ORIGINAL ARTICLE

Pulmonary Asbestos Fiber Burden Is Related to Patient Survival in Malignant Pleural Mesothelioma

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ABSTRACT

Introduction: Malignant pleural mesothelioma (MPM) is associated with poor prognosis and is strongly associated with occupational asbestos exposure. Given the importance of asbestos exposure in MPM pathogenesis, we retrospectively analyzed the types and concentrations of asbestos fibers within the lung tissues of patients with MPM and investigated their effects on all-cause mortality.

Methods: We formed a national data set of patients with MPM identified from the Finnish Cancer Registry and Statistics Finland. These data were merged with pulmonary asbestos fiber analysis results received from the Finnish Institute of Occupational Health.

Results: We identified 590 patients with MPM who underwent pulmonary asbestos fiber analysis. The median asbestos concentration within dry lung tissue was 3.20 million fibers/gram (range: 0 – 1700 million fibers/gram). Crocidolite and anthophyllite were the most prevalent asbestos fiber types detected in lung tissue. The multivariable risk of death analyses, where changes over time were accounted for, revealed that total asbestos fiber concentration was associated with increased mortality. Nevertheless, no difference in mortality was noted between different fiber types.

Conclusions: Our study revealed that pulmonary fiber concentrations correlated with the manner of asbestos usage. Anthophyllite was identified as the sole fiber in a sizable proportion of cases, supporting its independent role in the pathogenesis of MPM. Our findings suggest that asbestos fiber burden, but not fiber type, may have an impact on the prognosis of MPM.

Keywords: Malignant pleural mesothelioma; Pulmonary fiber analysis; Asbestos fibers; Mortality

Introduction

Malignant pleural mesothelioma (MPM), a type of cancer, has an extremely poor survival rate.[1] The incidence of MPM is higher in men than in women owing to a strong association with occupational asbestos exposure. MPM is usually diagnosed in advanced age owing to the decades-long latency period between asbestos exposure and disease development.[1,2] The term asbestos

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refers to a group of fibrous minerals, which are divided into the following two categories based on their mineralogy: the amphiboles, including crocidolite, anthophyllite, amosite, tremolite, and actinolite; and the serpentines, consisting solely of chrysotile.[3,4]

Restrictions leading to the complete prohibition of asbestos use were introduced in Europe as early as the 1970s.[5] Both anthophyllite mines located in Finland were closed by 1975,[6,7] but the incidence of mesothelioma remains high owing to the long latency period associated with this disease. The decades-long production of anthophyllite has also resulted in exceptionally diverse domestic utilization in Finland compared with that in many other nations.[6] Exposure to all types of asbestos fibers is considered a risk for MPM. Nevertheless, fiber types may have distinct potency.[4,8]

Several studies evaluating prognostic factors in MPM have been conducted in the past few decades, including well-recognized clinical scoring systems established by the European Organization for Research and Treatment of Cancer and the Cancer and Leukemia Group B.[9] In addition to other demographic parameters, the impact of asbestos exposure on survival time has been evaluated in mesothelioma, but the results have been conflicting.[10–14] Asbestos exposure is typically assessed using questionnaires or hospital records. Notably, only a few studies have addressed the role of pulmonary asbestos burden[10,14,15] or fiber type[16,17] in overall survival.

We identified a national cohort of patients diagnosed with having MPM in Finland between 2000 and 2012 from the Finnish Cancer Registry (FCR). Within this cohort, we identified 590 patients who had undergone pulmonary asbestos fiber analysis. The aim of our study was to identify the distribution and levels of asbestos fibers in these patients with MPM. In addition, we investigated the impact of asbestos fiber burden and fiber type on patient mortality. Owing to a national occupational exposure profile to anthophyllite, this study offers a unique opportunity to understand the role of anthophyllite in the pathogenesis of MPM.[6]

Materials and Methods

Patients

Patients with MPM were identified from the FCR, which harbors information concerning malignancies diagnosed in Finland. A recent study verified that the FCR has excellent data completeness for solid malignant tumors.[18] For this study, we screened for patients diagnosed with having MPM between 2000 and 2012. Demographics of this cohort are described in published research on the epidemiology of MPM.[19] The data collected by the FCR include, but are not limited to, name, sex, date of birth, side of the tumor, date of diagnosis, date of death, and histopathologic diagnosis received from pathology laboratories. We supplemented dates of death from the National Registry of Causes of Death, Statistics Finland, and the last update was performed on February 17, 2017.

Pulmonary Asbestos Fiber Analysis

The Finnish law mandates that all deaths for which an occupational disease is suspected be subjected to a forensic investigation to ascertain the cause of death. This process often entails a pulmonary fiber analysis of asbestos-related illnesses, to determine both asbestos fiber quantity and type in lung tissue. These analyses are performed at the pathology laboratory of the Finnish Institute of Occupational Health. We combined the asbestos fiber data from the Finnish Institute of Occupational Health with the FCR and Statistics Finland data, resulting in a study cohort of 590 patients. Fiber analysis was performed using scanning transmission electron microscopy (STEM),[20] and the analytical sensitivity limit was 0.2 million fibers/gram (f/g). Patients detected to have a pulmonary asbestos fiber concentration below this analytical sensitivity limit were reported to have a fiber count less than 0.2 million f/g. For technical purposes, an asbestos fiber concentration of 0 million f/g was used in the statistical analyses for this patient group. The collected fiber data included the total concentration of asbestos fibers detected in dry lung tissue (million f/g) and the proportions of different asbestos fiber types (anthophyllite, crocidolite, amosite, chrysotile, and tremolite or actinolite). This information was then used to calculate the concentration for each asbestos fiber type. For each patient, the asbestos fiber with the highest concentration was designated as the main asbestos fiber type. The main asbestos fiber type could not be established for 28 patients owing to equal concentrations of several different fibers, and these patients were therefore excluded from the analyses of the main asbestos fiber type. Patients detected to have only one fiber type in lung tissue were designated as the "sole fiber" group. Pulmonary asbestos fiber concentration above 1 million f/g indicates work-related exposure,[21] and therefore for statistical purposes, this value was used in the categorical variable as a cutoff limit to establish the highest-fiber concentration group. Median or mean values were reported depending on data skewness. This study has been given a positive statement by the Ethics Committee (418/13/03/02/2015) and was approved by the Institutional Review Board (HUS/152/2016) of the Hospital District of Helsinki and Uusimaa. The use of the pulmonary asbestos fiber results was approved by the National Supervisory Authority for Welfare and Health (Valvira; Dnro 752/06.01.03.01/2016).

Statistical Analyses

Follow-up time was calculated from the date of clinical or pathologic diagnosis to the date of death for all patients. Before performing detailed mortality analyses, the possible time dependency of the variables was assessed using tests and plots based on scaled Schoenfeld residuals and information criteria, such as Akaike information criterion and Bayesian information criterion. These assessments indicated that some of the effects of the study variables could be considered stable over time, whereas others (age at diagnosis, total asbestos fiber concentration, anthophyllite concentration, crocidolite concentration, and amosite concentration) varied over time and should be treated as time-dependent effects. For time-independent effects, a conventional Cox proportional hazards regression model was used. For time-dependent effects, a proportional hazards regression model extended for time-dependent effects was used, resulting in two separate hazard ratio (HR) values: one for the beginning of the follow-up time, referred to as initial HR, and the other for the change in HR over the follow-up time, referred to as a change in HR.[22] For both model types, a crude analysis was first performed for each variable, including sex, age at diagnosis (y), total asbestos fiber concentration (million f/g), side of the tumor (bilateral, left, right), histologic subtype (epithelioid including 3 cases of papillary mesothelioma, sarcomatoid, biphasic, or not otherwise specified), anthophyllite concentration (million f/g), crocidolite concentration (million f/g), and amosite concentration (million f/g). The follow-up time analysis for all-cause mortality was subsequently performed using two multivariable models. In the first multivariable model, each fiber group and total fiber concentration were adjusted for sex, age at diagnosis, side of the tumor, and histologic subtype. In the second multivariable analysis, each fiber concentration was considered as part of a total fiber composite for inclusion in a joint analysis of fiber exposure. This permitted an assessment of the impact of each fiber type in a joint analysis while accounting for the interrelatedness of the fiber types as part of a whole. The fiber concentrations were transformed based on the isometric logarithmic transformation of the positive amounts of logistic framework (aplus), enabling the use of fiber concentrations as linear predictors in the proportional hazards models.[23] In addition to the aforementioned confounding factors, this second multivariable analysis was adjusted for other fiber groups. Potential differences in contributions to mortality risk between fiber type pairs were assessed using the Wald's test. We analyzed the data with either IBM SPSS Statistics 24.0 and 25.0 or R statistical programming environment version 4.0.4. For the latter, we used survival version 3.2-7 and compositions version 2.0-1 packages. p values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 590 patients were identified, comprising 547 men (92.7%) and 43 women (7.3%). For 50 patients (8.5%), MPM was diagnosed at autopsy; these patients were excluded from the risk of all-cause mortality analyses to remove potential bias owing to patient-related diagnostic delays. The mean age of patients at diagnosis was 68.2 years (range: 40.9–92.1 y).

Asbestos Fibers

Men more often had higher total fiber concentrations than women: 0 to 0.2 million f/g occurring in 16.8% versus 34.9%, 0.3 to 0.9 million f/g in 15.7% versus 32.6%, and 1 to 1700 million f/g in 67.5% versus 32.6%, respectively ($p < 0.001$, chi-square test). Asbestos fiber concentration varied according to age at diagnosis (Table 1). The distribution of asbestos fiber types also differed between sexes ($p < 0.001$, Fisher's exact test). Crocidolite as the sole asbestos fiber type was more common in men than in women (27.6% versus 4.7%), whereas anthophyllite as the sole asbestos fiber type was more common in women than in men (41.9% versus 15.4%). The difference in fiber distributions between sexes was less evident when the sole asbestos fiber type observed in lung tissue was a more rare asbestos type (amosite, chrysotile, and tremolite or actinolite, 2.7% versus 4.7%). The distribution of total asbestos fiber concentration detected in lung tissue is presented in Figure 1*A*. The median total asbestos fiber concentration was 3.20 million f/g (range: 0–1700 million f/g). The maximum concentration of 1700 million f/g was attributed to crocidolite. Generally, lung tissue contained higher concentrations of crocidolite than anthophyllite. The distributions of anthophyllite, crocidolite, and amosite concentrations as the main fiber type are presented in Figure 1*B* to *D*, respectively. The median fiber concentration was 0.50 million f/g (range: 0.2 − 1.6 million f/g) for chrysotile and 0.20 million f/g (range: 0.2− 0.4 million f/g) for tremolite or actinolite. The quantity and distribution of each fiber type within the patient groups, categorized as fiber type present, main fiber, or sole fiber, are presented in Table 2.

Patient Mortality

All patients were deceased with active MPM at the end of the follow-up. Chrysotile and tremolite or actinolite patient groups were excluded in the all-cause mortality

Table 1. Asbestos Fiber Concentration According to Age at Diagnosis

	Age at Diagnosis (y)				
Fiber Concentration (Million f/g)	<50	51 – 60	61 – 70	>71	$p < 0.001$[a]
0 – 0.2	7 (41.2)	27 (20.5)	30 (13.5)	43 (19.7)	
0.3 – 0.9	2 (11.8)	19 (14.4)	27 (12.1)	52 (23.9)	
1 – 1700	8 (47.0)	86 (65.1)	166 (74.4)	123 (56.4)	

Million f/g, million fibers per gram.
Note: Data are given in *n* (%).
[a]Difference between the age groups, chi-square test.

risk analyses owing to the small number of patients in these two groups. The effects of asbestos fiber concentration and fiber type on all-cause mortality, including initial HRs and changes in HRs during the follow-up time, are presented in Table 3. In addition to total asbestos fiber concentrations, both anthophyllite and crocidolite concentrations were associated with all-cause mortality, even after adjusting for possible confounding factors (Table 3). In the composite model, where each variable was also adjusted for other fiber types, an increase in crocidolite concentration was associated with an elevated risk of mortality during the follow-up time (Table 3). Nevertheless, no difference in risk of all-cause mortality was identified between fiber types in pairwise comparisons (data not shown). For an elaboration of the observed time dependency, Schoenfeld residual plots were generated to visualize the HRs in relation to the follow-up time for total asbestos concentration (Figure 2*A*) and for each asbestos fiber type (Figure 2*B–D*). As illustrated in panels *A*1 and *A*2 in Figure 2*A*, the nonlinear relationships between two variables were investigated using curves. These plots indicated that individuals who died early (up to approximately 10 mo) during the follow-up were on average older and had lower pulmonary fiber

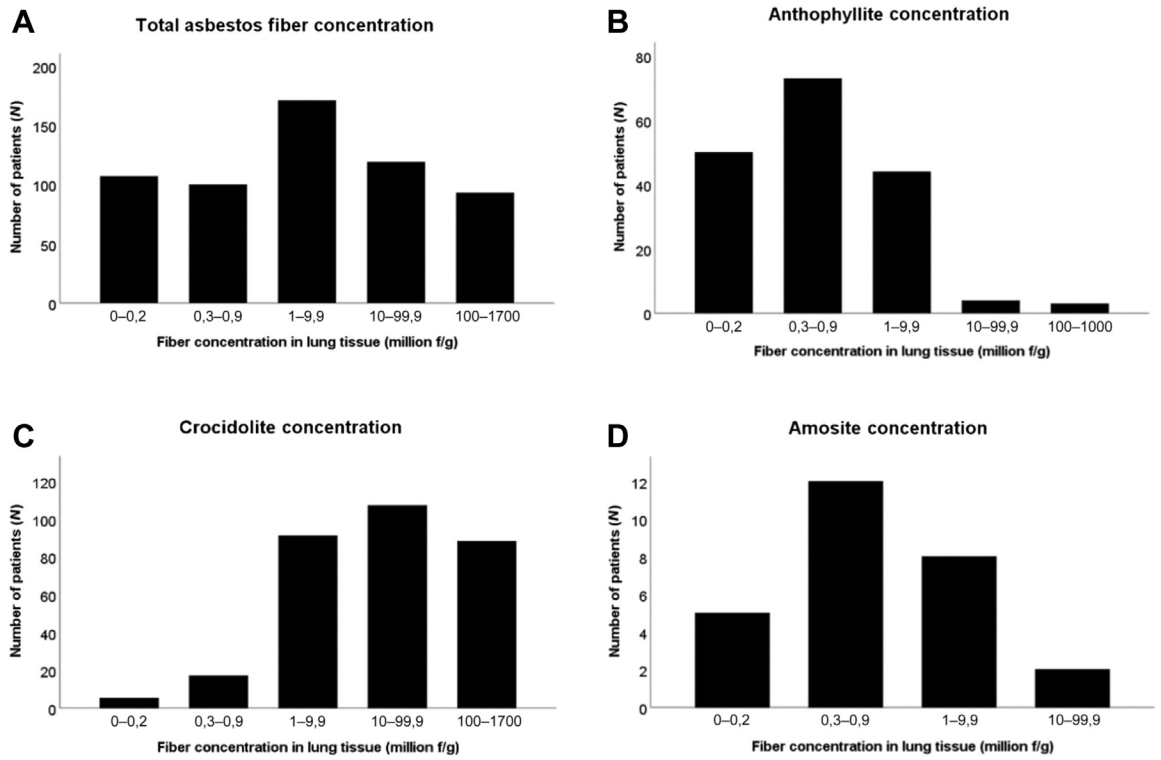

Figure 1. Asbestos fiber concentration distribution in the pulmonary fiber analysis. Columns reveal the number of patients (*N*) in each concentration range. Note the different scales in the *y* and *x* axes. (*A*) Total asbestos fiber concentration in the whole study cohort (median = 3.20 million f/g, IQR: 28.50). (*B*) Anthophyllite concentration as the main asbestos fiber type (median = 0.51 million f/g, IQR: 1.02). (*C*) Crocidolite concentration as the main asbestos fiber type (median = 23.34 million f/g, IQR: 116.12). (*D*) Amosite concentration as the main asbestos fiber type (median = 0.60 million f/g, IQR: 2.39). IQR, interquartile range; million f/g, million fibers per gram.

Table 2. Distribution of Asbestos Fiber Types Categorized as Main or Sole and Overall Detectable Concentration

	Anthophyllite	Crocidolite	Amosite	Chrysotile	Tremolite or Actinolite	No Asbestos Fibers
Overall asbestos fiber type detected in the pulmonary analysis						
n (%)	303 (51.4)	378 (64.1)	192 (32.5)	22 (3.7)	16 (2.7)	47 (8.0)
Concentration median (range, mil f/g)	0.48 (0.132 – 1000)	11.53 (0.132 – 1700)	0.58 (0.112 – 63)	0.42 (0.132 – 2.97)	0.20 (0.15 – 3.4)	0
Main asbestos fiber type[a]						
n (%)	174 (29.5)	308 (52.2)	27 (4.6)	3 (0.5)	3 (0.5)	N/A
Concentration median (range, mil f/g)	0.51 (0.2 – 1000)	23.34 (0.2 – 1700)	0.60 (0.2 – 25.76)	0.50 (0.2 – 1.6)	0.20 (0.2 – 0.4)	
Sole asbestos fiber type[b]						
n (%)	102 (17.3)	153 (25.9)	11 (1.9)	3 (0.5)	3 (0.5)	N/A
Concentration median (range, mil f/g)	0.40 (0.2 – 1000)	51.00 (0.2 – 1700)	0.30 (0.2 – 5.1)	0.50 (0.2 – 1.6)	0.20 (0.2 – 0.4)	

Mil f/g, million fibers per gram; N/A, not applicable.
[a]The main asbestos fiber type could not be determined for 28 patients (4.7%).
[b]Patients for whom only one type of asbestos fiber was detected in the pulmonary fiber analysis are also included in the main category for that fiber.

concentrations than those that died after 10 months. The Kaplan-Meier survival curves revealed no significant difference between groups with varying fiber concentrations of anthophyllite (see Supplementary Fig. 1*A* in Supplementary Data 1) or crocidolite (see Supplementary Fig. 1*B* in Supplementary Data 1).

Table 3. Effect of Asbestos Fiber Concentration and Fiber Type on Patient All-Cause Mortality

	Crude Analysis ($N = 540$)		Multivariable Model[a], Independent Fiber-Type Analysis ($n = 496$)		Multivariable Composite Model[a], Adjusted for Other Fiber-Type Concentrations ($n = 496$)	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Total asbestos fiber concentration (continuous)	–		–			
Initial level	0.823 (0.737-0.918)	**<0.001**	0.854 (0.759-0.960)	**0.008**	N/A	N/A
Change during the follow-up time[b,c,d]	1.096 (1.048 – 1.147)	**<0.001**	1.083 (1.033 – 1.135)	**0.001**	N/A	N/A
Anthophyllite (continuous)						
Initial level	0.998 (0.995 – 1.002)	0.318	0.992 (0.981 – 1.002)	0.123	1.011 (0.900 – 1.136)	0.851
Change during the follow-up time[b]	1.014 (1.003 – 1.024)	**0.010**	1.001 (1.000 – 1.003)	**0.041**	1.015 (0.995 – 1.035)	0.143
Crocidolite (continuous)						
Initial level	0.998 (0.996 – 1.000)	**0.013**	0.998 (0.996 – 1.000)	0.055	0.988 (0.941 – 1.037)	0.620
Change during the follow-up time[b]	1.038 (1.010 – 1.067)	**0.008**	1.029 (1.001 – 1.058)	**0.041**	1.014 (1.004 – 1.025)	**0.007**
Amosite (continuous)						
Initial level	0.967 (0.919 – 1.017)	0.192	0.978 (0.930 – 1.029)	0.393	1.040 (0.915 – 1.183)	0.549
Change during the follow-up time[b,d]	2.392 (0.937 – 6.110)	0.068	2.157 (0.828 – 5.618)	0.116	0.982 (0.950 – 1.015)	0.278

Note: Statistically significant *p* values ($p < 0.05$) are given in bold.
[a]Multivariable models adjusted for sex, age at diagnosis, side of the tumor, and tumor histology. Missing data: side of the tumor for 44 patients.
[b]A proportional hazards regression model extended for time-dependent effects was used, resulting in two different HR values. The second HR represents the change in HR over the follow-up time.
[c]Exposure log-transformed.
[d]Time log-transformed for time-dependent effects.
CI, confidence interval; HR, hazard ratio; N/A, not applicable.

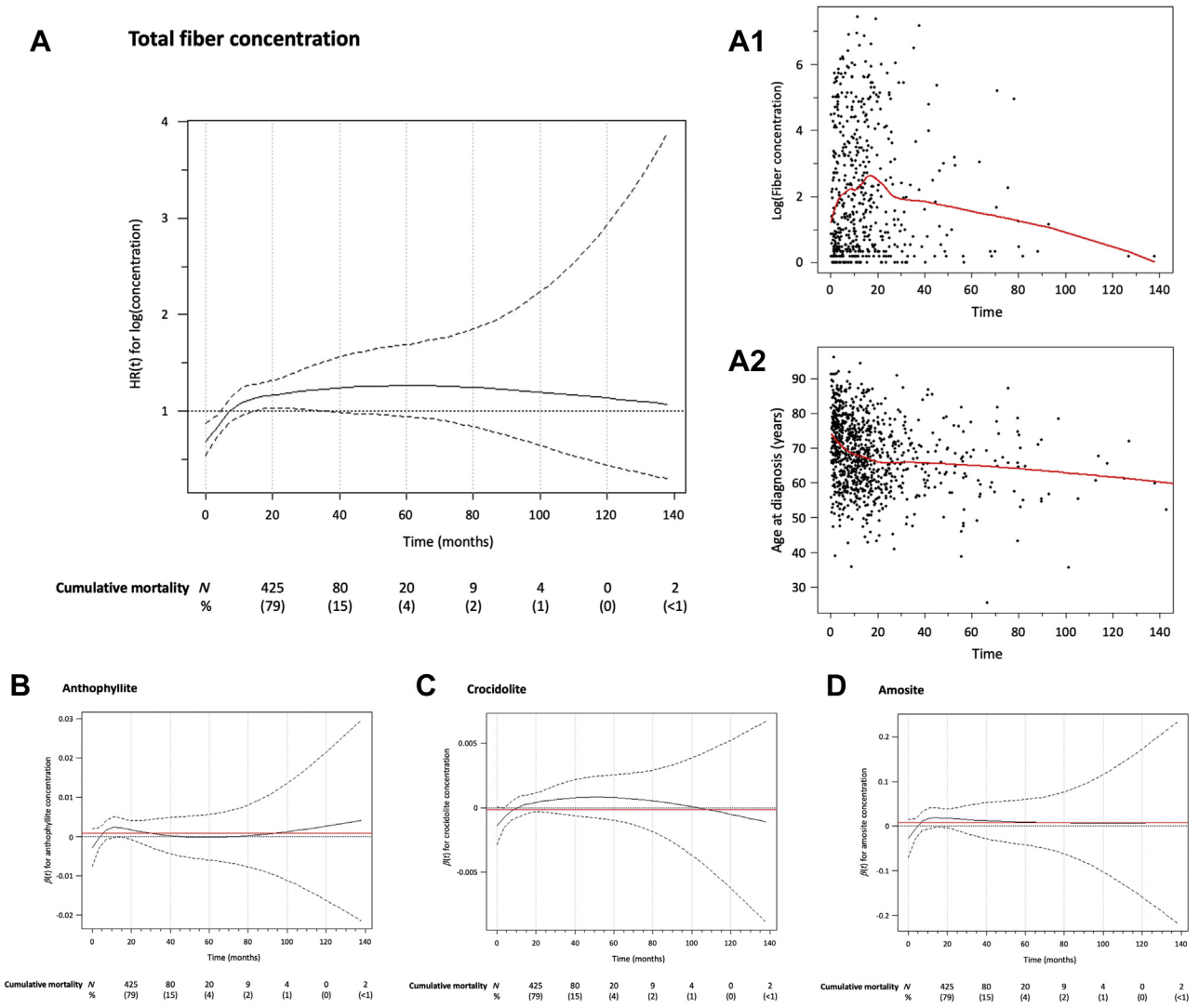

Figure 2. Scaled Schoenfeld residual plots for all-cause mortality during the follow-up time ($N = 540$). (*A*) Total fiber, (*B*) anthophyllite, (*C*) crocidolite, and (*D*) amosite concentrations. Solid curved black line indicates the approximate HR at a certain time point. The approximate 95% confidence interval is depicted with dashed curved lines. The solid red line indicates the corresponding hazard estimate from a proportional hazards model, and the dotted horizontal black line (at zero level) indicates the level of no difference in hazard rate. Scatter plots of log-total fiber concentrations (*A*, panel *A*1) and age at diagnosis (*A*, panel *A*2) according to the follow-up time with smooth nonparametric LOESS curves (solid red line) are presented. HR, hazard ratio; LOESS, local regression.

Discussion

In this study, we established an exceptionally large MPM cohort, comprising 590 patients with pulmonary asbestos fiber concentrations measured by STEM, in contrast to most previous studies on asbestos exposure that have relied predominantly on self-reported occupational histories. Accordingly, this study provides a unique opportunity to evaluate the prognostic significance of both asbestos fiber concentration and various asbestos fiber types that have been reported to be associated with mortality, with somewhat contradictory findings.[10,14–17] Table 4 summarizes published studies evaluating the predictive role of past asbestos exposure in patients with mesothelioma. Neumann et al.[15] previously reported no correlation between pulmonary asbestos fiber burden and survival. In contrast, Christensen et al.[14] observed in their single-center study that both low and high levels of asbestos bodies in lung tissue were an adverse prognostic factor. This past study revealed that patients with high asbestos burden had 4.8-fold elevated risk of death compared with patients with moderate burden.[14] Similarly, Kayser et al.[10] reported that asbestos fiber levels measured using a phase-contrast light microscope were associated with survival time.

Table 4. Review of Previously Published Studies Evaluating the Predictive Role of Past Asbestos Exposure

	Number of Mesothelioma Cases (*N*)[a]	Number of Controls (*N*)	Method Used to Collect Asbestos Exposure and/or Burden Data	Association Between Pulmonary Asbestos Burden and Survival Assessed in the Study	Association Between Pulmonary Asbestos Fiber Type and Survival Assessed in the Study	Main Findings
Musk and Woodward[16]	81	N/A	Medical records, registry data	No	Yes	No significant association was observed between asbestos fiber type and survival
Tammilehto et al.[17]	41[b]	N/A	SEM/TEM, radiograph microanalysis	Yes[c]	Yes	Lower pulmonary fiber concentration was associated with better prognosis; asbestos fiber type was found to affect survival
Kayser et al.[10]	73	77[d]	Light microscope, medical records	Yes	No	Lower pulmonary fiber concentration was associated with better prognosis
Edwards et al.[12]	142	N/A	Medical records	N/A	N/A	No significant association was observed between asbestos exposure and prognosis
Neumann et al.[15]	1605	N/A	Light microscope, registry data	Yes[e]	No	No significant association was observed between pulmonary fiber burden and survival
Christensen et al.[14]	128	N/A	Questionnaire/ interview, asbestos body burden measures[f]	Yes	No	Self-reported asbestos exposure failed to be a prognostic factor; lower and higher body burden of pulmonary asbestos was associated with poorer prognosis
Ak et al.[42]	235[g]	N/A	Medical records	N/A	N/A	No significant association was observed between asbestos exposure and prognosis
Nojiri et al.[13]	314	N/A	Medical records, questionnaire	N/A	N/A	No significant association was observed between asbestos exposure and prognosis
Berardi et al.[11]	62	N/A	Medical records	N/A	N/A	No significant association was observed between asbestos exposure and prognosis

[a]Some studies included other patients in addition to patients with pleural mesothelioma.
[b]The study cohort was divided into four separate groups based on the pulmonary fiber analysis results.
[c]Pulmonary fiber data were available for only 27 patients.
[d]The control group consisted of 18 patients with benign lung disease and 59 patients with NSCLC.
[e]Only 404 patients were included in this survival analysis.
[f]Asbestos burden data were only known for 83 patients.
[g]The study cohort was divided into three separate groups based on received treatment modalities.
N/A, not applicable; SEM, scanning electron microscope; TEM, transmission electron microscope.

In concordance with the findings of Christensen et al.[14] and Kayser et al.,[10] we observed that asbestos fiber concentration may have an impact on mortality. Nevertheless, in our study, pulmonary asbestos fiber burden initially decreased the HR for mortality, followed by a subsequent increase in relation to follow-up time.

The association between pulmonary asbestos concentration and prognosis, in patients with MPM, is not well known and requires further studies to confirm the underlying mechanism for a possible correlation. Nevertheless, one possible explanation could be that asbestos-induced inflammation precedes and accompanies MPM initiation and progression.[24] Reactive oxygen species–mediated inflammation and necrosis and some inflammatory markers, such as HMGB1, have been identified as pathogenetic and prognostic factors in MPM, thus supporting this theory.[25,26] Instead of assessing the asbestos bodies in lung tissue with a light microscope,[15] we measured the pulmonary asbestos fiber concentration using STEM; this methodological difference could explain the discrepancy between the findings by Neumann et al.[15] and those of ours.

The role of total fiber concentration in increased mortality became apparent after 7 months, with a rapid increase until 12 months of follow-up time (Figure 2*A*). This phenomenon was evident with similar latency for all fiber types (Figure 2*B*–*D*). The most probable explanation for the initial low HR for mortality in the short-term survivors was that these patients had lower total pulmonary fiber concentration and were older (Figure 2*A*, panels *A*1 and *A*2). Germline mutations, such as BAP1 gene mutation, are predisposed toward prolonged survival time[2,27,28] and the development of MPM with lower asbestos concentrations. Other determinants, such as patient performance status,[29] extent of disease,[30] other comorbidities,[31] and possible frailty, may have also contributed to the increased mortality during early follow-up. Additional biases could be caused by the healthy worker effect and lead-time bias. According to the healthy worker effect theory, the physical condition and habits of individuals influence their occupations, resulting in a selection bias that explains the reduced mortality rates detected in certain heavy trades.[32] For example, high-level exposure to asbestos has been reported during physically demanding tasks, including crocidolite spraying in shipyards and anthophyllite mining and refinement,[6] which may have resulted in the exclusion of physically weaker workers from these assignments. Moreover, lead-time bias may explain early deaths in patients with low fiber concentrations, as the workforce that has historically been heavily exposed to asbestos adhered to routine follow-up schemes, which could have resulted in earlier detection in these individuals.

Tammilehto et al.[17] reported that anthophyllite as the main asbestos fiber type was associated with the best survival, whereas crocidolite/amosite predicted the poorest outcomes. In contrast, Musk and Woodward[16] did not identify a difference in survival between various fiber groups. We did not observe a significant effect of individual fiber type on all-cause mortality during the follow-up, which could be explained by fiber shape, as suggested by the fiber paradigm.[33] Another possible explanation for these inconsistent results is the utilization of different analysis methods. In the two previous studies, survival analysis was conducted with a univariate method, in contrast to our study that used multivariable analyses, which takes into account potential confounding factors, including the effect of other fiber types and time-dependent effects.

Of note, we observed that crocidolite was the most common asbestos fiber in the pulmonary fiber analysis, despite the use of anthophyllite significantly exceeding that of crocidolite in Finland in the past.[34] In Finland, the total use of chrysotile, anthophyllite, and both crocidolite and amosite were 160,000 tons, 120,000 tons, and 5000 tons each, respectively.[35] The annual domestic anthophyllite consumption between 1950 and 1969 was approximately 3500 tons, whereas the annual consumption of crocidolite was approximately 300 tons to the end of 1960s, after which it decreased substantially, and its usage was banned from 1977 onward.[35] A smaller study analyzing asbestos fiber concentrations in Finnish patients with MPM and a reference group reported similar proportions of crocidolite and anthophyllite fibers to those in our study.[36] The Finnish anthophyllite miners were first studied in 1994, with only four cases of MPM[7]; a follow-up study on the same cohort was conducted in 2017 with a total of eight cases of MPM.[6] In contrast to those results, our study identified 102 patients with MPM that only had anthophyllite in their pulmonary fiber analysis, supporting a link between anthophyllite exposure and the development of pleural mesothelioma. Chrysotile differs in structure and size from the amphibole asbestos fibers,[3] and chrysotile is known to dissolve more rapidly from lung tissue after exposure than other asbestos fiber types; this explains the low level of chrysotile observed in our study.[21,37,38] Chrysotile, however, can cause molecular changes, similar to the amphiboles.[38] Of note, postmortem pulmonary tissue samples were used for the fiber analysis in this study, and therefore, the absence of chrysotile in these samples does not exclude that it had been present in the pleura or lungs at an earlier time point.

Crocidolite was almost exclusively the sole type of asbestos consumed in asbestos spraying in Finland owing to its fire-retardant properties. Asbestos spraying was used for shipbuilding and the construction of various types of public and industrial buildings but was rarely used for housing.[6,21] In this form of use, the fibers were unattached to any type of matrix, and fiber concentrations in the air were very high. In addition to sprayers, other workers were also present during the spraying and may have been exposed to fibers. In

contrast, anthophyllite was used in a wide range of construction materials, including heat shielding and asbestos cement.[21] In the guidelines for evaluating the attribution of malignancies to occupational exposure, any exposure during shipyard work is considered 10-fold higher than exposure during the construction of new buildings. Indeed, asbestos spraying is considered to cause 200-fold exposure compared with that during the construction of new buildings.[39] The amount of amosite consumed was equal to that of crocidolite in Finland but amosite was more typically used for insulation rather than spraying. In this regard, we observed similar concentrations of pulmonary amosite and anthophyllite. In contrast, amosite was used extensively for spraying in the United States, resulting in high pulmonary concentrations.[40] The different methods of using these fibers in the past may underscore the much higher concentration of crocidolite observed in our study. Furthermore, the high levels of crocidolite exposure may increase the risk of developing MPM compared with the lower exposure levels associated with other fiber types.[41]

Our study has similar limitations as those of registry studies in general. For example, reliable patient data regarding performance status, comorbidities, frailty, and the extent of MPM were unavailable. Nevertheless, this approach enabled the establishment of an exceptionally sizable cohort of patients with MPM with available asbestos fiber analysis results. Moreover, the pulmonary fiber analysis in this study was only performed for patients with a suspected occupational disease, which may have affected our results.

In conclusion, to the best of our knowledge, this is the largest study evaluating the impact of pulmonary asbestos fiber burden on the mortality of patients with MPM. Our main finding was that the total asbestos fiber concentration may be associated with an increased risk of all-cause mortality during the follow-up time; however, this risk could be confounded in the early follow-up by patient-related factors. Furthermore, crocidolite was more often associated with MPM than anthophyllite, despite its lesser gross consumption in the past, indicating that the increased pulmonary concentration of crocidolite could be owing to the manner of use, that is, asbestos spraying. Finally, anthophyllite was recognized as the sole fiber in a sizable portion of cases, supporting its independent role in the pathogenesis of MPM.

CRediT Authorship Contribution Statement

Sanna Laaksonen: Investigation, Writing - original draft, Formal analysis.

Eeva Kettunen: Investigation, Writing - review & editing.

Eva Sutinen: Project administration.

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Timo Törmäkangas: Formal analysis, Writing - review & editing.

Henrik Wolff: Conceptualization, Writing - review & editing.

Marjukka Myllärniemi: Supervision, Funding acquisition, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org/ and at https://doi.org/10.1016/j.jtho.2022.03.012

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