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Asbestos Exposure and Benign Asbestos Diseases in 772 Formerly Exposed Workers: Dose–Response Relationships

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Background *Since previous studies have provided conflicting results, we investigated the relationship between the risk of benign asbestos-related diseases and different aspects of asbestos exposure in previous asbestos workers who underwent low-dose computed tomography (CT).*

Methods *CT scans were carried out in 772 subjects. A questionnaire was employed to collect data on smoking habits and duration, peak and cumulative exposure, and time since first exposure to asbestos. Multiple logistic regression models with stepwise selection of variables were used to evaluate the associations.*

Results *Fourteen (1.8%) cases of asbestosis, 187 (24.2%) of pleural plaques (PP), and 50 (6.5%) of diffuse pleural thickening (DPT) were found. The significant risk factors were: cumulative exposure for asbestosis (P for trend = 0.004); time since first exposure (P for trend <0.001), and peak exposure (P for trend <0.001) for PP; and time since first exposure for DPT (P for trend = 0.024).*

Conclusions *Parenchymal asbestosis and PP are associated with different aspects of asbestos exposure. DPT appears to be less specific for asbestos exposure.* Am. J. Ind. Med. 52:596–602, 2009. *© 2009 Wiley-Liss, Inc.*

KEY WORDS: asbestos; occupational exposure; computed tomography; asbestosis; pleural plaques

INTRODUCTION

In epidemiological studies, the end-points for asbestosis are primarily the radiographic changes detected at chest X-ray (CXR) and are classified according to International Labour Office (ILO) subcategories [ILO, 1980]. Becklake [1983, 1991] demonstrated a 10-fold difference in the prevalence of radiographic change ILO subcategory 1/0 or

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more in relation to cumulative exposure in a small number of studies. Jakobsson et al. [1995] studied 203 asbestos-cement workers radiographically and found that the risk of asbestosis (radiographic profusion $\geq$1/0) was strongly dependent on cumulative asbestos exposure in a model of multiple logistic regression, where the influence of age and smoking was controlled. Both cumulative exposure to asbestos and lung fiber burden were strongly correlated with the severity of asbestosis in a necroscopy study of former workers in a chrysotile asbestos textile plant in South Carolina [Green et al., 1997]. In a longitudinal study of 181 asbestos-cement workers, the risk of developing small irregular opacities (profusion $\geq$1/0 according to 1980 ILO classification) significantly increased ($P < 0.001$) with increasing cumulative asbestos exposure [Finkelstein and Vingilis, 1984].

Sheers and Templeton [1968], in their survey of dockyard workers, found that the prevalence of pleural plaques (PP) increased with intensity of exposure. Others have reported similar findings, including Mollo et al. [1983] on the basis of autopsy findings. Jones et al. [1980] found that, whilst the radiographic appearance of asbestosis and diffuse pleural thickening (DPT) were related to cumulative exposure in their study of asbestos-cement workers, the appearance of plaques was directly related only to time from first exposure. A linear relationship between plaques incidence and time elapsed from first exposure to asbestos was also reported in shipyard workers by Jarvholm [1992].

In this respect, as Browne [1994] noted in Parkes' Occupational Lung Disorders, plaques follow the pattern of mesothelioma rather than of diseases of the lung, asbestosis and lung cancer, both of which appear to be more directly related to cumulative exposure.

However, in 1,011 previous asbestos workers examined with computed tomography (CT) by Paris et al. [2008], the best fitting model for asbestosis included age and mean exposure. Among 880 French workers previously exposed to asbestos, the prevalence of PP at CT was 42.0%, 36.3%, 40.1%, and 63.4% (P for trend $<$0.001) in four classes of cumulative exposure, respectively: $<$25; 25–99; 100–199; 200; and more fibers/ml $\times$ years [Paris et al., 1999]. The conflicting evidence could be due to the radiological technique used, since it is well known that CT has greater sensitivity and specificity for identifying asbestos diseases than CXR [Bégin et al., 1984; Aberle et al., 1988; Friedman et al., 1988; Ameille et al., 1993; Harkin et al., 1996]. Therefore, we investigated the exposure–response relationships for benign asbestos diseases in 772 past asbestos workers examined with low-dose CT, analyzing simultaneously different aspects of asbestos exposure, as well as the confounding effect of age and smoking.

SUBJECTS AND METHODS

Subjects and methods have been described in detail in a previous article [Mastrangelo et al., 2008]. Briefly, within the framework of a post-occupational medical surveillance program, supported by the Veneto Region and the Italian Ministry of Health, we examined 772 male asbestos workers engaged in manufacture of asbestos-cement products, railway rolling stock fabrication and repair, or employed as insulators in shipyards or elsewhere. After having given informed consent, subjects were examined by occupational physicians, using the same protocol for collecting clinical and occupational history and performing low-dose CT. Incidental findings were discussed with the patients and their primary care physicians and, where appropriate, referred for specialist evaluation.

Information on smoking habits was collected and smoking cessation was recommended and facilitated for all patients.

We used an internationally established questionnaire that permits estimation of past asbestos exposure using job-specific modules (JSM) [Magnani et al., 2000]. On the basis of defined scales, examiners scored the determinants of exposure: raw materials used (with fiber content and friability); jobs done (specified in terms of mechanical disturbance applied to materials through the tools used by the worker); and factors modulating exposure (particle emission speed, source surface, presence of localized air exhaust systems, dimension and physical characteristic of the rooms, etc.). Through direct knowledge or literature data, describing historical exposure levels in different jobs/tasks, a reference database was separately collected. Using this a priori knowledge, or integrating evaluation from all the above scores, an exposure intensity was attributed. Lastly, a semi-quantitative estimate of cumulative exposure was made by multiplying intensity (concentration), frequency (percent of the working time spent at a certain exposure level), and length of exposure in years, and by summing up as many products as were necessary to take into account the different jobs done. The interviewers were trained in the use of the questionnaire in order to minimize the information bias.

Low-dose CT of the entire thorax was performed with the subject in the supine position and at full inspiration without administering contrast material. The X-ray dose ranged from 20 to 40 mA/s; 7–8 mm thick lung scans were systematically reconstructed.

The diagnosis of asbestosis was based on CT features of parenchymal fibrosis including: thickened interstitial short lines in the subpleural parenchyma as septal and intralobular lines; curvilinear subpleural lines of opacity within 1 cm of the pleura and parallel to the inner chest wall; areas of ground-glass opacity accompanied or not by bronchiectasis [Remy-Jardin et al., 2004]. PP were defined as circumscribed, unilateral or bilateral, pleural areas of opacity with

well-demarcated edges. Pleural opacities were classified as DPT if they were more than 5 cm wide, more than 8 cm in craniocaudal extent, and more than 3 mm thick, unilateral or bilateral [Lynch et al., 1989].

Ambiguous cases were discussed in a consensus meeting and, if necessary, further diagnostic workup was performed. A final decision was made by consensus of all radiologists who read the case.

Approval by human subjects committee was not required as the medical surveillance of workers formerly exposed to asbestos was a mandatory activity according to the regional decree n. 5094 of Dec 28th 1998.

Statistical Analysis

The quartiles were obtained for the variables: time elapsed since first exposure, duration of exposure, peak asbestos level (highest asbestos exposure for any job held), cumulative asbestos exposure, and age. Smoking was coded in the categories of non-, ex-, and current-smokers, and subjects with unknown habits. All the above were used as either categorical or numerical (except smoking) variables in the statistical analysis.

Asbestos benign diseases were regressed against the above risk factor at univariate logistic regression analysis in order to estimate the odds ratio (OR) with 95% confidence interval (CI) in each quartile. The lowest class was the reference subgroup at a conventional risk of 1.0. The Cochrane-Armitage test for linear trend across the quartiles was obtained using the statistical package StatXact. Multiple logistic regression models were applied for a stepwise selection of the risk factor, with the different aspects of asbestos exposure expressed both as the original numerical variables both as quartiles (to assess the presence of a trend across quartiles). Thereafter, the final estimates were obtained through different approaches: (1) OR with CI was computed by exact logistic-regression analysis for asbestosis, which represents a category with small numbers; (2) prevalence ratio (PR) with CI was obtained by applying a log-binomial model for PP, which represent a common finding in the study population.

RESULTS

The cases of asbestosis, PP, and DPT were, respectively, 14 (prevalence of 1.8%), 187 (24.2%), and 50 (6.5%).

Table I shows the baseline characteristics (mean $\pm$ standard deviation; or number and percentage) of 772 male asbestos workers, broken down in four groups: subjects with no pleural lesions, cases of DPT, PP, and asbestosis. The average values of cumulative exposure and length of exposure, the percent of subjects exposed to $\geq$13.5 f/ml of asbestos (concentration typical of poorly protected/unprotected jobs/tasks with powerful sources), regularly increased going from subjects with no lesions to those with asbestosis.

Table II shows the number of cases and prevalence of asbestosis, as well as ORs with CI, by quartiles of risk indicators. Due to the presence of 0 in one cell, exact logistic regression was adopted to obtain risk estimates. A significant increase in asbestosis risk was found with increasing cumulative asbestos exposure, but not with time since first exposure, peak exposure, duration of exposure, age, and smoking. In our series, the least cumulative exposure in a subject with asbestosis was 23.1 fibers/ml $\times$ years.

Table III shows number of cases and prevalence of PP, as well as ORs with CI, by quartiles of risk indicators. The ORs for PP rapidly increased with peak exposure, cumulative exposure, time since first exposure and, less steeply, with age and length of exposure.

Table IV shows number of cases and prevalence of DPT, as well as ORs with CI, by quartiles of risk indicators. An increasing trend with increasing time since first exposure was the only significant (P for trend $= 0.024$) finding.

Table V shows the results of multiple logistic regression models with stepwise selection of variables. It can be seen that the significant risk factors were: cumulative exposure for

TABLE I. Baseline Characteristics (Mean $\pm$ Standard Deviation or Number and Percentage) of 772 Male Asbestos Workers, Broken Down in the Four Groups: Subjects With no Pleural Lesions, and Cases of Pleural Thickening, Pleural Plaques, and Asbestosis

	No pleural lesions N = 521	Pleural thickening N = 50	Pleural plaques N = 187	Asbestosis N = 14
Age (years)	56.2 $\pm$ 8.4	58.0 $\pm$ 8.5	58.7 $\pm$ 7.5	60.4 $\pm$ 6.6
Time since first exposure (years)	29.6 $\pm$ 8.5	32.8 $\pm$ 8.9	29.8 $\pm$ 8.5	32.6 $\pm$ 8.7
Cumulative exposure (f/ml $\times$ years)	91.9 $\pm$ 181.7	101.7 $\pm$ 96.9	180.5 $\pm$ 312.9	367.9 $\pm$ 682.0
Duration of exposure (years)	17.4 $\pm$ 8.4	18.7 $\pm$ 8.9	18.9 $\pm$ 8.6	20.9 $\pm$ 8.5
Peak exposure $\geq$13.5 f/ml	318 (60.3%)	37 (74.0%)	152 (81.3%)	13 (92.9%)
Non-smokers	88 (16.7%)	11 (22%)	26 (13.9%)	2 (14.3%)
Ex-smokers	213 (40.4%)	26 (52%)	82 (43.9%)	5 (35.7%)
Current smokers	173 (32.8%)	12 (24%)	66 (35.3%)	6 (42.9%)
Smoking unknown	53 (10.1%)	1 (2%)	13 (6.9%)	1 (7.1%)

TABLE II. Number (No.) and Prevalence (%) of Asbestosis, Odds Ratio (OR) With 95% Confidence Interval (CI), and Cochran-Armitage Trend Test *P*-Value, in Relation to Risk Indicators

Risk indicators	No.	%	OR	CI	Trend test *P*-value
Age (years)					
<52.1	2	1.0	1.00		0.153
52.1–56.2	2	1.1	1.04	0.14–7.40	
56.3–61.8	5	2.7	2.23	0.51–13.8	
>61.8	5	2.6	2.16	0.49–13.4	
Smoking habits					
Current smokers	2	1.6	1.00		
Former smokers	5	1.5	0.97	0.19–5.06	
Non-smokers	6	2.4	1.50	0.30–7.54	
Unknown	1	1.5	0.94	0.84–10.6	
Cumulative exposure (fibers/ml × years)					
≤8	0	0.0	1.00		0.004
8–42	2	1.0	2.41[a]	0.18 +INF	
43–159	4	2.0	5.22[a]	0.65 +INF	
≥160	8	4.2	11.6[a]	1.77 +INF	
Peak asbestos level (fibers/ml)					
<1.35	0	0.0	1.00		0.064
1.35	1	0.6	0.39[a]	0.01 +INF	
13.5	11	2.5	2.54[a]	0.41 +INF	
>13.5	2	2.4	2.11[a]	0.16 +INF	
Length of exposure (years)					
<12	3	1.5	1.00		0.120
13–18	1	0.5	0.33	0.03–3.15	
19–23	4	2.3	1.59	0.35–7.19	
≥24	6	3.1	2.16	0.53–8.77	
Time since first exposure (years)					
≤26	2	1.73	1.00		0.342
27–30	5	2.10	2.56	0.49–13.4	
31–33	2	0.83	1.06	0.15–7.58	
≥34	5	1.95	3.01	0.57–15.7	

INF, infinity.
[a]Estimated by the exact method.

TABLE III. Number (No.) and Prevalence (%) of Pleural Plaques, Odds Ratio (OR) With 95% Confidence Interval (CI), and Cochran-Armitage Trend Test *P*-Value, in Relation to Risk Indicators

Risk indicators	No.	%	OR	CI	Trend test *P*-value
Age (years)					
<52.1	32	16.2	1.00		0.004
52.1–56.2	46	24.1	1.64	0.99–2.71	
56.3–61.8	55	29.1	2.12	1.29–3.46	
>61.8	54	27.7	1.97	1.21–3.23	
Smoking habits					
Current smokers	26	20.6	1.00		
Former smokers	82	25.2	1.30	0.79–2.14	
Non-smokers	66	26.0	1.35	0.81–2.26	
Unknown	13	19.4	0.93	0.44–1.95	
Cumulative exposure (fibers/ml × years)					
≤8	30	15.6	1.00		0.000
8–42	34	17.6	1.15	0.67–1.98	
43–159	53	26.9	1.99	1.20–3.28	
≥160	70	35.8	3.15	1.93–5.13	
Peak asbestos level (fibers/ml)					
<1.35	8	11.3	1.00		0.000
1.35	27	14.8	1.37	0.59–3.18	
13.5	121	27.7	2.02	1.40–6.48	
>13.5	31	37.8	4.79	2.02–11.3	
Length of exposure (years)					
<12	40	19.7	1.00		0.074
13–18	51	24.8	1.34	0.84–2.14	
19–23	43	25.0	1.36	0.83–2.12	
≥24	53	27.8	1.57	0.98–2.50	
Time since first exposure (years)					
≤26	24	11.8	1.00		0.002
27–30	66	32.7	3.64	2.17–6.11	
31–33	48	24.9	2.48	1.45–4.25	
≥34	49	28.3	2.96	1.73–5.08	

asbestosis; time since first exposure and peak exposure for PP; and time since first exposure for DPT (time since first exposure in years did not enter in the model, but a significant trend across quartiles was found).

Table VI shows the final estimate for PP, obtained by applying a log-binomial model. Both peak exposure and time since first exposure had a significant effect, but a monotonic increase in PP risk was observed only with peak asbestos exposure. Smoking and age did not confound the pattern of the above associations.

For asbestosis, the final estimate obtained through exact logistic-regression analysis is already shown in Table II. For DPT, no variable entered the model of log-binomial regression.

DISCUSSION

Asbestos individual exposure was assessed retrospectively because quantitative exposure data for the different jobs were not available in the plants studied, with the exception of two plants. Through a detailed description of tasks performed, the fiber concentration was estimated in these tasks. The main limitations of JSM approach are: (i) the relative importance of the various determinants may prove difficult to assess; (ii) concordance among experts may be poor; (iii) the quality of the available information about the determinant(s) may be highly variable among the study subjects, with some carefully describing all the details of their job tasks, and others barely knowing the job title. Furthermore, in our study, the interviews took more than 1 hr,

TABLE IV. Number (No.) and Prevalence (%) of Diffuse Pleural Thickening, Odds Ratio (OR) With 95% Confidence Interval (CI), and Cochran-Armitage Trend Test *P*-value, in Relation to Risk Indicators

Risk indicators	No.	%	OR	CI	Trend test *P*-value
Age (years)					
<52.1	13	6.6	1.00		0.580
52.1–56.2	12	6.3	0.95	0.42–2.14	
56.3–61.8	8	4.2	0.63	0.25–1.54	
>61.8	17	8.7	1.35	0.64–2.86	
Smoking habits					
Current smokers	11	8.7	1.00		
Former smokers	26	8.0	0.91	0.43–1.90	
Non-smokers	12	4.7	0.52	0.22–1.21	
Unknown	1	1.5	0.16	0.02–1.25	
Cumulative exposure (fibers/ml × years)					
≤8	6	3.1	1.00		0.188
8–42	16	8.3	2.81	1.07–7.32	
43–159	15	7.6	2.55	0.97–6.73	
≥160	13	6.8	2.28	0.85–6.12	
Peak asbestos exposure (fibers/ml)					
<1.35	1	1.4	1.00		0.289
1.35	12	6.6	4.94	0.63–38.7	
13.5	33	7.6	5.71	0.77–42.5	
>13.5	4	4.9	3.59	0.39–32.9	
Length of exposure (years)					
<12	12	5.9	1.00		0.672
13–18	13	6.3	1.07	0.48–2.41	
19–23	12	7.0	1.19	0.52–2.73	
≥24	13	6.8	1.16	0.52–2.62	
Time since first exposure (years)					
≤26	9	4.4	1.00		0.024
27–30	10	5.0	1.12	0.45–2.83	
31–33	14	7.3	1.69	0.72–4.01	
≥34	17	9.8	2.36	1.02–5.44	

resulting in discomfort of interviewees who were often elderly.

Evidence supporting the reliability of our exposure estimates derives from the history of regulatory standards for asbestos. Between the late 1960s and the late 1980s, when most of our workers were exposed to asbestos, the threshold limit values (TLVs) issued by the American Conference of Governmental Industrial Hygienists were: 12 f/ml for 2 years (1968–1969); 5 f/ml for 9 years (1970–1978); 2 f/ml for 13 years (1978–1990). We calculated the time weighted average of TLVs over the 24 years of regulatory standard's history, obtaining 7.7 f/ml (=((12 × 2) + (5 × 9) + (2 × 13))/24), close to 6.4 f/ml (=114.6/17.8), average cumulative exposure over average length of exposure in our subjects.

TABLE V. Associations Between Benign Asbestos Diseases (Asbestosis, Asbestos Pleural Plaques, PP, Diffuse Pleural Thickening, DPT) and Different Aspects of Asbestos Exposure

Aspects of asbestos exposure	Asbestosis	PP	DPT
Time since first exposure (years)			
P-value	n.e.	<0.001	n.e.
P-trend	n.s.	<0.001	0.024
Duration of exposure (years)			
P-value	n.e.	n.e.	n.e.
P-trend	n.s.	n.s.	n.s.
Cumulative exposure (f/ml × years)			
P-value	<0.001	n.e.	n.e.
P-trend	0.004	n.s.	n.s.
Peak exposure (f/ml)			
P-value	n.e.	<0.001	n.e.
P-trend	n.s.	<0.001	n.s.

Multiple logistic regression models with stepwise selection of variables: significance level for untransformed variables entering the model (*P*-value) and for linear increase in risk across quartiles (*P*-trend).
ne, not entered the model; ns, not significant.

In the present study, where benign asbestos diseases were detected with CT, the exposure–response relationships appear consistent with those of early studies carried out with CXR. The significant risk factors were time since first exposure and peak exposure for the fibrotic disease of parietal pleura, and cumulative exposure for that of lung parenchyma. The strategy of statistical analysis was probably the source of conflicting results reported in Introduction Section. In fact, asbestosis was associated with cumulative exposure in 706 retired persons with documented occupational exposure to asbestos and examined with CT [Paris et al., 2004]. Furthermore, in 170 former asbestos workers the presence of

TABLE VI. Prevalence Ratio (PR) for Asbestos Pleural Plaques With 95% Confidence Interval (CI), and *P*-Value for a Two-Tail Test, Obtained Through Log-Binomial Regression

Risk indicators	PR	CI	*P*-value
Peak asbestos exposure (fibers/ml)			
<1.35	1.00		
1.35	1.23	0.59–2.57	0.578
13.5	2.34	1.20–4.55	0.012
>13.5	3.12	1.54–6.32	0.002
Time since first exposure (years)			
≤26	1.00		
27–30	2.62	1.72–4.00	0.000
31–33	2.18	1.40–3.40	0.001
≥34	2.50	1.61–3.88	0.000

PP at high resolution CT was linked to intensity of asbestos exposure ($P < 0.01$), and length of employment ($P < 0.05$) [Soulat et al., 1999].

The association of PP with intensity of asbestos exposure might be explained by a higher transfer of fibers from lung to the pleural space when lungs are overloaded by a high concentration of fiber. Since subjects were examined in a relatively short period ranging from 2000 to 2003, those with more than 26 years elapsed from first exposure to diagnosis began working in 1976 or before, when the asbestos levels were about 5 f/ml (TLV issued by the American Conference of Governmental Industrial Hygienists from 1970 to 1978) or even higher. On the other hand, among chrysotile miners and millers, Becklake et al. [1979] found that 20% showed an increase in pleural abnormality in a follow-up period averaging 17 years after removal from exposure: 17% experienced new lesions and the remaining 3% progression of an existing lesion. The increase of PP risk with TSFE could be due to either issue or to both.

In our study a doubtful relationship was found between asbestos exposure and DPT suggesting that the latter could be related also to non-occupational risk factors. In contrast to PPs, which are considered highly specific for asbestos exposure especially when bilateral [Consensus Report, 1997; Hosoda et al., 2008], DPT can occur in a variety of conditions affecting the pleura, including connective tissue disease and drug exposure [Malik et al., 1996]. Moreover, DPT is not precisely defined in radiological terms [Hillerdal et al., 1990]. According to Cugell and Kamp [2004], the hallmark of DPT is involvement of the visceral pleura, with blunting of the costophrenic angle and pleural shadows often extending up both chest walls, usually with some irregularity. However, McLoud et al. [1985] defined DPT on chest radiographs as ''a smooth, non-interrupted pleural density extending over at least one-fourth of the chest wall'' with or without costophrenic blunting; and Lynch et al. [1989] described DPT on CT scans as ''a continuous sheet of pleural thickening more than 5 cm wide, more than 8 cm in craniocaudal extent, and more than 3 mm thick.'' Nevertheless, both in clinical practice and in previous epidemiologic studies, the mere presence of pleural thickening, not just discrete or localized pleural thickening, has been often equated with the presence of PP.

In conclusion, occurrence of asbestosis and PP is associated with different aspects of asbestos exposure. DPT is less specific for asbestos exposure and, therefore, requires an accurate differential diagnosis.

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