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ORIGINAL ARTICLE

Examining the association of lung cancer and highly correlated fibre size-specific asbestos exposures with a hierarchical Bayesian model

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ABSTRACT

Background Asbestos is a known carcinogen. However, little is known about the differential effects of size-specific asbestos fibres. Previous research has examined the relationship with lung cancer of each fibre group in the absence of others. Attempts to model all fibre groups within a single regression model have failed due to high correlations across fibre size groups.

Methods We compare results from frequentist models for individual fibre size groups, and a hierarchical Bayesian model that included all fibre groups to estimate the relationship of size-specific asbestos fibre groups to lung cancer mortality. The hierarchical model assumes partial exchangeability of the effects of size-specific asbestos fibre groups to lung cancer, and is capable of handling the strong correlation of the exposure data.

Results When fibre groups are modelled independently with a frequentist model, there appears to be an increase in the dose-response with increasing fibre size. However, when subject to a hierarchical structure, this trend vanishes, and the effects of distinct fibre groups appear largely similar.

Conclusions This is the first occasion where distinct asbestos fibre groups have been assessed in a single regression model; however, even the use of a hierarchical modelling structure does not appear to overcome all the statistical fluctuations arising from the high correlations across fibre groups. We believe these results should be compared with other occupational cohorts with similar fibre group information. Finally, results for the smallest fibre group may be suggestive of a carcinogenic potential for nanofibres.

What this paper adds

- Asbestos is a known lung carcinogen; however, evidence regarding the differential effects of size specific fibres is sparse and incomplete.
- This study suggests that there may be little to no difference in carcinogenicity of different length and width of asbestos fibres.
- The most precise results are for fibres <0.25 μm in width and <1.5 μm in length: this may have implications for health effects of nanoparticles, which have received little attention in the epidemiologic literature.

INTRODUCTION

The carcinogenicity of asbestos has been studied thoroughly in epidemiology and toxicology[1 2]; it is classified as a Group 1 carcinogen by the International Agency for Research on Cancer.[3] Chrysotile is the most common form of asbestos in commercial use; it is composed of serpentine mineral fibres of varying length and diameter. Animal research has suggested that the carcinogenicity is greater for several types of asbestos fibres of greater length and thinner diameter.[4 5] Recent epidemiologic analyses of cohorts exposed to chrysotile reach similar conclusions to the experimental animal studies. By modelling each group of asbestos fibres individually, the authors show greater increases in lung cancer associated with thin chrysotile fibres compared with thick fibres.[6–8]

The processing of chrysotile in industrial use creates fibres of different length and diameter to which workers may be exposed simultaneously or serially during a working career. Thus, studying health risks associated with cumulative exposure to all sizes of chrysotile fibre should be conducted in a single regression model. However, high correlation across size classes has made this approach intractable. Hierarchical Bayesian modelling is an increasingly popular approach for addressing analytic challenges in environmental and occupational epidemiology. Bayesian models allow the researcher to model multiple exposure measures,[9] account for measurement error and misclassification,[10 11] and even model multiple exposures (different fibre groups) that are known to arise from a common source (chrysotile asbestos) and, thus, may share a common effect.[12–14]

Recent advancements in statistical programmes allow researchers to easily specify a hierarchical structure to a regression model. In this work, we apply a hierarchical Bayesian model to examine the relationship of distinct chrysotile fibre groups to lung cancer in a cohort of occupationally exposed textile workers from North Carolina. We discuss the implications of this work to further studies of silicate fibre groups and its relationship with nanofibres.

METHODS

Study population

The cohort of interest is identical to that studied by Loomis *et al*.[7] Details of employees and facilities included have been described in detail in their

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work and earlier publications,[7 15] so we will only provide a brief summary of the cohort here. Included are 2419 men and 1384 women employed in production jobs in an asbestos textile plant for a minimum of 1 day between 1 January 1950 and 31 December 1973 in North Carolina, USA. Workers for whom occupational exposure history could not be estimated (n=1969) are excluded from this analysis. There are a total of three textile facilities, two producing asbestos since the 1920s and the third since the 1940s. One facility ended production of asbestos in 1970 while the remaining two continued production into the late 1990s. Based on a thorough review of available records, one facility was known to have used a limited amount of amosite asbestos between 1963 and 1976; otherwise, production was limited to chrysotile asbestos.

Vital status was ascertained for cohort members through 31 December 2003. International Classification of Diseases (ICD) codes available at the event time were used to assign cause of death. In total, the cohort includes 181 lung cancer events among 1681 total deaths over 124 029 person years of follow-up. Procedures for study of human subjects were approved by the Institutional Review Boards of the University of North Carolina, Chapel Hill.

Exposure assessment

The methods of exposure assessment used in this cohort are described in detail in previous work.[8 16 17] Briefly, transmission electron microscopy (TEM) was used to estimate the fraction of airborne chrysotile fibres measured in micrometers (μm) in four diameter (<0.25, 0.25–1.0, 1.0–3.0, >3.0 μm) and six length (≤1.5, 1.5–5, 5–10, 10–20, 20–40, >40 μm) groups, creating 24 categories in total, for a subset of 77 dust samples collected from 1964 to 1971. The TEM size distributions by plant and operation were used with standard phase-contrast light microscopy estimates of concentrations of fibres >5 μm to determine size-specific fibre concentrations by plant, operation and time period. Estimates of annual, cumulative size-specific fibre exposures were generated using these estimated size-specific concentrations in conjunction with individual work histories, with fibre size-specific exposures expressed in units of fibre-years/mL (f-y/mL).

Statistical analyses

Analyses were based on the 181 observed lung cancer cases. Previous studies of this cohort use ungrouped Poisson regression, where the typical person-level data structure (1 record per person) is transformed, and subsequently analysed, in a person-period structure (1 record per person per year of observation).[18] Because this approach creates a large number of records it is less amenable to computationally intensive modelling procedures. Thus, we conducted a nested case-control analysis to reduce the complexity of the data. Ten controls were matched to each lung cancer case by continuous age in years using incidence density sampling. We conducted unconditional logistic regression where, similar to previous analyses,[6] models were adjusted for continuous age at lung cancer event (cases) or selection into the cohort (controls), sex (male=0, female=1), race (white=0, non-white=1), and year of observation in ordinal categories from 1950–1959 (reference), 1960–1969, 1970–1979, 1980–1989, 1990–1999, and 2000+. Because we matched on only one variable (age), unconditional logistic regression adjusted for age will yield the same results as a conditional logistic regression model. The first stage model is as follows:

$$\text{logit}(\Pr(D = 1)) = \alpha + \sum_{i=1}^{21} \beta_i x_i + \varphi_1 \times \text{age} + \varphi_2 \times \text{race} + \varphi_3 \times \text{sex} + \varphi_4 \times \text{year}$$

where β represents the change in the log odds of lung cancer associated with a 1 unit change in cumulative exposure to each chrysotile length/diameter group, x, from i=1…21 (3 of the 24 length/diameter groups did not have any observations and are excluded from analyses). We use a 10-year lag from age of event (cases) or selection into the cohort (controls); however, previous analyses showed that results are not sensitive to different specifications of lag time.[1]

The second stage of the model includes a single term representing the shared mean for fibre groups, x_i, in the first stage of the model, expressed as $\beta_i \sim N(\mu, \tau^2)$. This states that we believe β_{1-21} are exchangeable, or arise from the same prior distribution. We specify a diffuse, uniform prior for τ^2, so that the data determine the influence of the grouped mean, μ. For the remaining variables, we specify a very weakly informative prior such that $\alpha, \varphi_1 - \varphi_4 \sim N(0, 1000)$.

We followed conventions for diagnosing convergence of a Bayesian analysis using Markov chain Monte Carlo simulation, described in detail elsewhere.[19] Final models were run for 100 000 iterations with a burn-in of 5000 iterations and thinning=2 for 3 distinct chains. In addition to visual diagnostics for convergence, Gelman–Rubin diagnostics indicated model convergence. Samples from each chain are combined for final analyses to minimise simulation error. We fit the model above using a frequentist estimator for each individual fibre diameter/length group i independent of other fibre groups for comparison of results in the absence of a hierarchical modelling structure. We used just another Gibbs sampler (JAGS)[20] and No-U turn sampler (STAN)[21] packages to fit hierarchical Bayesian models and the EPI package to fit frequentist regression models with R (V.3.0.2).

RESULTS

Correlation across chrysotile fibres ranged from moderate to high. For example, fibres in 0.25–1.0 μm diameter by 10–20 μm length and 0.25–1.0 μm diameter by 5.0–10 μm length groups were almost perfectly correlated, with a Pearson correlation coefficient of 0.99. Correlation coefficients ranged from 0.40 to 0.99, with a median value of 0.79. We provide a table of these correlation coefficients as an online eSupplement. We attempted to overcome some of these high correlations by reducing the number of groups based on animal evidence discussed by Berman.[22] However, this approach did not improve correlations, and led to an increase in overall correlations among the reduced number of fibre groups (results not shown).

The proportions of the total chrysotile asbestos exposure represented by each fibre group are reported in table 1. The highest proportion of the total fibre count is represented by the smallest chrysotile group, which comprises 0.530, or 53%, of total counted fibres. Fibres of diameter and length <0.25 μm and 1.5–5.0 μm represent 0.264 (26.4%) of total counted fibres. In sum, these two groups represent the bulk of fibres counted with TEM, summing up to 79.4% of the total. All other fibre groups represent a small proportion of overall fibres counted relative to these two groups.

Table 1 Coefficients for change in the log odds of lung cancer associated with a 100 f-yr/mL change in exposure to chrysotile, by diameter and length groups, in a cohort of North Carolina asbestos textile workers

		Frequentist model		Hierarchical model			
Diameter	Length	Mean	SD	Mean	Median	SD	Overall proportion
<0.25	<1.5	0.0092	0.0047	0.0652	0.0619	0.0362	0.530
<0.25	1.5–5.0	0.0120	0.0082	−0.2458	−0.2353	0.1411	0.264
<0.25	5.0–10	0.0698	0.0359	0.3768	0.3687	0.2157	0.048
<0.25	10–20	0.1736	0.0965	0.1850	0.1432	0.3314	0.020
<0.25	20–40	0.6242	0.2618	0.1591	0.1135	0.4609	0.008
<0.25	>40	1.9191	0.7226	0.0707	0.0597	0.4715	0.003
0.25–1.0	<1.5	0.0809	0.1218	−0.1815	−0.1068	0.3745	0.014
0.25–1.0	1.5–5.0	0.0262	0.0271	0.1598	0.1377	0.1660	0.056
0.25–1.0	5.0–10	0.1826	0.1166	0.0290	0.0271	0.3331	0.022
0.25–1.0	10–20	0.3722	0.1907	0.1252	0.0883	0.4355	0.013
0.25–1.0	20–40	0.8560	0.3643	0.1575	0.1012	0.4491	0.007
0.25–1.0	>40	1.6669	0.6076	0.1203	0.0880	0.4543	0.004
1.0–3.0	1.5–5.0	0.4748	0.5333	−0.1215	−0.0382	0.4615	0.004
1.0–3.0	5.0–10	0.9287	0.4627	0.0092	0.0317	0.4247	0.005
1.0–3.0	10–20	1.0288	0.6278	0.0561	0.0510	0.4220	0.005
1.0–3.0	20–40	2.9358	1.1797	0.0735	0.0572	0.4858	0.003
1.0–3.0	>40	6.4449	2.2215	0.0939	0.0681	0.4699	0.002
>3.0	5.0–10	3.3816	4.1605	0.0467	0.0397	0.4733	0.001
>3.0	10–20	3.2620	1.8527	0.0572	0.0480	0.4665	0.002
>3.0	20–40	6.1264	2.0889	0.1153	0.0781	0.4784	0.001
>3.0	>40	3.5598	2.0575	0.0544	0.0469	0.4625	0.001

Both, frequentist† and Bayesian hierarchical modelling‡ results are presented. Models are adjusted for age (continuous), sex, race, and year of employment.
†Frequentist results are from 21 distinct regression models where fibre groups are modelled individually (ie, in the absence of other fibre groups).
‡Mean, median and SD of the second-stage prior are 0.0668, 0.0603 and 0.1378, respectively.

Estimated coefficients for the 21 fibre groups are provided in table 1. Three fibre groups (diameter and length: 1.0–3.0 μm and <1.5 μm, >3.0 μm and <1.5 μm, >3.0 μm and 1.5–5.0 μm) did not have any observations, and are excluded from the results. We present mean and median values of the posterior distributions for results from the hierarchical model and discuss median values here.

When fibre groups are modelled independently with a frequentist model, there appears to be an increase in the dose response with increasing diameter/length group. Within diameter groups, the change in the log odds of lung cancer per 100 f-y/mL of additional exposure to chrysotile increases with increasing fibre length. There is a similar trend with increasing diameter within length groups. For example, for fibres of length 10–20 μm, the coefficient (SE) for diameter groups <0.25, 0.25–1.0, 1.0–3.0, and >3.0 μm are 0.1736 (0.0965), 0.3722 (0.1907), 1.0288 (0.6278), and 3.2620 (1.8527), respectively.

When we impose a hierarchical structure, we do not see an increasing dose-response trend by increasing fibre diameter/length group. The second stage prior median (SD) estimated from the data was 0.0603 (0.1378) per 100 f-y/mL. Estimated coefficients for many of the fibre groups were very similar to the grouped mean. The smallest chrysotile fibre group with diameter <0.25 μm and length <1.5 μm had the most precise coefficient estimate, 0.0619 (0.0362). The coefficient for the next longest fibre group with the same diameter (length 1.5–5.0 μm) was on the opposite side of the null, or −0.2353 (0.1411). The coefficient for the fibre group of diameter <0.25 μm and length 5.0–10 μm, 0.3687 (0.2157), was furthest from the null and the grouped mean. For the remaining fibre groups, the SD of the estimated coefficient was greater than the mean and median.

Figure 1 shows the distribution of each asbestos fibre group compared to the estimated group median value. Points represent the median, and error lines represent the distribution of estimated values approximately one SD (thick lines) and two SDs (thin lines) from the mean. The high precision of diameter <0.25 μm and length <1.5 μm fibre group relative to other groups is apparent. There do not appear to be any trends in the effect of chrysotile fibres by increasing or decreasing diameter/length. Excepting fibre groups with diameter <0.25 μm and diameters <1.5 μm, 1.5–5.0 μm, and 5.0–10 μm, the remaining fibre groups are close to the grouped median with a great deal of variability in the estimated values (ie, high SDs).

DISCUSSION

We present results from a model estimating the effects of distinct chrysotile fibre groups subject to a hierarchical modelling structure. This is the first instance that we know of where distinct chrysotile fibre size groups have been examined within a single regression model. Results suggest a great deal of similarity across fibre size groups; median values for the posterior distribution of most fibre groups were near the grouped median.

Previous analyses have examined the relationship of distinct chrysotile fibre groups to lung cancer; however, these analyses considered each fibre group within a separate regression model.[6 7] By imposing a hierarchical structure, we are able to consider all fibre groups within a single model so long as we are willing to assume that the effects of each fibre group are partially exchangeable; that is, that they arise from a similar prior distribution.[12] We believe this is a reasonable prior, since fibre groups are estimated from a single exposure source and, likely exhibit a similar relationship to the outcome of interest. Additionally, by allowing the data to determine the weight of

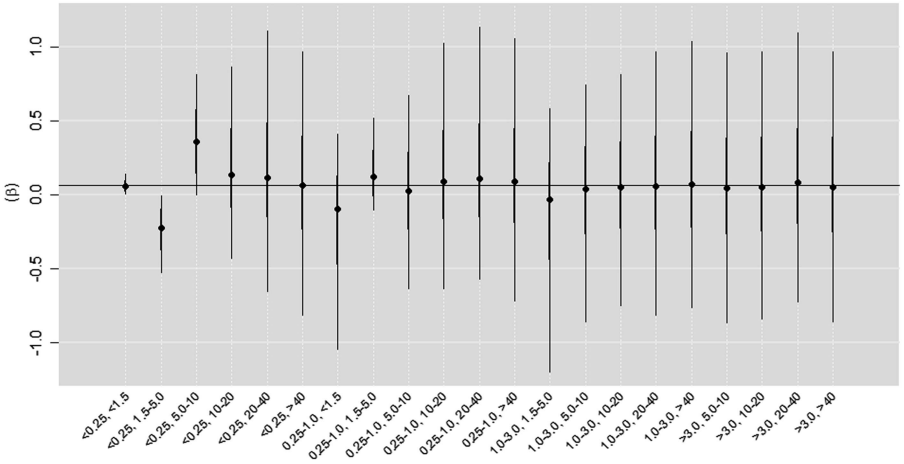

Figure 1 Median and estimated SD of coefficients for chrysotile fibre groups. Horizontal line represents the group median (0.0603). Thick and thin lines represent 16th–84th and 2.5th–97.5th percentile values of the distribution, respectively.

the second-stage prior, effects for which there is strong evidence against the grouped median will be allowed to diverge.[13 23]

The most statistically precise coefficient was estimated for fibres of diameter and length <0.25 and <1.5 μm. This fibre group estimate is very close to the prior grouped median value, which is consistent with prior evidence of a relationship between asbestos exposure and lung cancer risk. Additionally, this group accounts for the majority of fibres counted by TEM.[7] For this reason, it is possible that this group is most influential in determining the value for the second-stage, or grouped, median value. Prior to use of TEM, fibres shorter than 5 μm in length were not counted with the conventional phase-contrast microscopic method used to determine asbestos fibre concentrations for regulatory purposes, and in most previous epidemiologic studies. As a result, information on the human health effects of asbestos fibres in this size range is limited, being available only from our previous analyses based on TEM data.[6–8]

Toxicological hypotheses have suggested that shorter-thinner asbestos fibres may not contribute to the development of lung cancer.[24–26] While previous analyses of the North Carolina asbestos workers cohort suggest that this may not be the case,[7] the authors of the study cited failure to account for correlations across fibre groups as a limitation in finding a positive association between the shortest-thinnest fibres and lung cancer. A more current review concluded that asbestos fibres of all lengths induce pathological responses and cautioned against excluding any population of inhaled fibres, based on their length, from being contributors to the potential for development of asbestos-related diseases.[27] While some analyses have concluded that fibres <5 μm in length contribute little to the risk of lung cancer,[28] we are not aware of any study that suggests a protective effect for fibres of diameter <0.25 μm and length 1.5–5.0 μm. We caution against any interpretation of a protective effect of any asbestos fibre group on lung cancer and believe this finding is an artefact of the strong correlations for which the hierarchical model attempts to account. For example, the correlation between the two most prevalent fibre size categories (fibres diameter <0.25 μm and length <1.5 μm and diameter and length <0.25 and 1.5–5.0 μm) was >0.9 suggesting challenges in separating effects even for the Bayesian approach.[29] This finding also underlies the point that these analyses are preliminary and that these analyses should be replicated in other cohorts where information on different asbestos fibre size groups is available.

Effects of chrysotile fibres in the shortest, thinnest group may have implications for health risks associated with nanoparticles. Nanotechnology has a number of benefits; nonetheless, there are concerns about the health consequences of long-term exposure.[30] Nanofibres are <0.1 μm (or 100 nm) in diameter, which allows them to easily penetrate upper and lower regions of the lung, including the alveolar region.[31 32] If carcinogenic potential is strongest for the thinnest, shortest fibres, work examining similarly sized nanoparticles may be warranted.

These data have several limitations worth mentioning in addition to the lack of information about tobacco smoking and the possible impact of a medical surveillance programme discussed in connection with the original analysis.[15] First, calculations of exposure by fibre size were based on TEM analysis of dust samples, which were only available for the period 1964–1971.[16] While it is thought that fibre size distributions are unlikely to have changed over time due to consistent asbestos sources and textile processes,[7] we cannot test this assumption. Second, the number of samples that could be analysed was limited, giving rise to an unknown degree of uncertainty in the estimates of the fibre numbers and concentrations, which could have affected the parameter estimates.[6 7 15] Nevertheless, the current results are coherent with those based on conventional fibre counts, indicating increased risk associated with chrysotile fibres, in general. Finally, we studied these relationships among workers in the asbestos textile industry, which some data suggest may differ from other industries with respect to exposure response, and the distribution of fibre sizes.[33 34] The distribution of fibre sizes and the concentrations of fibres within categories may vary between workplaces, so this approach should be tested in other cohorts.

We were not able to directly compare these results with those that would be obtained in the absence of hierarchical model structure. When a model including all fibre groups was fit with a frequentist procedure, all fibre group parameter estimates showed evidence of quasicomplete separation.[35] In this situation, the maximum likelihood estimate does not truly exist; however, logistic regression is still able to provide some estimate of the parameter since the probability of the outcome is bounded to be between 0 and 1. For example, the estimated coefficient for fibres with diameter <0.25 μm and length <1.5 μm is −4947 (SE=11 620). Parameter estimates for all other fibre groups were equally implausible. In order to compare these results with those that would be obtained in the absence of the second-stage prior, we ran Bayesian models where each fibre group was assigned a very weakly informative prior, or $\beta_i \sim N(0, 1000)$. This specification should provide estimates similar to those obtained from a frequentist analyses of

the data.[19] However, these attempts also failed due to high autocorrelation and variability in estimates across different chains. Increasing the number of iterations and varying the specifications of the sampler did not solve this problem. This is likely attributable to the high correlation between fibre groups. We finally attempted to use a Hamiltonian Monte Carlo procedure, which is thought to better handle data with highly correlated variables. However, this did not resolve the problem.

Finally, these results do not support use of coefficients for size-specific fibre groups for risk estimation. Rather, we believe these results lend insight into the potential for differential effects of size-specific fibre groups. This begs further examination in other occupational cohorts, and for nanoparticles, for which there is currently little epidemiologic data. Hierarchical modelling provides a means of including multiple, correlated exposures within a single regression model.[36 37] When subjected to this modelling structure, we find that most chrysotile fibre size groups share a similar relationship with lung cancer risk. The thinnest (<2.5 μm) and three shortest (<1.5, 1.5–5.0, and 5.0–10 μm) fibre groups provide the most precise coefficients, and the shortest/thinnest seems to be the most influential in the estimation of the second-stage prior.

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Competing interests None.

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Data sharing statement The software code used for these analyses can be made available to interested researchers.

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Notes