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An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers

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Abstract

Background: Evidence from toxicologic studies indicates that the risk of respiratory diseases varies with asbestos fiber length and width. However, there is a total lack of epidemiologic 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 fiber size-specific exposure estimates using data from a reanalysis of samples by transmission electron microscopy (TEM). Cox proportional hazards models were fit using alternative exposure metrics for single and multiple combinations of fiber 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 fiber 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 fibers (< 0.25 µm). Longer (> 10 µm) fibers were found to be the strongest predictors of lung cancer, but an inconsistent pattern with fiber length was observed for asbestosis. Cumulative exposures were highly correlated across all fiber sizes categories in this cohort (0.28-0.99, p-values < 0.0001), which complicates the interpretation of the study findings.

Conclusions: Asbestos fiber dimension appears to be an important determinant of respiratory disease risk. Current PCM-based methods may underestimate asbestos exposures to the thinnest fibers, 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 fiber dimension and type.

Introduction

There is extensive evidence that exposure to asbestos fibers is associated with an increased risk of lung cancer, mesothelioma, pleural disease and asbestosis. However, the role of fiber 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 fibers were 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 (e.g., > 8 µm) thin (e.g., < 0.25 µm) fibers. Davis et al. [2] observed a higher proportion of lung tumors and more advanced fibrosis in rats exposed by long-term inhalation to chrysotile enriched for fibers > 5 µm compared to an equal mass of chrysotile containing more short fibers. Berman et al.[3] reported in a re-analysis of rat inhalation studies that the most significant predictor of lung tumor response were fibers > 20 µm in length.

Human data on the relationship between fiber dimensions and respiratory disease risks is extremely limited because previous epidemiologic studies have either measured exposures using gravimetric methods (i.e., mass), or fiber 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 Occupational Safety and Health and Administration's (OSHA) asbestos regulation requires counting of fibers that are > 5 µm in length, and have an aspect ratio (i.e., ratio of length to width) ≥ 3.[4] This counting rule is largely based on pragmatic concerns related to what could be measured accurately and reproducibly with PCM rather than on what is the most biologically important fiber dimensions for predicting risk.

The primary objective of this study was to examine which fiber 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 fiber size distribution using Tramsmission Electron Microscopy (TEM).

Material and Methods

The study population is a cohort of 3,072 workers from an asbestos textile plant in Charleston, South Carolina that 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 fibers 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 stopped using asbestos material by the end of 1977.

The original study only included white male workers employed in the textile production operations for at least 1 month between January 1, 1940 and December 31, 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 December 31, 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 (ICD10) C33 and C44) was the underlying cause of death have been identified and were available for this analysis. Sixty two cases of asbestosis (ICD10 J61) were identified for this analysis using a multiple cause of death approach.[11] There were only 3 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 study that includes detailed information on the bivariate (length and diameter) fiber 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 (e.g. fiber 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 (UJC) 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 analyze 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 analyzed by TEM to determine the diameter and length for 18,840 fibers or fiber bundles. The TEM analysis used a minimum aspect ratio of 3:1 to define fibers and structures for consistency with PCM methods. Only two fibers of the 18,840 fiber structures (0.01%) were found to be amphiboles and the remainder was chrysotile based on morphology. The TEM results for these samples were combined within each of 10 exposure zones in the study facility.[12]

Using the length and diameter data within each zone, counts of each fiber or fiber bundle were placed into a matrix of 24 categories based on 6 length (≤ 1.5, > 1.5 to 5.0, > 5.0 to 10, > 10 to 20, > 20 to 40, > 40 μm) and 4 diameter (< 0.25, 0.25 to ≤ 1.0, > 1.0 to ≤ 3.0, > 3.0 μm) categories.

An airborne fiber size-specific JEM was developed for this study using the adjustment factor method proposed by Quinn et al.[14-16] This method adjusts standard fiber concentration measures by PCM to the size-specific fiber concentrations by using proportions from the bivariate fiber size distributions derived from TEM.[12] Approximate estimates of fiber surface area were also developed based on the assumption that fibers and fiber 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 fiber count ([fibers/ml*days]/10,000) or fiber surface area ([μm^2/ml*days]/10,000) for single and multiple combinations of the length/diameter fiber 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 chi-square statistic ($\chi^2_{1\ df}$) 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 (i.e. lag period) prior to the time at risk are irrelevant in terms of disease causation and are 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 were 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. It has been 24 years from the time when 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 fiber 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 (betas) was complicated by the high degree of correlation between the alternative size specific exposure measures. Fiber size categories that have relatively few fibers may have a larger beta coefficient than fiber size categories with a larger number of fibers even if they are equally potent when the measures are highly correlated. Thus direct comparisons of the magnitude of the betas or relative risks derived from these regression coefficients can produce misleading results.

Results

The bivariate distribution of fibers for all exposure zones combined is presented in Figure 1. The vast majority (93%) of the fibers were very short (i.e., ≤ 5 µm) and thin (i.e., < 0.25 µm), which would not have been counted using traditional PCM methods. This pattern was consistent across exposure zones, although the specific fiber 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 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 fiber (i.e., > 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 fibers (length > 5 µm) was observed in the models based on either PCM or TEM for both lung cancer (PCM: $\hat{\beta}$=0.20, χ^2_{1df}=53.6 and TEM: $\hat{\beta}$=0.09, χ^2_{1df}=58.1) and asbestosis (PCM: $\hat{\beta}$=0.26, χ^2_{1df}=78.9 and TEM: $\hat{\beta}$=0.12, χ^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 fibers counted by TEM.

Short Fibers: In order to evaluate the possible role of shorter fibers (≤ 5 µm) in lung cancer and asbestosis, analyses were performed in which models were fit for cumulative exposure to fibers ≤ 5 µm, to fibers > 5 µm and to both (Table 1). For lung cancer, models based on cumulative exposure for fibers > 5 µm (-2LL=2494.2, $\hat{\beta}$=0.09, χ^2_{1df}=58.1) provided only a slightly better fit to the data than models based on fibers ≤ 5 µm (-2LL=2495.3, $\hat{\beta}$=0.016, χ^2_{1df}=57.1). For asbestosis, models based on cumulative exposure for fibers ≤ 5 µm (-2LL=742.0,

$\hat{\beta}$=0.022, χ^2_{1df}=87.1) gave a slightly better fit to the data than models based on fibers > 5 µm (-2LL=743.6, β=0.12, χ^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).

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Lung Cancer and TEM based categories: The findings from fitting Cox models for lung cancer using TEM and varying cutpoints for fiber 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 χ^2_{1df}=15.9, p<0.0001) predictors of lung cancer. When examining the results for fibers categorized by diameter only, improved model fit was observed as fiber diameter decreases, and very thin fibers (< 0.25 µm: -2LL=2495.9, $\hat{\beta}$=0.015, χ^2_{1df}=56.4) were found to be the strongest predictors of lung cancer. Among the models examining fiber length only, the goodness of fit of the models substantially increased for the categories with fibers longer than 10 µm (χ^2_{1df} values: 60.1-62.1 for fibers > 10 µm in length; 53.0-54.1 for fibers ≤ 10 µm in length), with the strongest relationship being observed for fibers between 20 and 40 µm in length (-2LL=2490.3, $\hat{\beta}$=0.71, χ^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, χ^2_{1df}=65.9).

Asbestosis and TEM based categories: The findings from fitting Cox models for asbestosis using TEM and varying cutpoints for fiber 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 χ^2_{1df}=33.4, p<10^{-8}). When examining the results for fibers categorized by diameter only, improved model fit was also seen for asbestosis as fiber diameter decreases, and very thin fibers < 0.25 µm (-2LL=744.8, $\hat{\beta}$=0.02, χ^2_{1df}=84.3) were the strongest predictors. Among the model examining fiber length only, a clear trend with fiber length is not seen, although fibers 10-20 µm in length (-2LL=736.8, $\hat{\beta}$=0.45, χ^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, χ^2_{1df}=110.6).

Alternative Exposure Metrics: Cumulative exposure based on total fiber surface area also provided highly statistically significant predictions of either lung cancer (χ^2_{1df}=59.0, p<10^{-9}) or asbestosis mortality (χ^2_{1df}=81.2, p<10^{-9}). However, the fiber surface area exposure metrics did not appreciably improve the fit of the model for lung cancer or asbestosis relative to the fits using cumulative exposure

(all sizes). For lung cancer, 19 of the 32 models in Table 2 fit slightly better using cumulative exposure based on fiber count compared to fiber surface area. For asbestosis, 21 of the 32 models in Table 3 fit better using cumulative exposure based on fiber count than fiber 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 the one 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[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 fibers > 40 µm and < 0.25 µm diameter (-2LL=2489.3) and not as well as a model for fibers 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 ($p<0.0001$). These correlations were particularly strong among the length categories that included fibers < 0.25 µm in diameter, which ranged from 0.93 to 0.99.

Discussion

This is the first epidemiologic investigation that has examined the association between respiratory diseases and asbestos using fiber 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 mortality. Models using cumulative exposure based on TEM provided a far better 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 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 fiber size concentrations in biologically-relevant fiber 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 fiber size length and diameter examined in this study appeared to be highly significant predictors of both lung cancer and asbestosis. 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 etiologically 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 was a much larger number of short fibers than long fibers, the regression coefficients for short fibers would be expected to be much smaller than for long fibers 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 fiber dimensions because of the patterns observed in the strength of predictions of lung disease mortality by fiber dimension.

Short Fibers: Fibers 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 fiber exposure. The findings from our analysis show that cumulative exposure to all fiber size indices, including fibers ≤ 5 µm in length, were highly statistically significant predictors of lung cancer or asbestosis mortality. However, because of the correlations in these fiber size distributions, it is not possible to clearly distinguish between a biological basis for a specific fiber dimension (e.g., ≤ 5 µm) versus a simple association with exposures to the longer fibers in this facility. The models comparing the shorter (≤ 5 µm) and longer (> 5 µm) fibers did not completely resolve this question. That is, for asbestosis cumulative exposure to fibers ≤ 5 µm in length provided a slightly better fit to the data than did fibers > 5 µm, while for lung cancer, cumulative exposure to fibers > 5 µm provided a slightly better fit (in univariate analyses). Multivariate models containing cumulative exposure indices for both fiber 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 fiber length. In contrast, other findings in this study did provide support for a role of increasing fiber length (especially > 10 µm) in predicting lung cancer mortality, while a trend with fiber length was not as apparent for asbestosis.

Fiber Diameter: Cumulative exposure measures based on very thin fibers (< 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

fibers 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 epidemiologic 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 fibers 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 fibers 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 fibers would be highly desirable for producing some textile products. [23]

Our findings for lung cancer and fiber diameter are consistent with predictions made by Stanton et al.[1] based upon toxicologic data that lung cancer is most strongly related to exposure to fibers < 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 fibers > 0.15 µm in diameter; however, we did not specificially 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 coworkers[2] reported that respiratory cancer risk was most strongly related to exposures to very thin fibers (< 0.3 µm), which is similar to our findings. Berman et al[3] also reported that lung cancer risk was related to fibers with a diameter greater than 5 µm. Exposures based on thick fibers (> 3.0 µm) were not found to be especially strong predictors of lung cancer or asbestosis mortality in our investigation.

Fiber Length: Exposures using relatively long fibers were found to be the strongest predictors of lung cancer mortality in this study. Cumulative exposure to fibers 20-40 µm in length demonstrated the strongest association, but cumulative exposure to fibers 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. Stanton et al[1] proposed based on studies in rats that asbestos fibers > 8 µm in length are most important in predicting respiratory cancer risk. Lippman[18] in a review of toxicologic and human lung burden studies suggested that fibers > 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 tumor response were fibers > 20 µm in length.

Berman et al[3] also reported that the carcinogenic potency of fibers increased with fiber length and that fibers longer than 40 µm and thinner than 0.3 µm had 500 times the potency of fibers between 5 and 40 µm in length and thinner than 0.3 µm. Potency comparisons based on fiber count as the exposure metric can be misleading when the fiber dimensions are correlated. This is because exposure to a fiber count of lower frequency (long fibers) can appear to have a greater

potency than exposure to a fiber count of greater frequency (short fibers) due to the reduced magnitude of the exposure metric, while the disease response remains fixed. . As discussed earlier, fiber 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 fiber size distributions. Because of these correlations, we were not able to evaluate the fiber-length potency estimates of Berman et al[3] from the results in our study. Independent data from other cohorts with exposures to different fiber size distributions are needed to further elucidate the role of fiber 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 would be most strongly related to the surface area of fibers with lengths greater than 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 fibers in predicting asbestosis risk. Short fibers (≤ 5 µm) were stronger predictors of asbestosis than longer fibers (> 5 µm), but in more detailed analysis (Table 3) the strongest association observed was with relatively long fibers (i.e., 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[25], 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 is 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 during a relatively short period of the study (1965-1968). Thus an inherent assumption in development of the JEM is that airborne fiber size characteristics have remained constant over a study period covering the late 1930s through the end of asbestos textile production in approximately 1977.[i] This assumption seems reasonable since production methods and equipment remained essentially unchanged over

[i]

this time frame as did the engineering controls for asbestos dust, which were installed in the 1930s. [5,7] Although difficult to quantify, there is 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 fiber 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 fiber size distributions. Pooled analyses of several cohorts may be necessary before we can fully resolve questions concerning the role of fiber dimension in lung diseases in asbestos-exposed workers.

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Table 1: Results from Cox models for lung cancer and asbestosis using PCM based cumulative exposure (fiber-days/ml/10,000) for fibers > 5 µm in length, and from TEM based cumulative exposure for fibers ≤ 5 µm and > 5 µm in length.[a]

Model	Lung Cancer			Asbestosis		
	-2LL	Beta	χ^2_{1df} (p)	-2LL	Beta	χ^2_{1df} (p)
PCM L>5 µm	2498.7	0.20	53.6 (<0.0001)	750.2	0.26	78.9 (<0.0001)
TEM L≤5 µm	2495.3	0.016	57.1 (<0.0001)	742.0	0.022	87.1 (<0.0001)
TEM L>5 µm	2494.2	0.090	58.1 (<0.0001)	743.6	0.120	85.5 (<0.0001)
TEM L≤5 µm TEM L>5 µm	2493.8	0.005 0.060	0.4 (0.52) 1.5 (0.23)	740.9	0.013 0.048	2.7 (0.10) 1.0 (0.31)

[a] Results from models with a 0 year lag that included variables controlling for gender, race, calendar time and time since first employment.

Table 2: Results from Cox models for **lung cancer** using TEM based cumulative exposures (fiber-days/ml/10,000) based on combinations of fiber length and diameter. [b]

Diameter (μm)	Length (μm)						
	≤ 1.5	**1.5-5**	**5-10**	**10-20**	**20-40**	**> 40**	**All**
< 0.25							
Beta	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							
Beta	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							
Beta		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}	na[a]	16.2	40.3	48.5	57.0	59.0	45.8
>3.0							
Beta			5.268	4.935	7.562	5.978	2.047
-2LL			2536.4	2518.0	2517.7	2516.1	2509.4
χ^2_{1df}	na[a]	na[a]	15.9	34.3	34.7	36.3	42.9
All							
Beta	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

[a] These categories do not meet the 3:1 length to width fiber definition that was a part of our TEM analysis counting rules. There were, however, a very small percentage (<0.1%) of fibers counted that did fall into these categories.

[b] Results from models with a 0 year lag that included variables controlling for gender, race, calendar time and time since first employment.

Table 3: Results from Cox models for **asbestosis** using TEM based cumulative exposures (fiber-days/ml/10,000) based on combinations of fiber length and diameter.[b]

Diameter (µm)	Length (µm)						
	≤ 1.5	**1.5-5**	**5-10**	**10-20**	**20-40**	**> 40**	**All**
< 0.25							
Beta	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							
Beta	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							
Beta		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}	na[a]	46.2	58.9	74.7	77.8	110.6	74.3
>3.0							
Beta			6.768	6.138	10.335	7.057	2.474
-2LL			795.7	784.6	767.6	795.5	772.3
χ^2_{1df}	na[a]	na[a]	33.4	44.5	61.5	33.6	56.8
All							
Beta	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

[a] These categories do not meet the 3:1 length to width fiber definition that was a part of our TEM analysis counting rules. There were, however, a very small percentage (<0.1%) of fibers counted that did fall into these categories.

[b] Results from models with a 0 year lag that included variables controlling for gender, race, calendar time and time since first employment.

Table 4: Results for lung cancer from modeling cumulative exposure using alternative indices of fiber exposure.

Reference	Index Criteria [a]	Beta(SE)	χ^2_{1df} (p value)	Model -2LL
Pott 1987	D<1, L>3	0.058(0.006)	57.0 (<0.0001)	2495.3
Stanton et al. 1981	D<0.25, L>8.0 [b]	0.334(0.034)	59.3 (<0.0001)	2493.1
Lippman 1990	D>0.15 [c], L>10.0	0.412(0.042)	60.6 (<0.0001)	2491.8
Quinn et al. 2000	D<6.0, L>5.0	0.090(0.009)	58.1 (<0.0001)	2494.2
Berman et al. 1995	D<0.25, 5<L≤40 D<0.25, L>40	0.036(0.045) 2.81 (0.956)	0.65 (0.42) 7.21 (0.007)	2488.7

[a] 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 criteria used in our fiber counting procedure.

[b] Stanton et al. proposed a length criterion of greater than 8 µm. However we used greater than 10 µm since that was the closest category cut-off in our study.

[c] Lippman proposed a diameter criterion of greater than 0.15 µm. However we used a cutoff of ≥ 0.25 µm since that was the closest category in our study.

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Figure 1: Distribution of asbestos fibers and fiber 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 fibers not counted by PCM.