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Relationship between pleural plaques prevalence and extension and biomarkers of cumulative asbestos dose. A necropsy study

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Key words: Pleural plaques; lung asbestos fibre burden

Parole chiave: Placche pleuriche; carico polmonare di fibre di asbesto

Summary

Background: *The relationship between pleural plaques and cumulative asbestos exposure is controversial.* **Objectives:** *To evaluate the relationship between lung asbestos bodies (AB) and fibres (AF) and plaques presence and extension.* **Methods:** *In a necropsy series of shipyard workers with asbestos-related diseases, we measured counts (per g of dry lung tissue) of AB (thousands) and AF>1 μm (millions). Pleural plaques were classified into three extension grades. We fitted univariate and multivariable linear (dependent variables: AB and AF, log_{10} transformed) and multinomial (dependent variable: plaques grade) regression models.* **Results:** *We analysed 124 subjects, 13 without plaques 20 with grade 1, 69 with grade 2, and 22 with grade 3 plaques. Geometric means (GM) of AB were 10.6, 23.3, 126, and 140 in the four groups respectively (P=0.0001). GMs for AF (mostly amphiboles) were 1.2, 1.4, 7.3, and 12.9 (P=0.0001). AB and AF were strongly correlated (r=0.81). The likelihood of no plaques and grade 1 plaques decreased with increasing AB and AF doses, with a corresponding increase of grade 2 and 3 plaques. Plaque presence and extension was also associated with histologically verified asbestosis (P<0.001).* **Conclusions:** *Our study showed a strong positive relationship between pleural plaque presence and extension and both lung asbestos burden and asbestosis.*

Riassunto

«Correlazione tra presenza ed estensione delle placche pleuriche e indicatori biologici di esposizione ad asbesto. Uno studio autoptico». **Introduzione:** *La correlazione tra presenza ed estensione delle placche pleuriche ed esposizione cumulativa ad asbesto è oggetto di controversia.* **Obiettivi**: *Valutare la correlazione tra carico polmonare di corpuscoli (AB) e fibre (AF) di asbesto e presenza e grado di severità di placche pleuriche.* **Metodi:** *In una serie di autopsie eseguite su lavoratori di un cantiere navale affetti da patologie asbesto-correlate si sono misurate le concentrazioni (per g di tessuto secco polmonare) di AB (migliaia) e AF>1 μm (milioni). Le placche pleuriche sono state classificate in tre gradi di estensione. Sono stati utilizzati modelli grezzi e multivariati di regressione lineare (variabili dipendenti: AB e AF, log_{10} trasformate) e multinomiale (variabile dipendente: placche pleuriche).* **Risultati:** *Si sono analizzati 124 soggetti, 13 senza placche, 20 con placche di grado 1, 69 di grado 2 e 22 di grado 3. Le medie geometriche (GM) di AB erano 10.6, 23.3, 126 e 140 rispettivamente nei quattro gruppi. (P=0.0001). Le GM di*

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AF (prevalentemente anfiboli) erano 1.2, 1.4, 7.3 e 12.9 (P=0.0001). AB e AF erano altamente correlati (r=0.81). La probabilità di assenza di placche e di placche di grado 1 diminuiva all'aumentare delle dosi di AB e AF, con un corrispondente incremento delle frequenze di placche di grado 2 e 3. L'estensione delle placche pleuriche era anche correlata con l'asbestosi istologicamente verificata (P<0.001). **Conclusioni:** *Questo studio ha evidenziato una forte correlazione positiva tra la presenza e l'estensione delle placche pleuriche, il carico polmonare di amianto e l'asbestosi.*

Introduction

Pleural plaques (PP) are circumscribed areas of fibrous thickening, often bilateral and calcific, typically of the parietal pleura. They represent the most common asbestos-related disease (ARD) and may occur even after low cumulative exposure, usually many years after first exposure (14, 16, 28). The majority (80-90%) of radiologically well-defined plaques are attributable to past asbestos exposure (34). Therefore, they are considered a marker of asbestos exposure; in particular, they are an indicator of past occupational asbestos exposure (i.e., at higher levels than the general population) (19). Although the presence of pleural plaques is not sufficient to infer past levels of exposure, bilateral diffuse pleural thickening is often associated with moderate or heavy exposure, as seen in cases of asbestosis (34).

In 1972, two studies found a positive association between radiological pleural plaque occurrence and asbestos intensity or duration exposure among mine and mill (27) and naval dockyard workers respectively (15). A moderate positive association between pleural plaque, asbestos bodies (AB) and asbestos fibres (AF) in the bronchoalveolar lavage (BAL) fluid has also been found (2). In the early eighties necropsy studies showed a higher AB and AF (amphiboles) lung burden in subjects with PP compared to subjects without plaques (10, 13, 33). A necropsy study among 169 subjects in Italy found a positive relationship between PP extension and intensity of past asbestos exposure (reconstructed based on work history) (22). Another Italian study showed higher AB concentration in subjects with PP in a series of 57 autopsies (4). In a series of 996 autopsies a positive association was found between PP extension and AB, and the Authors argued that AB were a good marker of recent exposure, while PP were more indicative of past asbestos exposure (3). Conversely, among 73 asbestos-exposed subjects (51 with pleural plaques) no association was found between PP extension (evaluated with high resolution computed tomography, HCRT) and cumulative asbestos exposure (fibres/cc-years) (32).

Lung AB and AF are valid markers of cumulative asbestos exposure (1, 7, 23). In this study, we evaluated the association between PP prevalence and extension and lung AB and AF concentrations and pleural plaques in a necropsy series of workers formerly employed in a large shipyard in Monfalcone, Friuli-Venezia Giulia region, North-East Italy (2008-2017).

Methods

Subjects

Subjects were selected from a necropsy study among former workers of a large shipyard in Monfalcone, North-East Italy, who died from asbestos-related diseases (mesothelioma, lung cancer or asbestosis) (5). From this series, we extracted subjects with information on PP and lung asbestos burden (AB and AF). Presence and extension of pleural plaques had been determined from necropsies performed in the Pathology Department of the Monfalcone Hospital. Pathologists who performed necropsy had classified PP blind of AB and AF lung burden as follows: no plaques, grade 1 (moderate), pleural plaques with major diameter 1-4 cm; grade 2 (intermediate), PP with major diameter >4 cm, extended to <50% of the inner chest wall; and grade 3 (severe), PP extended to ≥50% of the inner chest wall (8). A single pathologist performed plaque measurements in 73% of the subjects.

Information on underlying disease, year of birth, age at death, length of exposure to asbestos, time since first exposure (TSFE), and time since last ex-

posure (TSLE) was available. Moreover, presence of asbestosis at histological examination was ascertained according to the criteria of Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society, i.e., presence of "two or more asbestos bodies per square centimetre of a 5-µm-thick lung section, in combination with interstitial fibrosis of the appropriate pattern" (26).

Analysis of asbestos bodies and fibres analysis

Following the guidelines proposed the European Respiratory Society (ERS), lung tissue samples of 1 cm^3 were collected from different part of the lung and stored in a formaldehyde solution (12). Samples were then prepared by lyophilization, plasma asher digestion, filtration. The analyses were carried out using a scanning electron microscope (SEM) equipped with X-ray fluorescence microanalyser at 12,000 magnifications (ZEISS EVO 40 and Oxford XMAX microanalyser) as described in detail elsewhere (6, 9, 29).

Fibre concentration was expressed as total number of fibres (amphibole: amosite and crocidolite, chrysotile, non-commercial amphibole: tremolite and actinolite) with length >1 µm per gram of dry lung tissue with 95% confidence interval. This method does not allow differentiation of amphibole fibres crocidolite and amosite if they have a diameter less than 0.08 µm, for this reason crocidolite and amosite are counted together and reported as amphibole.

In the same laboratory, 50 mg freeze-dryed lung sample were treated according the method ISTISAN 17/12 (20) to count AB with optical microscope at 500 magnifications. The concentration was expressed as number of AB per gram of dry lung tissue with 95% confidence interval. The laboratory is accredited according the ISO standard 17025 by ACCREDIA on both methods (lab n. 1324 sede E).

Both AF and AB analyses were performed between 2008 and 2017 blindly of subjects' disease and occupational history.

Statistical analysis

AB and AF concentrations were expressed in thousands and millions per g of dry lung tissue, respectively. Since AB and AF were approximately log-normally distributed, for these variables we reported either the geometric mean (GM) or the median. We compared categorical (gender, underlying disease, histological asbestosis) and quantitative variables (age at death, length of exposure to asbestos, TSFE, TSLE, AB, and AF) using chi-square and Kruskal-Wallis test, respectively. Correlation between quantitative variables and $\log_{10}$-transfomed AB and AF was assessed using Pearson's r correlation coefficient.

To analyse the relationship between $\log_{10}$(AB) or $\log_{10}$(AF) (dependent variables) and pleural plaque grade (independent variable), we fitted multiple linear regression models adjusted for year of birth, age at death, and TSLE treated as continuous variables. Then we calculated geometric mean ratios (GMRs) and confidence intervals (CI) by taking the antilog_{10} of regression coefficients. P-value for trend across grade was also calculated.

To analyse the relationship between pleural plaque grade (dependent variable) and $\log_{10}$(AB) or $\log_{10}$(AF) (independent variables), we fitted univariate and adjusted (for year of birth, age at death, and TSLE) multinomial (polytomous) regression models to calculate prevalence odds ratios (ORs) and CI. From the adjusted models we then calculated the predicted probabilities of plaque presence and extension, where age and TSLE were fixed at their mean values. We calculated 90% CIs in order to avoid a reductive interpretation of confidence intervals as statistical significance tests at the conventional two-tailed 5% level (11). Statistical analysis was performed with Stata 15 (StataCorp. 2017) (30). Predicted plaque probabilities were obtained and graphed with the "margins" and "marginsplot" commands.

Results

From 2008 to 2017 we retrieved information regarding 142 subjects, but for 18 of them the pathologist could not determine pleural plaque extension because of massive diffuse pleural adhesions and metastases which prevented the possibility to explore the thoracic cavity, leaving 124 subjects for analysis, 117 men and 7 women (table 1). Of these,

Table 1 - Characteristics of shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

	All		Pleural plaques								
			No		Grade 1		Grade 2		Grade 3		
	N	%	N	%	N	%	N	%	N	%	P*
All subjects	124	100	13	100	20	100	69	100	22	100	
Men	117	94.4	10	76.9	17	85.0	68	98.6	22	100	0.003
Women	7	5.6	3	23.1	3	15.0	1	1.4	0	0.0	
Year of birth, mean (SD)	1936.1	7.7	1938.9	9.9	1935.8	9.7	1935.4	7.2	1937.0	7.6	0.38
Age at death, mean (SD)	76.6	8.3	72.2	9.5	76.7	10.2	77.9	7.2	75.2	8.3	0.10
Length of exposure, mean (SD)	22.1	12.3	21.5	14.5	20.6	12.6	23.4	11.8	19.0	12.4	0.58
Time since first exposure, mean (SD)	54.8	10.0	54.2	13.1	55.0	11.2	55.6	8.6	52.3	10.9	0.52
Time since last exposure, mean (SD)	32.7	8.2	32.7	9.7	34.3	7.2	32.2	8.0	32.7	9.2	0.56
Disease											
Isolated plaques	1	0.8	0	0.0	0	0.0	1	1.4	0	0.0	0.71
Lung cancer	48	38.7	5	38.5	7	35.0	25	36.2	11	50.0	
Asbestosis	9	7.3	0	0.0	0	0.0	7	10.1	2	9.1	
Mesothelioma	66	53.2	8	61.5	13	65.0	36	52.2	9	40.9	
Histologically verified asbestosis											
No	80	64.5	10	76.9	20	100	41	59.4	9	40.9	<0.001
Yes	44	35.5	3	23.1	0	0.0	28	40.6	13	59.1	
Thousands of asbestos bodies, GM/median (Q1-Q3)**	75/90	21.5-345	10.6/20	2.7-34	23.3/21	9.3-120	126/120	41-560	140/165	86-450	0.0001
Millions of asbestos fibres, GM/median (Q1-Q3)**	5.1/4.5	1.1-20	1.2/0.8	0.4-4.2	1.4/1.1	0.7-4.3	7.3/6.3	1.5-30	12.9/21.0	2.6-45	0.0001
Millions of amphibole fibres, GM/median (Q1-Q3)**	4.7/4.0	1-19.8	1.1/0.8	0.3-4.2	1.3/1.1	0.5-3.2	6.8/6.1	1.3-30	11.5/17.0	2.3-45	0.0001

*P-value for comparison of variables across pleural plaque grades, from chi-square (categorical variables) or Kruskal-Wallis (continuous variables) test

**Per gram of dry lung tissue

Abbreviations: GM, geometric mean, SD, standard deviation; Q1-Q3, first and third quartile

13 (10.5%) had no PP, while 20 (16.1%) were classified as grade 1, 69 (55.7%) as grade 2, and 22 (17.7%) as grade 3 plaques. Year of birth, age at death, length of exposure, TSFE, and TSLE were similar across PP presence and extension. The majority of subjects were affected by mesothelioma. Presence of histologically verified asbestosis was positively associated with PP extension. AB, AF, and amphiboles showed clear increasing trends of geometric means and medians with increasing PP presence and extension (table 1, figures 1 and 2). Among the 13 subjects without pleural plaques we observed AB and AF concentrations slightly lower than subjects with grade 1 plaques (P=0.36 and P=0.63, respectively).

The correlation between log_{10}-transformed AF and amphiboles was very high (r>0.99). In 70 (56.5%) subjects all fibres were amphiboles, in 27 (21.8%) the percentage of amphiboles was 90-99%, in 14 (11.3%) was 80-89%, and only in 13 (10.5%) was less than 80%. Therefore, in subsequent analyses we focus on total fibres (AF).

There was no or little correlation between log_{10}-AB and year of birth (r=-0.08), age at death (r=0.14), length of exposure (r=0.03), TSFE (r=0.10), and TSLE (r=0.08). Similarly, there was no or little correlation between log_{10}-AF and year of birth (r=-0.11), age at death (r=0.15), length of exposure (r=0.03), TSFE (r=0.11), and TSLE (r=0.08). AB and AF (log_{10}-transformed) were strongly correlated (r=0.81, P<0.001). From the linear regression model with log_{10}-AB as dependent variable and log_{10}-AF as independent variable the intercept was 1.22 (90% CI: 1.12-1.33) and the slope was 0.91 (90% CI: 0.82-1.01) (figure 3).

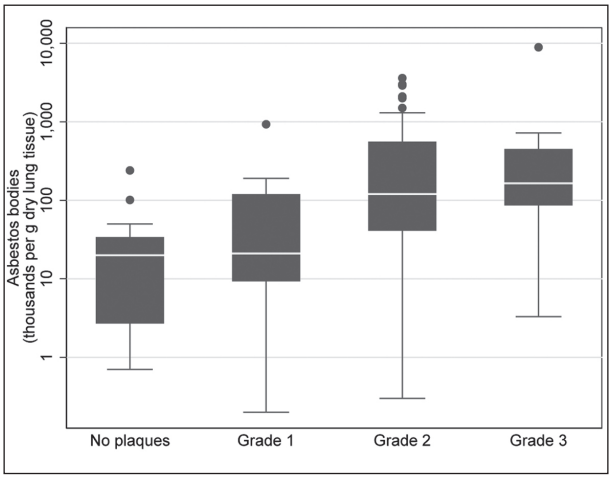

Figure 1 - Box-plot of asbestos bodies concentrations (AB, thousands per gram of dry lung tissue), according to plaque presence and extension, among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

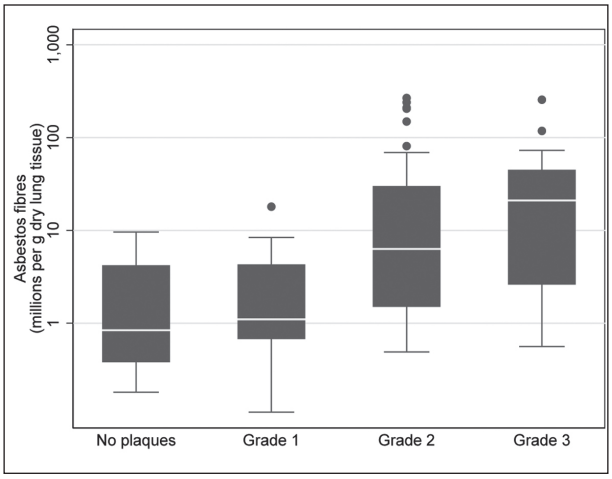

Figure 2 - Box-plot of asbestos fibres concentrations (AF, millions per gram of dry lung tissue), according to plaque presence and extension, among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

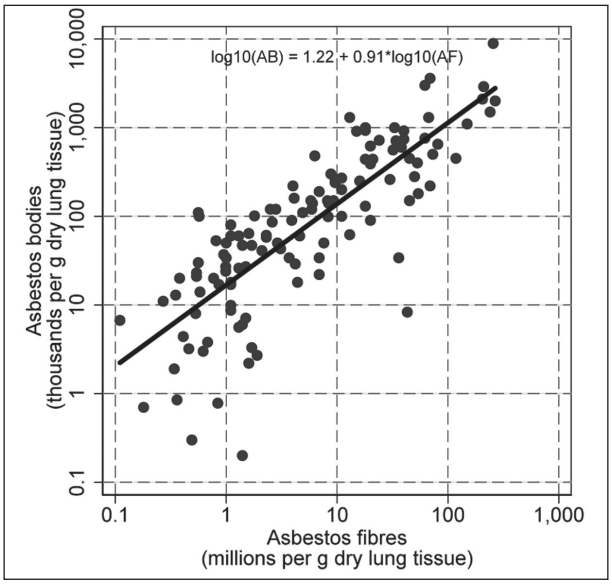

Figure 3 - Scatter plot of asbestos fibres (AF, millions per gram of dry lung tissue) and asbestos bodies (AB, thousands per gram of dry lung tissue) concentrations, among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

The strong association between log_{10}(AB) or log_{10}(AF) (dependent variables) and PP presence/extension (independent variable), was confirmed in adjusted linear regression models (table 2): compared with subjects without plaques, subjects with grade 1 plaques had slightly higher GMs of AB and AF, while subjects with grade 2 and 3 plaques had much higher GMs (5 to 11 times).

The number of subjects with AB concentrations of 100 (thousands) or more were 2 (15.4%) among those without plaques, 6 (30.0%) for grade 1, 37 (53.6%) for grade 2, and 15 (68.2%) for grade 3 plaques (table 3, upper part). Subjects with AF concentrations of 10 (millions) or more were 0 in those without plaques, 1 (5%) for grade 1, 30 (43.5%) for grade 2, and 14 (63.6%) for grade 3 plaques (table 3, lower part).

We found a strong association between PP presence/extension (dependent variable) and AB or AF (independent continuous variables, on a log_{10} scale) (table 4). Compared to subjects without plaques, for a ten-fold increase in AB and AF concentrations the

Table 2 - Adjusted geometric mean ratios (GMR)* and 90% confidence intervals (CI) of asbestos bodies (AB) and asbestos fibres (AF) concentrations across pleural plaque presence and grade (reference: subjects with no plaques) among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

	Pleural plaques						P-trend
	Grade 1		Grade 2		Grade 3		
	GMR	90% CI	GMR	90% CI	GMR	90% CI	
Thousands AB**	1.76	0.57-5.46	8.83	3.23-24.2	11.3	3.74-34.1	<0.001
Millions AF**	1.07	0.39-2.89	5.49	2.26-13.3	10.2	3.83-26.9	<0.001

*GMR adjusted for year of birth, age at death, and time since last exposure (continuous variables)
**Per gram of dry lung tissue

Table 3 - Number (%) of subjects across categories of asbestos bodies (AB) and asbestos fibres (AF) concentrations* and pleural plaque presence and grade, among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

	Pleural plaques								P
	No		Grade 1		Grade 2		Grade 3		
	N	%	N	%	N	%	N	%	
	13	100	20	100	69	100	22	100	
Thousands AB*									
<1	3	23.1	1	5.0	1	1.5	0	0.0	0.001
1 - <10	2	15.4	5	25.0	6	8.7	3	13.6	
10 - <100	6	46.2	8	40.0	25	36.2	4	18.2	
100 - <1000	2	15.4	6	30.0	26	37.7	14	63.6	
1000+	0	0.0	0	0.0	11	15.9	1	4.6	
Millions AF*									
<1	7	53.8	7	35.0	9	13.0	3	13.6	0.008
1 - <10	6	46.2	12	60.0	30	43.5	5	22.7	
10 - <100	0	0.0	1	5.0	25	36.2	12	54.5	
100+	0	0.0	0	0.0	5	7.3	2	9.1	

*Per gram of dry lung tissue
**From chi-square test

crude prevalence ORs were 1.55 and 1.31 (grade 1) 4.53 and 5.84 (Grade 2), and 4.89 and 9.00 (grade 3).

The adjusted model yielded substantially similar results (table 4, lower part). The adjusted predicted probabilities of plaque prevalence/extension are shown in figures 4 and 5. With increasing AB concentrations, the likelihood of having no plaques decreased from 40% at the lowest dose to 0.4% at the highest dose. Similarly, the probability of grade 1 plaques decreased from 43.4% to 2.0%; correspondingly, the predicted frequencies of grade 2 plaques increased from 14.0%% to 66.0% and those of grade 3 plaques from 2.3% to 31.5%) (figure 4). With increasing AF concentrations, the likelihood of no plaques and grade 1 plaque decreased from 32.1% to 2.8%, and from 46.3% to 0.8%, respectively, while predicted frequencies of plaque 2 and 3 increased from 19.8% to 57.3% and from 1.9% to 41.6%, respectively (figure 5). These trends were monotonic, except for grade 2 plaques, which showed a plateau at AB doses >100,000 and AF doses >10 millions.

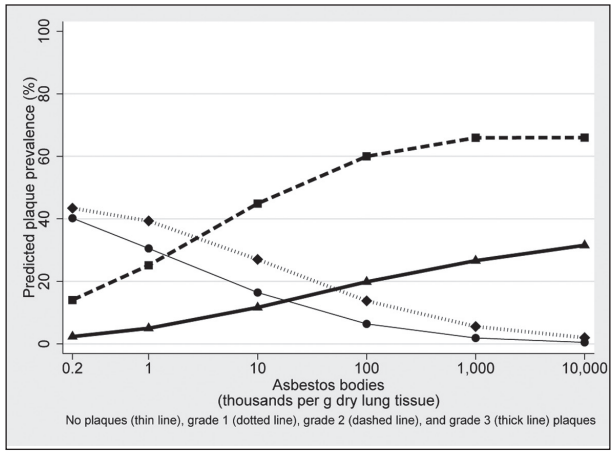

Figure 4 - Predicted plaque prevalence and extension (from a multivariable multinomial logistic regression model adjusted for year of birth, age at death, and time since last exposure), according to asbestos bodies concentrations (AB, thousands per gram of dry lung tissue), among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

Discussion

This study showed a strong relationship between prevalence and extension of pleural plaques and lung asbestos burden. In particular, AB and AF doses were much higher in subjects with grade 2 and 3 plaques in comparison with those without or with grade 1 plaques. Correspondingly, prevalence of grade 2 and 3 plaques strongly increased with increasing AB and AF concentrations. A strong association was also found between plaques prevalence and extension and histologically verified asbestosis, a well-defined biological index of high cumulative

Table 4 - Odds ratios (OR) and 90% confidence intervals (CI) of pleural plaque presence and extension (reference: subjects with no plaques) according to asbestos bodies (AB) asbestos fibres (AF) concentrations*, calculated with crude and adjusted multinomial regression models, among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

	Pleural plaques					
	Grade 1		Grade 2		Grade 3	
	OR	90% CI	OR	90% CI	OR	90% CI
Crude						
Log_{10}(thousands AB)	1.55	0.79-3.05	4.53	2.32-8.86	4.89	2.26-10.6
Log_{10}(millions AF)	1.31	0.46-3.75	5.84	2.27-15.0	9.00	3.18-25.5
Adjusted**						
Log_{10}(thousands AB)	1.41	0.68-2.94	3.97	1.92-8.22	4.70	2.09-10.6
Log_{10}(millions AF)	1.33	0.45-3.86	6.27	2.25-17.5	10.6	3.49-32.3

*Per gram of dry lung tissue

**Adjusted for year of birth, age at death, and time since last exposure (continuous variables)

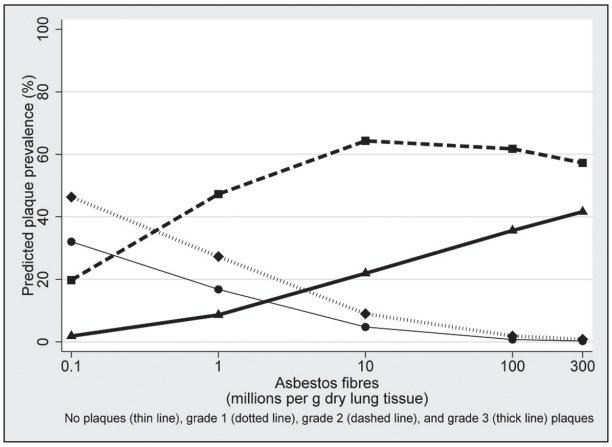

Figure 5 - Predicted plaque prevalence and extension (from a multivariable multinomial logistic regression model adjusted for year of birth, age at death, and time since last exposure), according to asbestos fibres concentrations (AF, millions per gram of dry lung tissue), among shipyard workers included in the necropsy study, Monfalcone, North-East Italy, 2008-2017

exposure. Time-related variables (age, duration of exposure, time since first and last exposure) show little or no correlation with either AB or AF levels.

This study had a number of strengths, including careful measurement of plaque extent performed in the same department (with three fourths of autopsies made by a single pathologist) and accurate lung burden assessment performed in a reference regional laboratory. The main limitation was the low number of subjects without plaques.

Results were robust to adjustment for year of birth, age, and time since last exposure. Information about tobacco smoking was not available. Nevertheless, we think that this does not represent a limitation, because the literature shows that there is little or no evidence that smoking can modify asbestos burden (25, 31).

The literature on PP extent and asbestos fibre burden is not univocal. In the nineties, a literature review concluded that this relationship was controversial (21). More recently, mainly based on a single study (32), the American Thoracic Society (ATS) in its 2003 consensus document on diagnosis and management of non-malignant asbestos-related diseases stated there was no relationship between extent of PP and cumulative asbestos exposure (32). Only a few studies were performed by measuring the lung fibre burden directly in the lung or in the BALF. Kishimoto and colleagues in 1989, based on radiological and necropsy findings, found higher AB concentrations in patients with definite PP on chest x-ray (compared with "indefinite" PP) (18). Orlowski and colleagues in 1994 analysed 66 subjects with PP diagnosed by HRCT scan (in absence of other asbestos-related diseases). Their cumulative asbestos exposures were estimated by job history and AB concentrations in BALF. They found no relationship between PP extent and duration of, frequency of, and cumulative exposure. No association was found between AB concentration and PP extent (24).

In the same year, Karjalainen et al. (17) evaluated PP extent at necropsy examination in 288 men. PP were confirmed for 58% of the subjects and were classified in three groups: 1) no PP; 2) moderate plaques (bilateral, total surface <100 cm^2 or unilateral); and 3) diffuse plaques (bilateral, total surface 100+ cm^2). The median concentration of lung amphiboles AF, analysed by SEM, was three-fold higher in group 3 compared with subjects without plaques (17). A positive association between lung AB concentration and PP extent was also found in the 1999 study by Bianchi et al. in the Monfalcone Hospital, Italy on 414 autopsy cases performed on lung cancer patients (309 cases with PP). A recent study in Japan was performed on 207 lung cancer cases of occupationally exposed subjects (35). Pleural plaques extent was based on HRCT findings and AB counts were performed with optical microscopy at 400 magnitudes according to Smith and Naylor (1972) and Kohyama and Suzuki (1991) standard. A clear relationship was found between PP extent (three grades) and AB levels; only a few subjects with grade 3 PP showed low AB count. Since several lung cancer patients without PP had high AB concentrations, the Authors stated that other determinants are predictive of PP extent, including age, fibre type and dimension, and time since first exposure.

Conclusions

In conclusion, our results showed a strong association between asbestos lung fibre and pleural plaque presence and extension evaluated at necropsy. These

findings are in agreement with previous studies, but are in contrast with the ATS statement on the absence of a relationship between PP and cumulative asbestos exposure. The extension of plaques might serve as an approximate index of asbestos bodies and fibres concentrations. Therefore, in the *ante-* or *post-mortem* diagnostic work-up of asbestos-related diseases, it would be useful to describe in as much detail as possible plaque presence and their extension.

Conflict of interest

Pietro Gino Barbieri served as a consultant for the prosecutor or for the victims' families in litigations concerning asbestos-related diseases. Dario Consonni served as a consultant for the court in litigations concerning asbestos-related diseases.

References

1. Albin M, Johansson L, Pooley FD, et al: Mineral fibres, fibrosis and asbestos bodies in lung tissue from deceased asbestos cement workers. Br J Ind Med 1990; 47: 767-774
2. American Thoracic Society Documents: Diagnosis and initial management of non-malignant diseases related to asbestos. Am J Respir Crit Care Med 2004; 170: 691-715
3. Andrion A, Colombo A, Mollo F: Lung asbestos bodies and pleural plaques at autopsy. Ric Clin Lab 1982; 12: 461-468
4. Andrion A, Bellis D, Bertoldo E, Mollo F: Coated and uncoated lung mineral fibres in subjects with and without pleural plaques at autopsy. Pathol Res Pract 1984; 178: 611-616
5. Barbieri PG, Somigliana A: Patologie asbesto-correlate e indicatori biologici di dose cumulativa in lavoratori di cantiere navale (1996-2015). Med Lav 2016; 107: 315-326
6. Barbieri PG, Mirabelli D, Somigliana A, et al: Asbestos fibre burden in the lung of patients with mesothelioma who lived near asbestos-cement factories. Ann Occu Hyg 2012; 56: 660-670
7. Barbieri PG, Somigliana A, Lombardi S, et al: Carico polmonare di fibre di asbesto e indici di esposizione cumulativa in lavoratori del cemento-amianto. Med Lav 2008; 99: 21-28
8. Bianchi C, Brollo A, Ramani L, Zuch C: Asbestos exposure in lung carcinoma: a necropsy-based study of 414 cases. Am J Ind Med 1999; 36: 360-364
9. Casali M, Carugno M, Cattaneo A, et al: Asbestos Lung Burden in Necroscopic Samples from the General Population of Milan, Italy. Ann Occup Hyg 2015; 59: 909-921
10. Churg A: Asbestos fibres and pleural plaques in a general autopsy population. Am J Pathol 1982; 109: 88-96
11. Consonni D, Bertazzi PA. Health significance and statistical uncertainty. The value of P-value. Med Lav 2017; 108: 327-331
12. De Vuyst P, Karjalainen A, Dumortier P, et al: Guidelines for mineral fibre analyses in biological samples: report of the ERS Working Group. Eur Respir J 1998; 11: 1416-1426
13. Gylseth B, Mowé G, Skaug V, Wannag A: Inorganic fibers in lung tissue from patients with pleural plaques or malignant mesothelioma. Scand J Work Environ Heath 1981; 7: 109-113
14. Henderson DW, Rantanen J, and working group: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 1997; 23: 311-316
15. Harries PG, Mackenzie FA, Sheers G, et al: Radiological survey of men exposed to asbestos in naval dockyards. Brit J Ind Med 1972; 29: 274-279
16. Hillerdal G. Pleural plaques. Occurrence, exposure to asbestos, and clinical importance. Acta Universitatis Upsaliensis, Uppsala, 1980
17. Karjalainen A, Karhunen PJ, Lalu K, et al: Pleural plaques and exposure to mineral fibres in a male urban necropsy population. Occup Environ Med 1994; 51: 456-460
18. Kishimoto T, Ono Y, Okada K, Ito H: Relationship between number of asbestos bodies in autopsy lung and pleural plaques on chest X-ray film. Chest 1989; 95: 549-552
19. IIAC (The Industrial Injuries Advisory Council). Position Paper 23. Pleural Plaques. (downloaded from: www.iiac.org.uk)
20. Istituto Superiore di Sanità, Biofibre working group: Asbestos bodies in human lung tissue and biological fluids: analytical method and photo atlas. Rapporti ISTISAN 17/12 (in Italian). 2017, iv, 58
21. Meirelles GSP, Kavakama IJ, Jasinowodolinski D, et al: Asbestos-related pleural plaques: a literature review. Rev Port Pneumol 2005; 5: 487-497
22. Mollo F, Andrion A, Pira E, Barocelli MP: Indicators of asbestos exposure in autopsy routine. 2. Pleural plaques and occupation. Med Lav 1983; 74: 137-114
23. Murai Y, Kitagawa M: Asbestos fibre analysis in 27 malignant mesothelioma cases. Am J Ind Med 1992; 22: 193-207
24. Orlowski E, Pairon JC, Ameille J, et al: Pleural plaques, asbestos exposure, and asbestos bodies in bronchoalveolar lavage fluid. Am J Ind Med 1994; 26: 349-358
25. Roggli VL, Pratt PC, Brody AR: Asbestos content of lung tissue in asbestos associated diseases: a study of 110 cases. Br J Ind Med 1986; 43: 18-28

26. Roggli VL, Gibbs AR, Attanoos R, et al: Pathology of asbestosis. An update of the diagnostic criteria. Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. Arch Pathol Lab Med 2010; 134: 462-480
27. Rossiter CE, Bristol LJ, Cartier PH, et al: Radiographic changes in chrysotile asbestos mine and mill workers of Quebec. Arch Environ Health 1972; 24: 388-400
28. Rudd RM: New developments in asbestos-related pleural diseases. Thorax 1996; 51: 210-216
29. Somigliana A, Quaglini A, Orsi M, Albiero S: Analisi del contenuto di fibre di amianto in tessuto polmonare umano: problemi di precisione ed esattezza. Giornale degli Igienisti Industriali 2008; 33: 413-424
30. StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC
31. Takahashi K, Case BW, Dufrense A, et al: Relation between lung asbestos fibre burden and exposure indices based on job history. Occup Environ Med 1994; 51: 461-469
32. Van Cleemput J, De Raeve H, Verschakelen JA, et al: Surface of localized pleural plaques quantitated by computed tomography scanning: no relation with cumulative asbestos exposure and no effect on lung function. Am J Respir Crit Care Med 2001; 163: 705-710
33. Warnock ML, Prescott BT, Kuwahara TJ: Numbers and types of asbestos fibers in subjects with pleural plaques. Am J Pathol 1982; 109: 37-46
34. Wolff H, Vehmas T, Oksa P, et al: Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health 2015; 41: 5-15
35. Yusa T, Hiroshima K, Sakai F, et al: Significant relationship between the extent of pleural plaques and pulmonary asbestos body concentration in lung cancer patients with occupational exposure. Am J Ind Med 2015; 58: 444-455