An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers

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ABSTRACT

Background: Evidence from toxicological studies indicates that the risk of respiratory diseases varies with asbestos fibre length and width. However, there is a total lack of epidemiological evidence concerning this question.

Methods: Data were obtained from a cohort mortality study of 3072 workers from an asbestos textile plant which was recently updated for vital status through 2001. A previously developed job exposure matrix based on phase contrast microscopy (PCM) was modified to provide fibre size-specific exposure estimates using data from a re-analysis of samples by transmission electron microscopy (TEM). Cox proportional hazards models were fit using alternative exposure metrics for single and multiple combinations of fibre length and diameter.

Results: TEM-based cumulative exposure estimates were found to provide stronger predictions of asbestosis and lung cancer mortality than PCM-based estimates. Cumulative exposures based on individual fibre size-specific categories were all found to be highly statistically significant predictors of lung cancer and asbestosis. Both lung cancer and asbestosis were most strongly associated with exposure to thin fibres (<0.25 μm). Longer (>10 μm) fibres were found to be the strongest predictors of lung cancer, but an inconsistent pattern with fibre length was observed for asbestosis. Cumulative exposures were highly correlated across all fibre size categories in this cohort (0.28–0.99, p values <0.001), which complicates the interpretation of the study findings.

Conclusions: Asbestos fibre dimension appears to be an important determinant of respiratory disease risk. Current PCM-based methods may underestimate asbestos exposures to the thinnest fibres, which were the strongest predictor of lung cancer or asbestosis mortality in this study. Additional studies are needed of other asbestos cohorts to further elucidate the role of fibre dimension and type.

There is extensive evidence that exposure to asbestos fibres is associated with an increased risk of lung cancer, mesothelioma, pleural disease and asbestosis. However, the role of fibre dimensions in determining the risk of respiratory diseases associated with asbestos exposure remains poorly understood.

It has long been suspected, based on experimental studies in rodents, that long thin fibres are the most highly pathogenic. Stanton and coworkers[1] observed in studies of pleural injections of asbestos in rats that carcinogenicity was best predicted by long (eg, >8 μm) thin (eg, <0.25 μm) fibres. Davis *et al*[2] observed a higher proportion of lung tumours and more advanced fibrosis in rats exposed by long-term inhalation to chrysotile enriched for fibres >5 μm in length compared to an equal mass of chrysotile containing more short fibres. Berman *et al*[3] reported in a re-analysis of rat inhalation studies that the most significant predictor of lung tumour response was fibres >20 μm in length.

Human data on the relationship between fibre dimensions and respiratory disease risks are extremely limited because previous epidemiological studies have either measured exposures using gravimetric methods (ie, mass) or fibre counting with phase contrast light microscopy (PCM), as required by regulations. The National Institute for Occupational Safety and Health (NIOSH) asbestos measurement method, and the asbestos regulation of the Occupational Safety and Health and Administration (OSHA) require counting of fibres that are >5 μm in length and have an aspect ratio (ie, ratio of length to width) ⩾3.[4] This counting rule is largely based on pragmatic concerns related to what can be measured accurately and reproducibly with PCM rather than on what are the most biologically important fibre dimensions for predicting risk.

The primary objective of this study was to examine which fibre dimensions are the most strongly predictive of lung cancer and asbestosis risk. We were able to address this question by developing new information on the exposure fibre size distribution using transmission electron microscopy (TEM).

METHODS

The study population is a cohort of 3072 workers from an asbestos textile plant in Charleston, South Carolina which has been described in detail in several earlier publications.[5–9] Briefly, the plant produced asbestos products beginning in 1896 and asbestos textile products beginning in 1909. The plant exclusively used chrysotile asbestos fibres obtained from Quebec, British Columbia and Zimbabwe; however, small amounts of crocidolite yarn were used from the 1950s until 1975. Since crocidolite was never carded, spun or twisted, the predominant exposure at the plant was to chrysotile asbestos. The plant had stopped using asbestos material by the end of 1977.

The original study only included white male workers employed in textile production operations for at least 1 month between 1 January 1940 and 31 December 1965. The cohort was subsequently expanded to include white and non-white males and white females,[8 9] and has recently been

updated to also include non-white females and to extend vital status follow-up through to 31 December 2001.[10] As of 2001, approximately 64% of the cohort had died and 90% of the cohort was successfully followed. A total of 198 deaths in which lung cancer (International Classification of Diseases, 10th revision codes (ICD-10) C33 and C44) was the underlying cause of death have been identified and were available for this analysis. Sixty two cases of asbestosis (ICD-10 J61) were identified for this analysis using a multiple cause of death approach.[11] There were only three deaths from mesothelioma in this study and no attempt was made to perform analyses for this outcome due to small numbers.

Exposure assessment

A job exposure matrix (JEM) has been developed that includes detailed information on the bivariate (length and diameter) fibre size distributions by job, department and calendar time. The methods used to develop this JEM are discussed briefly here and in more detail in another paper.[12] The JEM was derived using information from the prior JEM developed for this cohort for the Charleston plant[5 7] and new information derived from TEM analyses of archived filter samples collected from the study facility in 1965 and 1968. The prior JEM, based on PCM exposure estimates, used airborne dust samples (n = 5952) covering the period 1930–1975, to fit parameters of statistical models to predict mean PCM exposure levels by department, job and calendar time period. For purposes of model development, the plant was divided into 10 exposure zones that corresponded closely to textile departments (eg, fibre preparation, carding, spinning, twisting, weaving, finishing, etc) based on the similarity of processes and characteristics of exposures. Within each exposure zone, jobs were further divided into four or more uniform job categories in order to capture differences in PCM exposure levels by job tasks within zones. Changes in exposure levels by calendar time were accounted for in the models by inclusion of covariates for changes in processes or engineering controls based on plant records.

The ISO direct-transfer method,[13] with specific modifications by NIOSH, was used to analyse archived airborne dust samples from the Charleston textile facility collected in 1965 and 1968.[12]

A total of 84 archived airborne dust samples were selected using stratified random sampling and analysed by TEM to determine the diameter and length for 18 840 fibres or fibre bundles. The TEM analysis used a minimum aspect ratio of 3:1 to define fibres and structures for consistency with PCM methods. Only two fibres of the 18 840 fibre structures (0.01%) were found to be amphiboles and the remainder were chrysotile based on morphology. The TEM results for these samples were combined within each of the 10 exposure zones in the study facility.[12] Using the length and diameter data within each zone, counts of each fibre or fibre bundle were placed into a matrix of 24 categories based on six length ($\leqslant$1.5, >1.5 to 5.0, >5.0 to 10, >10 to 20, >20 to 40, >40 μm) and four diameter (<0.25, 0.25 to $\leqslant$1.0, >1.0 to $\leqslant$3.0, >3.0 μm) categories.

An airborne fibre size-specific JEM was developed for this study using the adjustment factor method proposed by Quinn *et al*.[14–16] This method adjusts standard fibre concentration measures by PCM to the size-specific fibre concentrations by using proportions from the bivariate fibre size distributions derived from TEM.[12] Approximate estimates of fibre surface area were also developed based on the assumption that fibres and fibre bundles could be considered cylinders.[12]

Statistical methods

The Cox proportional hazards model[17] was the primary method used for statistical analysis of exposure–response relationships for lung cancer and asbestosis mortality in this study. Models were fit using the PHREG procedure of SAS. Gender and race (white and other) were controlled for in all analyses by adding indicator variables to the models. Age was controlled for by using this variable as the time dimension for the model. Calendar time and time since first employment were included in the final models as continuous variables since they significantly improved the fit of the models. Models for lung cancer and asbestosis were fit including estimated cumulative exposure as either fibre count ((fibres/ml*days)/10 000) or fibre surface area ((μm^2/ml*days)/10 000) for single and multiple combinations of the length/diameter fibre categories (10 000 was used to provide more manageable units in model coefficients). Models were also fit for lung cancer using alternative regulatory and biologically-based exposure indices that have been proposed for assessing cancer.[15]

The goodness of fit of different models was evaluated based on the −2 log likelihood (−2LL) of the models, with the lowest −2LL indicating the best fit. The statistical significance of univariate exposure measures was tested by computing a 1 degree of freedom χ^2 statistic (χ^2_{1df}) based on the likelihood ratio test (difference between −2LL of models with and without inclusion of the exposure parameter).

Models were fit with the assumption of either a 0, 5, 10, 15 or 20-year lag period. A lag period assumes that exposures received for a certain number of years (ie, lag period) prior to the time at risk are irrelevant in terms of disease causation and thus are not counted. Results are only presented in this paper for models with a 0 lag period assumption, since the fit of the models was generally not found to improve when alternative lag periods were assumed. The lack of improvement in model fit with the assumption of a lag period may be in part explained by the long follow-up of this cohort. There were 24 years between the time the plant stopped using asbestos (1977) and the end of follow-up (2001), and thus lagging will not change estimates of exposures for much of the cohort's follow-up time.

The primary focus in this analysis was in determining which fibre size dimension categories were most strongly related to the risk of lung cancer or asbestos based on the goodness of fit statistic (−2LL). Comparison of the actual magnitude of the regression coefficients (βs) was complicated by the high degree of correlation between the alternative size-specific exposure measures. Fibre size categories that have relatively few fibres may have a larger β coefficient than fibre size categories with a larger number of fibres, even if they are equally potent, when the measures are highly correlated. Thus direct comparisons of the magnitude of the βs or relative risks derived from these regression coefficients can produce misleading results.

RESULTS

The bivariate distribution of fibres for all exposure zones combined is presented in fig 1. The vast majority (93%) of the fibres were very short (ie, $\leqslant$5 μm) and thin (ie, <0.25 μm) and would not have been counted using traditional PCM methods. This pattern was consistent across exposure zones, although the specific fibre size proportions varied.[12]

TEM- versus PCM-based exposures

As a first step to determine whether or not the use of TEM resulted in an improved exposure metric as compared with

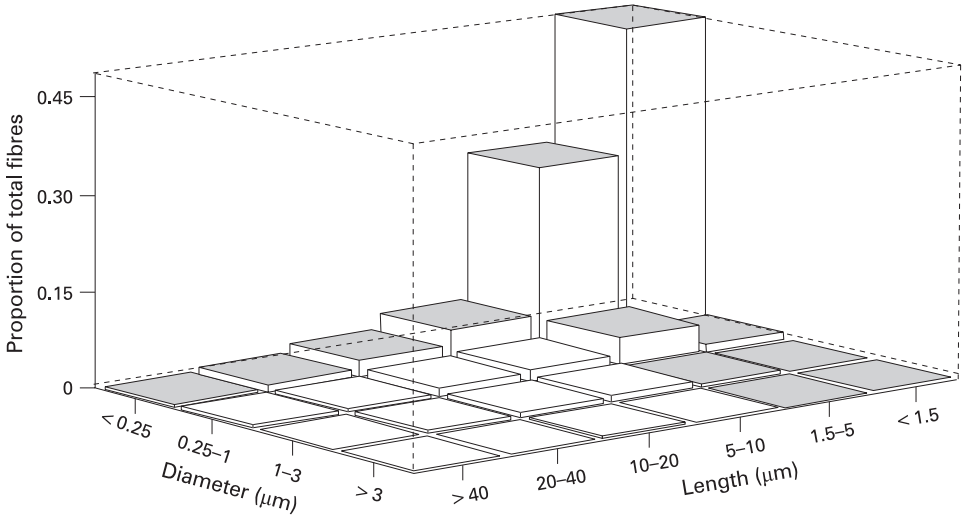

Figure 1 Distribution of asbestos fibres and fibre bundles by length and diameter based on TEM analysis of archived airborne samples from Charleston, South Carolina textile facility (all departments, jobs and operations combined). Bars with grey tops indicate categories of fibres not counted by PCM.

PCM, we fit models that included continuous variables for cumulative exposure based on either counting method. We used the OSHA and NIOSH definitions of a fibre (ie, >5 μm in length, with at least a 3:1 aspect ratio) for both of these analyses. An improved model fit was observed using cumulative exposure based on TEM rather than PCM with substantial reductions in the −2LL for both lung cancer (TEM: −2LL = 2494.2 and PCM: −2LL = 2498.7) and asbestosis (TEM: −2LL = 743.6 and PCM: −2LL = 750.2, respectively). A strong effect of cumulative exposure to fibres (length >5 μm) was observed in the models based on either PCM or TEM for both lung cancer (PCM: $\hat{\beta} = 0.20$, $\chi^2_{1df} = 53.6$ and TEM: $\hat{\beta} = 0.09$, $\chi^2_{1df} = 58.1$) and asbestosis (PCM: $\hat{\beta} = 0.26$, $\chi^2_{1df} = 78.9$ and TEM: $\hat{\beta} = 0.12$, $\chi^2_{1df} = 85.5$), although TEM-based exposure was a substantially better predictor of mortality than PCM-based exposure. The decrease in the magnitude of the coefficient ($\hat{\beta}$) for the TEM- versus the PCM-based exposure estimate can be attributed to the increased number of fibres counted by TEM.

Short fibres

In order to evaluate the possible role of shorter fibres (⩽5 μm) in lung cancer and asbestosis, analyses were performed in which models were fit for cumulative exposure to fibres ⩽5 μm, to fibres >5 μm and to both (table 1). For lung cancer, models based on cumulative exposure for fibres >5 μm (−2LL = 2494.2, $\hat{\beta} = 0.09$, $\chi^2_{1df} = 58.1$) provided only a slightly better fit to the data than models based on fibres ⩽5 μm (−2LL = 2495.3, $\hat{\beta} = 0.016$, $\chi^2_{1df} = 57.1$). For asbestosis, models based on cumulative exposure for fibres ⩽5 μm (−2LL = 742.0, $\hat{\beta} = 0.022$, $\chi^2_{1df} = 87.1$) gave a slightly better fit to the data than models based on fibres >5 μm (−2LL = 743.6, $\hat{\beta} = 0.12$, $\chi^2_{1df} = 85.5$). Fitting models which included parameters for cumulative exposure to both ⩽5 μm and >5 μm weakened the relationship for both exposure metrics and only slightly improved the model fit relative to the models with each exposure variable alone. These differences would not be considered statistically significant in a hierarchical model framework (ie, χ^2_{1df} of 3.84).

Lung cancer and TEM-based categories

The findings from fitting Cox models for lung cancer using TEM and varying cutpoints for fibre length and diameter to estimate cumulative exposure are presented in table 2. All combinations of length and diameter were found to be highly statistically significant (minimum $\chi^2_{1df} = 15.9$, $p<0.001$) predictors of lung cancer. When examining the results for fibres categorised by diameter only, improved model fit was observed as fibre diameter decreased, and very thin fibres (<0.25 μm: −2LL = 2495.9, $\hat{\beta} = 0.015$, $\chi^2_{1df} = 56.4$) were found to be the strongest predictors of lung cancer. Among the models examining fibre length only, the goodness of fit of the models substantially increased for the categories with fibres longer than 10 μm (χ^2_{1df} values: 60.1–62.1 for fibres >10 μm in length; 53.0–54.1 for fibres ⩽10 μm in length), with the strongest relationship being observed for fibres between 20 and 40 μm in length (−2LL = 2490.3, $\hat{\beta} = 0.71$, $\chi^2_{1df} = 62.1$). Among the models examining length and diameter simultaneously, the combined category of 20–40 μm length and 0.25–1.0 μm diameter produced the best fit (−2LL = 2486.5, $\hat{\beta} = 2.99$, $\chi^2_{1df} = 65.9$).

Asbestosis and TEM-based categories

The findings from fitting Cox models for asbestosis using TEM and varying cutpoints for fibre length and diameter to estimate cumulative exposure are presented in table 3. All length and diameter combinations were found to be highly statistically significant predictors of asbestosis (minimum $\chi^2_{1df} = 33.4$, $p<0.001$). When examining the results for fibres categorised by diameter only, improved model fit was also seen for asbestosis as fibre diameter decreased, and very thin fibres <0.25 μm (−2LL = 744.8, $\hat{\beta} = 0.02$, $\chi^2_{1df} = 84.3$) were the strongest predictors. Among the models examining fibre length only, a clear trend with fibre length was not seen, although fibres 10–20 μm in length (−2LL = 736.8, $\hat{\beta} = 0.45$, $\chi^2_{1df} = 92.3$) were the strongest predictors. Among the models examining length and diameter simultaneously, the combined category of >40 μm length and 1–3.0 μm diameter produced the best fit of any of the models (−2LL = 718.5, $\hat{\beta} = 22.93$, $\chi^2_{1df} = 110.6$).

Alternative exposure metrics

Cumulative exposure based on total fibre surface area also provided highly statistically significant predictions of either lung cancer ($\chi^2_{1df} = 59.0$, $p<0.001$) or asbestosis mortality ($\chi^2_{1df} = 81.2$, $p<0.001$). However, the fibre surface area exposure metrics did not appreciably improve the fit of the model for lung cancer or asbestosis relative to the fits using cumulative

Table 1 Results from Cox models for lung cancer and asbestosis using PCM-based cumulative exposure (fibres/ml*days/10 000) for fibres >5 μm in length, and from TEM-based cumulative exposure for fibres ⩽5 μm and >5 μm in length*

	Lung cancer			Asbestosis		
Model	−2LL	β	χ^2_{1df} (p)	−2LL	β	χ^2_{1df} (p)
PCM L>5 μm	2498.7	0.20	53.6 (<0.001)	750.2	0.26	78.9 (<0.001)
TEM L⩽5 μm	2495.3	0.016	57.1 (<0.001)	742.0	0.022	87.1 (<0.001)
TEM L>5 μm	2494.2	0.090	58.1 (<0.001)	743.6	0.120	85.5 (<0.001)
TEM L⩽5 μm	2493.8	0.005	0.4 (0.52)	740.9	0.013	2.7 (0.10)
TEM L>5 μm		0.060	1.5 (0.23)		0.048	1.0 (0.31)

*Results from models with a 0-year lag that included variables controlling for gender, race, calendar time and time since first employment.
L, length.

exposure (all sizes). For lung cancer, 19 of the 32 models in table 2 fit slightly better using cumulative exposure based on fibre count compared to fibre surface area. For asbestosis, 21 of the 32 models in table 3 fit better using cumulative exposure based on fibre count than fibre surface area, and the differences were larger than those for lung cancer.

The findings from fitting models for lung cancer using cumulative exposure based on previously proposed biologically based exposure indices are presented in table 4. All exposure indices were highly statistically significant predictors of lung cancer mortality. The best fit (−2LL = 2488.7) was provided by the model using the exposure index developed by Berman *et al*[3] which was based on a re-analysis of rat asbestos inhalation studies. Although this model included one more model parameter than the others, the improvement in fit was substantial compared with the other models. The next best fitting model was that using the index proposed by Lippman[18] which differed from the Berman[3] model by 3.1 units in the −2LL. The indices proposed by Pott,[19] Stanton *et al*[1] and Quinn *et al*[15] did not fit the data as well. The Berman[3] model fit the data just slightly better (−2LL = 2488.7) than a model with a single parameter for fibres >40 μm in length and <0.25 μm in diameter (−2LL = 2489.3) and not as well as a model for fibres 20–40 μm in length and 0.25–1.0 μm in diameter (−2LL = 2486.5) (table 2).

Finally, an attempt was made to fit multivariable models including several categories of length and diameter in the same model for either lung cancer or asbestosis using forward and backward selection techniques. These models generally failed because of the high degree of correlation between the exposure variables. The Pearson correlation coefficients between the categories of cumulative exposure displayed in tables 2 and 3 estimated at the end of the study for each individual ranged from 0.28 to 0.99 and were all highly statistically significant (p<0.001). These correlations were particularly strong among the length categories that included fibres <0.25 μm in diameter, which ranged from 0.93 to 0.99.

DISCUSSION

This is the first epidemiological investigation that has examined the association between respiratory diseases and asbestos using fibre size-specific TEM-based estimates of exposure. Perhaps our most striking finding is that exposure estimates derived from TEM are superior to those derived from PCM in terms of predicting mortality for both lung cancer and asbestosis. Models using cumulative exposure based on TEM provided a far better

Table 2 Results from Cox models for lung cancer using TEM-based cumulative exposures (fibre-days/ml/10 000) based on combinations of fibre length and diameter*

	Length (μm)						
Diameter (μm)	⩽1.5	1.5–5	5–10	10–20	20–40	>40	All
<0.25							
β	0.023	0.047	0.259	0.493	1.311	3.503	0.015
−2LL	2499.2	2496.7	2498.0	2496.2	2492.5	2489.3	2495.9
χ^2_{1df}	53.2	55.7	54.3	56.2	59.9	63.0	56.4
0.25–1.0							
β	1.089	0.237	0.646	1.190	2.986	2.861	0.134
−2LL	2513.9	2516.7	2504.5	2501.9	2486.5	2495.5	2506.4
χ^2_{1df}	38.5	35.6	47.8	50.5	65.9	56.9	46.0
1.0–3.0							
β	NA†	1.693	1.061	1.840	3.558	14.107	0.490
−2LL		2536.1	2512.1	2503.9	2495.4	2493.4	2506.6
χ^2_{1df}		16.2	40.3	48.5	57.0	59.0	45.8
>3.0							
β	NA†	NA†	5.268	4.935	7.562	5.978	2.047
−2LL			2536.4	2518.0	2517.7	2516.1	2509.4
χ^2_{1df}			15.9	34.3	34.7	36.3	42.9
All							
β	0.023	0.041	0.164	0.323	0.705	1.255	0.013
−2LL	2498.7	2498.2	2499.3	2492.2	2490.3	2491.8	2494.7
χ^2_{1df}	53.7	54.1	53.0	60.1	62.1	60.5	57.6

*Results from models with a 0-year lag that included variables controlling for gender, race, calendar time and time since first employment.
†These categories do not meet the 3:1 length to width fibre definition that was a part of our TEM analysis counting rules. However, a very small percentage (<0.1%) of the counted fibres did fall into these categories.

Table 3 Results from Cox models for asbestosis using TEM-based cumulative exposures (fibre-days/ml/10 000) based on combinations of fibre length and diameter*

	Length (μm)						
Diameter (μm)	**⩽1.5**	**1.5–5**	**5–10**	**10–20**	**20–40**	**>40**	**All**
<0.25							
β	0.032	0.062	0.346	0.679	1.802	5.088	0.020
−2LL	750.2	749.2	748.7	746.9	747.1	741.7	744.8
χ^2_{1df}	78.9	79.8	80.4	82.2	82.0	87.4	84.3
0.25–1.0							
β	1.825	0.323	0.848	1.584	4.189	3.710	0.182
−2LL	741.1	767.3	753.3	747.4	735.8	763.8	753.0
χ^2_{1df}	88.0	61.8	75.8	81.7	93.3	65.3	76.1
1.0–3.0							
β	NA†	3.009	1.321	2.513	4.737	22.932	0.678
−2LL		782.9	770.2	754.4	751.3	718.5	754.8
χ^2_{1df}		46.2	58.9	74.7	77.8	110.6	74.3
>3.0							
β	NA†	NA†	6.768	6.138	10.335	7.057	2.474
−2LL			795.7	784.6	767.6	795.5	772.3
χ^2_{1df}			33.4	44.5	61.5	33.6	56.8
All							
β	0.032	0.053	0.215	0.448	0.968	1.691	0.019
−2LL	748.7	749.6	749.7	736.8	742.2	753.4	741.3
χ^2_{1df}	80.4	79.5	79.4	92.3	86.9	75.7	87.8

*Results from models with a 0-year lag that included variables controlling for gender, race, calendar time and time since first employment.
†These categories do not meet the 3:1 length to width fibre definition that was a part of our TEM analysis counting rules. However, a very small percentage (<0.1%) of counted fibres did fall into these categories.

fit to the data than those based on PCM. This finding may have important policy implications for evaluating and controlling risks associated with asbestos exposures in both the workplace and the general environment. Although the costs of TEM methods may make them impractical in some settings, there are techniques available to adjust PCM metrics with a limited number of TEM air sample analyses or to predict the airborne fibre size concentrations in biologically relevant fibre size categories using product and process information.[16] Also, there may in the future be automated or direct reading instruments that could provide these measurements in a more efficient manner.

Exposures based on any of the combinations of fibre size length and diameter examined in this study appeared to be highly significant predictors of both lung cancer and asbestosis. However, interpretation of these findings is greatly complicated by the high degree of correlation between the cumulative exposure measures based on the various combinations of length and diameter examined in this study. It is possible that some of the associations are spurious and are solely explained by the correlation between a particular size category and another size category that is aetiologically related to the diseases under study. The high degree of correlation between the exposure measures also complicates the interpretation of the magnitude of the regression parameters observed in the various models fitted. Because there were far more short fibres than long fibres, the regression coefficients for short fibres would be expected to be much smaller than for long fibres even if they were perfectly correlated. Unfortunately, we only had limited success in fitting models with more than one cumulative exposure at a time due to the high degree of collinearity between these exposure variables. Despite these limitations we believe our findings provide evidence regarding the relative hazards of different fibre dimensions because of the patterns observed for asbestosis in the strength of predictions of lung disease mortality by fibre dimension.

Short fibres

Fibres shorter than 5 μm have traditionally not been counted by methods used for regulatory standards for asbestos because these methods were developed to provide a reproducible index of fibre exposure. The findings from our analysis show that cumulative exposures to all fibre size indices, including fibres ⩽5 μm in length, were highly statistically significant predictors of lung cancer or asbestosis mortality. However, because of the

Table 4 Results for lung cancer from modelling cumulative exposure using alternative indices of fibre exposure

Reference	Index criteria*	β (SE)	χ^2_{1df} (p value)	Model −2LL
Pott, 1987[19]	D<1, L>3	0.058 (0.006)	57.0 (<0.001)	2495.3
Stanton *et al*, 1981[1]	D<0.25, L>8.0†	0.334 (0.034)	59.3 (<0.001)	2493.1
Lippman, 1990[18]	D>0.15‡, L>10.0	0.412 (0.042)	60.6 (<0.001)	2491.8
Quinn *et al*, 2000[15]	D<6.0, L>5.0	0.090 (0.009)	58.1 (<0.001)	2494.2
Berman *et al*, 1995[3]	D<0.25, 5<L⩽40	0.036 (0.045)	0.65 (0.42)	2488.7
	D<0.25, L>40	2.81 (0.956)	7.21 (0.007)	

*Diameter (D) and length (L) in μm. All of the indices also include the criteria that the aspect ratio (length:diameter) is at least 3:1 except for Pott's which was 5:1. It was not possible to use a 5:1 aspect ratio because this was not the criterion used in our fibre counting procedure.
†Stanton *et al* proposed a length criterion of >8 μm. However we used >10 μm since that was the closest category cut-off in our study.
‡Lippman proposed a diameter criterion of >0.15 μm. However we used a cut-off of ⩾0.25 μm since that was the closest category in our study.

correlations in these fibre size distributions, it is not possible to clearly distinguish between a biological basis for a specific fibre dimension (eg, ⩽5 μm) versus a simple association with exposures to the longer fibres in this facility. The models comparing the shorter (⩽5 μm) and longer (>5 μm) fibres did not completely resolve this question. That is, for asbestosis cumulative exposure to fibres ⩽5 μm in length provided a slightly better fit to the data than did fibres >5 μm, while for lung cancer, cumulative exposure to fibres >5 μm provided a slightly better fit (in univariate analyses). Multivariate models containing cumulative exposure indices for both fibre dimensions (⩽5 μm and >5 μm in length) did not significantly improve the fit of either lung cancer or asbestosis models over those containing a single parameter for fibre length. In contrast, other findings in this study did provide support for a role of increasing fibre length (especially >10 μm) in predicting lung cancer mortality, while a trend with fibre length was not as apparent for asbestosis.

Fibre diameter

Cumulative exposure measures based on very thin fibres (<0.25 μm) were consistently found to provide the strongest predictions for both lung cancer and asbestosis mortality. This is an important finding given that very thin fibres are not identifiable using PCM methods, which has a limit of resolution of approximately 0.2–0.3 μm.[13] PCM-based methods have been used in all of the prior epidemiological research, which may have resulted in a large degree of exposure misclassification in these studies. This misclassification would be particularly severe for chrysotile asbestos since these fibres are generally thinner than amphiboles. This could conceivably explain the large discrepancy in the slopes for lung cancer that have been previously reported from studies of chrysotile exposed workers in Quebec,[20] and of our study population.[21] There is some evidence indicating that the asbestos fibres used in textiles were considerably longer and thinner than those generated in chrysotile mining and milling operations.[22 23] This would be expected since long fibres would be highly desirable for producing some textile products.[23]

Our findings for lung cancer and fibre diameter are consistent with predictions made by Stanton *et al*[1] based upon toxicological data that lung cancer is most strongly related to exposure to fibres <0.25 μm in width. Our findings are less consistent with the predictions of Lippman[18] that lung cancer and asbestosis risk is related to exposure to fibres >0.15 μm in diameter; however, we did not specifically investigate this hypothesis since we could not examine the category of >0.15 μm. Most recently, Berman *et al*[3] in a re-analysis of rat inhalation studies performed by Davis and Jones[2] reported that respiratory cancer risk was most strongly related to exposures to very thin fibres (<0.3 μm), which is similar to our findings. Berman *et al*[3] also reported that lung cancer risk was related to fibres with a diameter >5 μm. Exposures based on thick fibres (>3.0 μm) were not found to be especially strong predictors of lung cancer or asbestosis mortality in our investigation.

Fibre length

Exposures using relatively long fibres were found to be the strongest predictors of lung cancer mortality in this study. Cumulative exposure to fibres 20–40 μm in length demonstrated the strongest association, but cumulative exposure to fibres 10–20 μm and >40 μm also showed very strong associations with lung cancer mortality. These findings are largely consistent with predictions based upon experimental studies. Based on studies in rats, Stanton *et al*[1] proposed that asbestos fibres >8 μm in length are most important in predicting respiratory cancer risk. Lippman[18] in a review of toxicological and human lung burden studies suggested that fibres >10 μm are the most important predictors of lung cancer risk. The findings from the Berman *et al*[3] re-analysis of rat inhalation studies suggest that the strongest predictor of lung tumour response was fibres >20 μm in length.

Berman *et al*[3] also reported that the carcinogenic potency of fibres increased with fibre length and that fibres >40 μm and <0.3 μm had 500 times the potency of fibres 5–40 μm in length and <0.3 μm in diameter. Potency comparisons based on fibre count as the exposure metric can be misleading when the fibre dimensions are correlated. This is because exposure to a fibre count of lower frequency (long fibres) can appear to have a greater potency than exposure to a fibre count of greater frequency (short fibres) due to the reduced magnitude of the exposure metric, while the disease response remains fixed. As discussed earlier, fibre size correlations were clearly an issue in the current study, but it may also have been an issue in the Berman *et al*[3] analysis of data from multiple experiments because it was not feasible to generate monodispersed aerosol fibre size distributions. Because of these correlations, we were not able to evaluate the fibre-length potency estimates of Berman *et al*[3] from the results in our study. Independent data from other cohorts with exposures to different fibre size distributions are needed to further elucidate the role of fibre dimension in predicting lung disease.

Our findings for asbestosis did not provide consistent support for previous predictions by Lippman,[18] who suggested that the risk of asbestosis was most strongly related to the surface area of fibres with lengths of >2 μm. Using surface area did not improve the fit for most of our models for asbestosis, although there was improvement in model fit for some size categories. Surface area may not have been a stronger predictor of asbestosis risk because of the relatively crude method used for estimating surface area in our study. Our findings also suggest a role for both short and long fibres in predicting asbestosis risk. Short fibres (⩽5 μm) were stronger predictors of asbestosis than longer fibres (>5 μm), but in more detailed analysis (table 3) the strongest association observed was with relatively long fibres (ie, 10–20 μm).

Study limitations

There are several important limitations of our study that should be considered in interpreting our findings. Our study was unable to include other risk factors for lung cancer, most notably cigarette smoking. Substantial confounding by smoking is generally regarded to be unlikely in analyses where comparisons are made between different groups within a study population,[24] such as those performed in this study. However, based on previous studies for lung cancer, an interaction between smoking and asbestos is likely. This implies that our findings represent risks that are a mix of higher risks for smokers and lower risks for non-smokers.

Inherent limitations in the exposure data and the resulting uncertainties in the estimation of exposures are a major limitation of this study as it is generally with all retrospective cohort mortality studies. The original JEM developed by Dement *et al*[7] was based on an unusually large database which included nearly 6000 airborne samples covering virtually the entire study period. However, the number of TEM-based samples that were used to adjust the JEM in this study was quite small (n = 84). Furthermore, the TEM samples were taken

Main messages

- All fibre size-specific cumulative exposure estimates were highly statistically significant predictors of lung cancer or asbestosis mortality in this study.
- TEM-based exposure estimates were more predictive of lung cancer or asbestosis than were the PCM-based estimates.
- Asbestosis and lung cancer risks were more strongly associated with exposure to very thin fibres in analyses based on fibre width.
- Longer fibres were more strongly associated with lung cancer than shorter fibres, but length was not as important for asbestosis.
- Strong correlations between the fibre size categories limited inferences that could be made based on this single study and additional studies are need using TEM-based exposure measures.

Policy implications

Asbestosis fibre dimension appears to be an important determinant of respiratory disease risk which should be considered in conducting risk assessments and setting policies for protecting workers and the public.

during a relatively short period of the study (1965–1968). Thus an inherent assumption in development of the JEM is that airborne fibre size characteristics have remained constant over a study period covering the late 1930s through the end of asbestos textile production in approximately 1977. This assumption seems reasonable since production methods and equipment remained essentially unchanged over this time frame, as did the engineering controls for asbestos dust, which were installed in the 1930s.[5 7] Although difficult to quantify, there are likely to have been substantial errors in exposure misclassification in this study, which may generally (but not always) be expected to result in a dilution of the risk and a dampening of the exposure–response relationship.[25]

Perhaps the most serious limitation of our investigation is the high degree of correlation between the size-specific cumulative exposure measures used in our study. These correlations severely limit the interpretation of our findings in several respects, especially with regard to teasing out the precise role of fibre dimension in predicting asbestos-related lung disease. While we believe this study is an important first step forward, similar studies need to be conducted in asbestos cohorts with different fibre size distributions. Pooled analyses of several cohorts may be necessary before we can fully resolve questions concerning the role of fibre dimension in lung diseases in asbestos exposed workers.

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