production jobs only.

amosite may have been used were flagged for later evaluation of potential amosite exposure. Cumulative exposures were estimated in fibre-years/ml (f-y/ml) as the product of the 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 a modified life table method to estimate standardised mortality ratios (SMRs) and 95% confidence intervals (CIs) adjusted for age, race, sex and calendar year. The Windows version of the NIOSH Life Table Analysis System[15] was used to implement the computations. Person-time at risk was censored on the date last observed for workers lost to follow-up before 1979 (the first year of the NDI), while workers observed alive after that year were assumed to be alive at the end of follow-up if no death indication was found. Deaths in the cohort were coded by underlying cause and national mortality rates were used to generate expected numbers of deaths. Parallel analyses were conducted using North Carolina rates, but state rates were available only from 1960 onward.

Mesothelioma was not coded as a separate cause of death until the 10th revision of the ICD in 1999, so for some analyses observed and expected numbers of deaths coded to mesothelioma in the 10th revision and to cancer of the pleura in revisions 6–9 were pooled to calculate a combined SMR. Population mortality rates for asbestosis were unavailable, so SMRs for that cause separate from other pneumoconioses could not be estimated.

Information on race was missing for 19% of the workers. Because mortality rates for the general population are provided in tables that include race, when race was missing we imputed it using a statistical model, as described in the online supplement, rather than exclude those workers from the estimation of SMRs.

Exposure–response relations for lung cancer and asbestosis within the cohort were estimated with Poisson regression.[16] The estimated rate ratio (RR) for the effect of exposure X was obtained as $\exp(\beta X)$, where β is a regression coefficient associated with X and 95% confidence intervals CI are estimated from the standard error of β using a normal approximation. Deaths with any mention of lung cancer or asbestosis on the death certificate were included in these internal analyses. Workers who did not have a complete work history specifying at least the department for all jobs or who had worked in non-production jobs were excluded from exposure–response analyses because exposure could not be reliably estimated. Workers who had ever been employed at plant 2 were also excluded due to the lack of adequate exposure data at that facility.

Models for lung cancer and asbestosis were developed as described in the online supplement. The final models included age, sex, race, calendar time and birth cohort for lung cancer and the same variables minus birth cohort for asbestosis. Adjustment for smoking was not feasible because of the very limited data available for the cohort. After evaluating several categorisation schemes for fit and control of confounding, age was entered with categories <60, 60–69, 70–79 and ≥80 years, race with categories of white and other/unknown, calendar

time with categories for each decade of follow-up, and birth cohort with categories of <1920, 1920–1939, and ≥1940.

Fibre exposures were entered as categorical or continuous variables with lags of 0–30 years to investigate latency effects. Conventional Poisson regression models were fit in Stata 9 (Stata, College Station, Texas, USA), using the ungrouped form of Poisson regression so that predictors could be entered in continuous or categorical form.[17] The shapes of exposure–response curves also were evaluated by estimating penalised spline functions of exposure and plotting the smooth curves generated by fitting those to mortality. Penalised spline models[18] were fit using the mgcv package in R, which determines the optimum degree of smoothing from the data.[19 20]

RESULTS

After exclusion of workers with missing hire or birth dates, the cohort consisted of 5770 individuals, resulting in 181 640 person-years of observation and 2583 deaths as of 31 December 2003. Exclusion of the 373 workers ever employed at plant 2 and 1596 workers with incomplete work histories or non-production jobs left 3803 workers, of whom 1680 (44.2%) were deceased, available for inclusion in the exposure–response analysis. Descriptive details of both cohorts and their vital status are shown in table 2.

For the full cohort including all four plants, the workers' mortality from all causes (SMR 1.47, 95% CI 1.41 to 1.53) and all cancers (SMR 1.41, 95% CI 1.31 to 1.53) was higher than

Table 3 Standardised mortality ratios for all workers employed in four North Carolina asbestos textile plants, 1950–1973 and followed 2003

Cause	O	E	SMR (95% CI)
All causes	2583	1757.6	1.47 (1.41 to 1.53)
Tuberculosis	4	7.27	0.55 (0.15 to 1.41)
All cancers	642	454.08	1.41 (1.31 to 1.53)
Buccal cavity and pharynx	16	10.90	1.47 (0.84 to 2.38)
Digestive and peritoneum	109	111.15	0.98 (0.81 to 1.18)
Oesophagus	10	13.49	0.74 (0.36 to 1.36)
Stomach	8	15.55	0.51 (0.22 to 1.01)
Intestine	35	37.61	0.93 (0.65 to 1.29)
Rectum	13	8.15	1.59 (0.85 to 2.73)
Peritoneum, other and unspecified	1	1.68	0.60 (0.02 to 3.32)
Respiratory	289	148.21	1.95 (1.73 to 2.19)
Larynx	6	5.21	1.15 (0.42 to 2.51)
Trachea, bronchus and lung	277	141.66	1.96 (1.73 to 2.20)
Pleura	4	0.32	12.43 (3.39 to 31.83)
Breast	23	26.63	0.86 (0.55 to 1.30)
Female genital organs	19	15.91	1.19 (0.72 to 1.86)
Male genital organs	40	27.67	1.45 (1.03 to 1.97)
Urinary organs	21	17.98	1.17 (0.72 to 1.79)
Other and unspecified sites	75	55.39	1.35 (1.06 to 1.70)
Mesothelioma*	4	0.37	10.92 (2.98 to 27.96)
Lymphatic and haematopoietic	50	40.24	1.24 (0.92 to 1.64)
Non-Hodgkin's lymphoma	18	14.94	1.20 (0.71 to 1.90)
Hodgkin's disease	2	2.70	0.74 (0.09 to 2.67)
Leukaemia	18	14.88	1.21 (0.72 to 1.91)
Multiple myeloma	12	7.72	1.56 (0.80 to 2.72)
Benign and unspecified	6	5.87	1.02 (0.38 to 2.22)
Diabetes mellitus	46	39.82	1.16 (0.85 to 1.54)
Diseases of blood and blood-forming organs	5	6.36	0.79 (0.26 to 1.83)
Mental and psychiatric disorders	48	20.65	2.32 (1.71 to 3.08)
Nervous system disorders	42	26.76	1.57 (1.13 to 2.12)
Diseases of the heart	730	553.68	1.32 (1.22 to 1.42)
Other circulatory diseases	229	155.41	1.47 (1.29 to 1.66)
Respiratory diseases	237	122.54	1.93 (1.70 to 2.20)
Chronic obstructive pulmonary disease	91	55.02	1.65 (1.33 to 2.03)
Pneumoconiosis	73	20.97	3.48 (2.73 to 4.38)
Digestive diseases	131	82.75	1.58 (1.32 to 1.88)
Genito-urinary diseases	44	29.80	1.48 (1.07 to 1.98)
Diseases of the skin	3	2.12	1.41 (0.29 to 4.13)
Musculoskeletal and connective tissues diseases	6	5.58	1.08 (0.39 to 2.34)
Symptoms and ill-defined conditions	16	23.59	0.68 (0.38 to 1.10)
Accidents	150	107.99	1.39 (1.18 to 1.63)
Violence	100	64.45	1.55 (1.26 to 1.89)
Other and unspecified causes†	144		

*Identified only for years 1999 onward; †includes deaths with missing cause; SMR not reported.
E, expected number of deaths based on national mortality rates; O, observed number of deaths; SMR, standardised mortality ratio.

expected relative to the national population. Elevated death rates were also observed for other major cause of death categories, including cardiovascular diseases, digestive diseases and non-malignant respiratory diseases (table 3). Mortality from pneumoconiosis, which includes asbestosis, was also elevated (SMR 3.48, 95% CI 2.73 to 4.38).

Among specific cancers, mortality rates for lung cancer (SMR 1.96, 95% CI 1.73 to 2.20), cancer of the pleura (SMR 12.43, 95% CI 3.39 to 31.83) and mesothelioma (SMR 10.92, 95% CI 2.98 to 27.96) were all significantly higher than expected. There were only four deaths each from cancer of the pleura and mesothelioma, however (table 3). Although not statistically significant, mortality was also slightly higher than expected for some other possibly asbestos-related cancers, including cancers of the larynx and rectum, non-Hodgkin's lymphoma and multiple myeloma, and lower than expected for others, including cancers of the stomach and peritoneum (table 3). Analysis using state reference rates for 1960–2002 gave similar results, with SMRs of 1.35 (95% CI 1.30 to 1.40), 1.40 (1.29 to 1.51) and 1.80 (1.60 to 2.03) for all causes, all cancers and respiratory cancers, respectively, and 1.81 (95% CI 1.60 to 2.03) for lung cancer. Consideration of mortality by race and gender also gave similar results for major causes of death and for lung cancer and pneumoconiosis (online table S1).

Most deaths occurred among workers followed for 20 or more years since first employment (online table S2). The SMR for lung cancer among this subcohort was 2.14 (95% CI 1.88 to 2.42), and SMRs for cancer of the pleura, pneumoconiosis and several other causes were also increased with respect to the cohort as a whole (online table S2).

The SMR for lung cancer was significantly greater than expected among workers employed for <1 year and increased with the duration of employment (table 4). No deaths from pleural cancer or mesothelioma were observed among workers employed for <1 year (0.31 expected). SMRs for pleural cancer and mesothelioma combined were substantially greater than expected, although imprecise due to small numbers, for employment duration of 1 year or more (table 4). All four of the workers whose deaths were coded to mesothelioma had worked at least 5 years, and two had worked 10 years or more. For pneumoconiosis, SMRs were greater than unity for all categories of employment duration and largest in magnitude for workers employed the longest (table 4).

Within the cohort, fitting Poisson regression models to cumulative fibre exposure grouped to form five quantiles of cases' total exposure showed increasing RRs with increasing exposure for lag intervals of 0–30 years for both lung cancer and asbestosis (table 5). For lung cancer, the strongest associations and the best fit for models with exposure entered in categorical form were obtained with a 30-year lag, although model fit was similar under each of the lag intervals considered. RRs for lung cancer also increased with duration of exposure, reaching 2.35 (95% CI 1.27 to 4.33) among workers employed for 20 or more years (online table S2). For asbestosis, fit and strength of association for grouped fibre exposure data were maximised with 0–10-year lags (table 5).

Smoothed exposure–response plots suggested that the effect of cumulative fibre exposure on the rate of mortality from lung cancer was linear (data not shown), so models were fit with a continuous linear term for cumulative fibre exposure. For total cumulative exposure, the RR for lung cancer was 1.102 per 100 f-y/ml (95% CI 1.044 to 1.164) with adjustment for age, sex, race, calendar decade and birth cohort. The RR was statistically significant and increased modestly with longer lags, reaching 1.134 per 100 f-y/ml (95% CI 1.057 to 1.217) with a 30-year lag, but the model for a 10-year lag fit the data best (table 6). Goodness of fit was improved when cumulative exposure was entered as a continuous linear variable rather than in categorical form (cf tables 6 and 5).

In further analyses, average fibre exposure level was not significantly related to lung cancer mortality, and models including both average and cumulative fibre exposure levels fit no better than models for cumulative exposure alone (online table S3). Omission of workers employed for fewer than 30 days also had no appreciable effect on the RR (data not shown). Adjustment for potential exposure to amosite was not possible because none of the workers who died of lung cancer had worked in insulation areas of the plants.

Fitting a model for asbestosis with terms for age, sex, race and decade and a continuous variable for total cumulative exposure yielded an RR of 1.258 per100 f-y/ml (95% CI 1.181 to 1.340). The RR increased slightly with a lag of 10 years, but models for longer lag periods failed to converge (data not shown). To improve model fit, age was collapsed to two categories (<60, ⩾60) and decade was dropped. These simplified models gave results similar to the full model for unlagged exposure and suggested modest increases in the RR for longer lags, with the best fit obtained with a 0-year lag (table 6).

There were too few deaths from pleural cancer and mesothelioma for exposure–response analysis of those outcomes. Three workers with deaths coded to pleural cancer had been employed at plant 3, where some processing of amosite is known to have occurred, but none of them had worked in insulation areas. The remainder, including all four workers whose deaths were coded to mesothelioma, had worked at plant 4, where there is no record of amphibole asbestos having been

Table 4 Standardised mortality ratios (SMR), 95% confidence intervals (CI) and observed deaths (O) by employment duration among production workers at three North Carolina asbestos textile plants, 1950–2003

Employment duration (years)									
<1		1–<5		5–<10		10–<20		⩾20	
O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)
Lung cancer									
107	1.82 (1.50 to 2.19)	71	1.86 (1.45 to 2.34)	36	2.06 (1.44 to 2.85)	31	2.34 (1.59 to 3.32)	24	2.50 (1.60 to 3.72)
Pleural cancer and mesothelioma combined									
0	E = 0.31*	2	10.52 (6.63 to 24.7)	3†	37.78 (25.06 to 75.19)	1‡	16.03 (9.29 to 54.17)	2‡	46.7 (29.4 to 110)
Pneumoconiosis									
15	1.75 (0.98 to 2.89)	7	1.28 (0.51 to 2.63)	16	5.72 (3.27 to 9.29)	17	7.32 (4.26 to 11.7)	18	9.92 (5.88 to 15.7)

*Where the observed number of deaths is 0, the expected number is reported in place of the SMR and CI; †category includes two deaths coded to mesothelioma; ‡category includes one death coded to mesothelioma.

Table 5 Rate ratios for lung cancer and asbestosis by category of cumulative fibre exposure and lag interval among production workers at three North Carolina asbestos textile plants, 1950–2003

Lag (years)	Fibre exposure (f-y/ml)	Deaths	Person-years	RR*	95% CI	LR (4)	AIC
Lung cancer							
0	<2.3	37	37210	1.00		7.18	2350.2
	2.3–<11.5	36	32079	1.00	0.63 to 1.59		
	11.5–<34.8	36	20371	1.50	0.95 to 2.39		
	34.8–<152.7	36	21788	1.12	0.70 to 1.79		
	>152.7	36	12581	1.78	1.09 to 2.91		
10	<2.3	37	59163	1.00		8.23	2350.5
	2.3–<11.5	37	23304	1.13	0.71 to 1.78		
	11.5–<34.8	35	15151	1.58	0.99 to 2.53		
	34.8–<152.7	37	16738	1.25	0.79 to 2.00		
	>152.7	35	9673	1.88	1.14 to 3.08		
20	<2.3	42	81605	1.00		9.62	2349.1
	2.3–<11.5	34	14790	1.23	0.77 to 1.96		
	11.5–<34.8	35	9945	1.82	1.15 to 2.89		
	34.8–<152.7	39	11307	1.52	0.97 to 2.40		
	>152.7	31	6382	1.88	1.14 to 3.10		
30	<2.3	65	101968	1.00		13.85	2344.9
	2.3–<11.5	27	7244	1.32	0.82 to 2.14		
	11.5–<34.8	32	5144	2.09	1.32 to 3.29		
	34.8–<152.7	29	6237	1.40	0.87 to 2.24		
	>152.7	28	3436	2.13	1.30 to 3.49		
Asbestosis							
0	<232.2	8	115487	1.00		76.08	520.3
	232.2–<356.9	7	3000	22.42	7.77 to 64.69		
	356.9–<532.0	7	2513	29.14	9.94 to 85.43		
	532.0–<842.4	7	2117	23.26	7.80 to 69.36		
	>842.4	7	912	68.46	21.43 to 218.63		
10	<232.2	9	117579	1.00		75.58	520.8
	232.2–<356.9	8	2350	25.84	9.50 to 70.30		
	356.9–<532.0	5	1859	21.51	6.76 to 68.43		
	532.0–<842.4	7	1564	24.24	8.28 to 70.90		
	>842.4	7	677	66.17	21.20 to 206.50		
20	<232.2	14	119859	1.00		53.44	542.9
	232.2–<356.9	6	1549	14.58	5.22 to 40.73		
	356.9–<532.0	5	1256	14.87	4.88 to 45.31		
	532.0–<842.4	6	987	15.33	5.32 to 44.20		
	>842.4	5	378	35.54	10.88 to 116.08		
30	<232.2	18	121828	1.00		46.02	550.4
	232.2–<356.9	7	913	15.33	5.77 to 40.72		
	356.9–<532.0	3	677	9.40	2.58 to 34.31		
	532.0–<842.4	6	466	19.89	6.98 to 56.71		
	>842.4	2	145	21.74	4.51 to 104.78		

*Adjusted via Poisson for age (<60, 60–69, 70–79 or ⩾80 years), sex, race (white or other/unknown), decade of follow-up and birth cohort (<1920, 1920–1939 and ⩾1940) for lung cancer and age, sex, race and decade for asbestosis.
Exposure category boundaries selected to define five quantiles of total exposure among cases.
AIC, Akaike information criterion; LR (4), likelihood ratio for addition of exposure terms with 4 degrees of freedom; RR, rate ratio.

used. All eight workers who died from mesothelioma and cancer of the pleura had been followed for 20 or more years since hire (online table S2).

DISCUSSION

This study of workers employed in North Carolina asbestos textile plants showed higher than expected mortality from all causes, all cancers, lung cancer, pleural cancer and asbestosis relative to national and state reference populations. Statistically significant increases in rates of mortality from lung cancer and asbestosis with increasing cumulative exposure to fibres were also observed.

Studies of asbestos textile workers exposed to chrysotile consistently report excess mortality from lung cancer.[21–26] In a 1999 meta-analysis, Goodman *et al*[27] pooled data from five asbestos textile cohorts to generate a weighted average SMR of 1.42 (95% CI 1.25 to 1.60) for lung cancer, suggestive of somewhat lower risk than the SMR of 1.95 we observed in this study.

Most studies of asbestos textile workers have not included quantitative exposure–response estimates, however, and some cohorts have been exposed to significant amounts of amphibole asbestos, as well as to chrysotile. The most recent reviews assessing the quantitative risk of lung cancer associated with asbestos exposure in textile production[9 10 28] are based on studies of only three cohorts: workers in Pennsylvania, USA and Rochdale, UK who produced textiles and other products from chrysotile and amphibole fibres and a third cohort in South Carolina, USA that made textile products from essentially pure chrysotile.[29] Despite the small number of studies, significant heterogeneity has been noted in the association of lung cancer

Table 6 Rate ratios for lung cancer and asbestosis per 100 f-y/ml of cumulative fibre exposure by exposure lag interval among production workers at three North Carolina asbestos textile plants, 1950–2003

Lag (years)	RR*	95% CI	LR (1)	AIC
Lung cancer (181 deaths)				
0	1.102	1.044 to 1.164	9.10	2343.6
10	1.106	1.047 to 1.169	9.58	2343.1
20	1.113	1.049 to 1.181	9.42	2343.3
30	1.134	1.057 to 1.217	9.21	2343.5
Asbestosis (36 deaths)				
0	1.249	1.186 to 1.316	47.88	551.4
10	1.264	1.195 to 1.337	47.68	551.6
20	1.282	1.206 to 1.364	41.99	557.3
30	1.334	1.242 to 1.433	36.00	563.3

*Adjusted via Poisson regression for age (<60, 60–69, 70–79 or ⩾80 years), sex, race (white or other/unknown), decade of follow-up and birth cohort (<1920, 1920–1939 and ⩾1940) for lung cancer and for age (<60 or ⩾60), sex and race for asbestosis.
AIC, Akaike information criterion; LR (1), likelihood ratio for addition of exposure term with 1 degree of freedom; RR, rate ratio.

risk with exposure to chrysotile, both between different industries and among cohorts of asbestos textile workers. Among industries using chrysotile, the highest risks per unit exposure are seen among asbestos textile workers and the lowest are observed among workers manufacturing friction products, with intermediate risks for miners and millers and cement production workers.[9 28 30]

Among asbestos textile cohorts, the risk coefficient for lung cancer is notably higher for the South Carolina workers compared with others. In the most recent report on the South Carolina cohort, Hein *et al*[24] estimated an excess relative risk of 0.0198 per f-y/ml for a 10-year lag. That analysis used an additive relative risk model rather than the multiplicative model used here, however, so the risk coefficients are not directly comparable. An earlier review by Stayner *et al*[28] reported an excess relative risk for lung cancer of 0.031 per f-y/ml for the South Carolina cohort compared with 0.015 and 0.017 for the Rochdale and Pennsylvania cohorts, respectively. Hodgson and Darnton[9] estimated the per cent of excess lung cancer per unit exposure and reported excess risks of 6.7% and 4.6% per f-y/ml for South Carolina women and men and excess risks of 0.37% and 0.80% per f-y/ml, respectively, for the Rochdale and Pennsylvania cohorts. Application of the Hodgson-Darnton index to our data suggests an excess risk intermediate between those sets of estimates: 1.38% per f-y/ml for all workers included in the exposure–response analysis and 1.67% per f-y/ml for the subgroup followed for ⩾20 years.

This study provides evidence that workers exposed to chrysotile are at increased risk of mesothelioma, as well as lung cancer. The number of mesothelioma deaths recorded in other studies of workers exposed only to chrysotile has been small, suggesting a hypothesis that chrysotile does not cause mesothelioma.[31] However, we observed an SMR of approximately 11 for mesothelioma based on four deaths observed and 0.37 expected after mesothelioma began to be coded as a separate cause of death in 1999 with the 10th revision of the ICD. In every case when mesothelioma was mentioned on the death certificate of a worker in the cohort, it was coded as the underlying cause of death. Mesothelioma is believed to have been under-reported in the early years of this study, however, so it is possible that additional cases before 1999 were missed.

Earlier studies were often unable to estimate SMRs for mesothelioma due to the lack of population reference rates, so the proportion of all deaths due to mesothelioma or the proportion of expected mortality per unit exposure are sometimes used as surrogate indicators of comparative risk. In this study, the eight deaths coded to mesothelioma and cancer of the pleura comprise 0.31% of all deaths during follow-up, while the four known mesothelioma deaths from 1999 to 2003 are 1.1% of deaths in those years, consistent with reported increases in mesothelioma mortality with increasing follow-up time.[32] Using the indicator proposed by Hodgson and Darnton,[9] the proportion of expected mortality from mesothelioma and pleural cancer is 0.0058% per f-y/ml (0.0098% per f-y/ml for workers followed for ⩾20 years). Mortality due to mesothelioma and pleural cancer in this population is consistent with the average of 0.3% reported by Stayner *et al*[28] based on 12 studies of workers exposed to chrysotile, but notably higher than Hodgson and Darnton's estimate of 0.0010% per f-yr/ml for cohorts exposed to chrysotile.

The current study has important strengths, including the large size and long follow-up of the cohort and the high proportion of workers whose vital status was ascertained. In addition, a large number of historical industrial hygiene measurements from the study period were available, including quantitative data that allowed particle counts obtained with the older impinger method to be converted to f/ml. We also had access to extensive historical descriptions of the plants and production process from investigations conducted by state and national agencies.

The study was limited by several aspects of the historical records, however. The lack of sufficient industrial hygiene data for one of the four plants and for non-production jobs precluded estimation of exposures for some workers. These individuals and workers whose exposures could only be estimated by the plant average because of missing work history data were excluded. While the intent of these exclusions was to improve the validity of exposure estimation, as a side effect they reduced the precision of exposure–response estimates. In addition, contrasts in estimated exposure between workers may have been reduced to an unknown degree by retaining workers with complete information about departments, but not job titles. Job data were missing for about a quarter of the cohort, most often for workers employed early in the study period or for short periods. Under most circumstances, reduced contrast in exposure intensity attenuates exposure–response associations.[33] Information on smoking among the workers was also inadequate. Numerous evaluations suggest that inability to control for smoking is unlikely to be a source of strong bias in internal analyses of occupational cohorts.[34–36] However, interaction between smoking and asbestos is a question of scientific interest that could not be assessed in this study.

Our estimates of lung cancer risk per unit exposure are substantially lower than those reported in studies of the South Carolina cohort, despite similarities in the era of operation and the production processes used. A difference in the potency of the exposures in the two plants, which could result from different distributions of fibre length and diameter, is one possible explanation for the divergence in lung cancer risk. Fibre size distributions for the two cohorts appear to be similar, however, despite generally higher dust concentrations in the North Carolina plants.[14 37]

While a comprehensive comparison of exposure–response associations for lung cancer in the North Carolina and South Carolina asbestos textile cohorts would require parallel analyses using a common protocol, several factors may contribute to different findings for the two cohorts. In North Carolina, but not

in South Carolina, the asbestos textile industry was subject to a surveillance program that removed workers from exposure if they developed *x* ray changes attributable to dust exposure. Schull reviewed chest *x* ray films of 71 workers discharged from these plants in the first wave of surveillance examinations and confirmed a high prevalence of pneumoconiosis.[38] Although there is disagreement about whether non-malignant disease is a necessary precursor to the development of lung cancer following exposure to asbestos, it is established that the risk of lung cancer is increased among workers with certain *x* ray changes.[39–41] Consequently, it is conceivable that the surveillance program resulted in the selection of workers at high risk of lung cancer for reduced cumulative exposure, while those believed to be at lower risk were allowed to continue working and accruing exposure. The elevated SMR for lung cancer observed among North Carolina workers employed for <1 year is consistent with this hypothesis. The quality of both workers' occupational histories and the historical exposure data available in North Carolina was also lower compared with South Carolina. In North Carolina, we had access to some 3500 air samples in three plants, compared with 6000 for the single plant in South Carolina. In addition, in North Carolina there were no records of the dates of process or ventilation changes that could be used to refine the exposure models, so we modelled time-related changes in exposure using spline terms as empirical descriptors of unknown changes. Thus, while we estimated exposures using an approach similar to that taken in earlier studies of the South Carolina plant,[42] the uncertainty of the exposure estimates and the tendency toward attenuation of associations may be greater in North Carolina.

In conclusion, this study of provides further evidence that exposure to chrysotile asbestos in textile manufacturing is associated with increased risk of lung cancer, asbestosis and mesothelioma. Further investigation is needed, however, to reconcile the exposure–response slopes we observed here with those seen in studies of other populations of asbestos textile workers.

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Correction

As a result of an inquiry from a reader, the authors of this article have discovered that the figure for mean cumulative exposure published in table 2 of this paper is incorrect. The correct figure for mean cumulative exposure is 64.6 f-years/mL. The range of cumulative exposures is correct as printed, however.

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