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Factors associated with early-stage pulmonary fibrosis as determined by high-resolution computed tomography among persons occupationally exposed to asbestos

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Objectives Asbestosis remains difficult to diagnose, particularly in its early stages. The aim of this study was to determine criteria for independently associated features of pulmonary fibrosis in high-resolution computed tomograms among persons occupationally exposed to asbestos.

Methods Retired persons with documented occupational asbestos exposure and no known asbestos-related diseases were assessed for occupational, clinical, functional respiratory, and chest X-ray criteria. In addition, they all underwent high-resolution computed tomography (HRCT) in the prone position.

Results Altogether 51 (7.2%) of the 706 enrolled participants had features of pulmonary fibrosis consistent with asbestosis in the HRCT. Among those with small irregular opacities of <1/0 according to the 1980 International Labour Office Classification (ILO-C) in their X-rays, 5% had asbestosis in the HRCT. In a multivariate analysis, only age [odds ratio (OR) per year 1.08, 95% confidence interval (95% CI) 1.02–1.14], cumulative-exposure index (CEI) for asbestos (OR 6.4, 95% CI 1.5–28.4 for a CEI of ≥ 100 fibers/ml \times years), and the presence of small irregular X-ray opacities of $\geq 1/0$ ILO-C (OR 3.0, 95% CI 1.6–6.0) were independently associated with HRCT asbestosis. No combinations of these criteria simultaneously yielded high sensitivity and specificity for the diagnosis of early-stage HRCT asbestosis. Moreover, only 2% of the persons with a CEI of <25 fibers/ml \times years had HRCT asbestosis, the finding confirming the low incidence of asbestosis for such low exposure, as previously reported on the basis of X-ray data.

Conclusions Additional research is needed to better identify the persons most likely to benefit from HRCT screening for asbestosis.

Key terms occupational exposure, radiography (thoracic), sensitivity, specificity, tomography (scanners, X-ray, computed).

The diagnosis of asbestosis in people exposed to asbestos is a highly sensitive issue because of its medicolegal implications (ie, compensation). Moreover, asbestosis has been shown to be an independent risk factor for lung

cancer (1). Unfortunately, asbestosis remains difficult to diagnose, particularly in its early stages.

A standard posteroanterior chest X-ray is still widely used to screen for asbestos-related interstitial diseases

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because of the low cost, low irradiation level, and wide accessibility. Accordingly, in addition to the presence of basilar crackles, pulmonary restrictive pattern, and carbon monoxide (CO) diffusion abnormalities, the American Thoracic Society (ATS) has included the presence of small irregular opacities [profusion $\geq 1/1$ according to the 1980 International Labour Office Classification (ILO-C) (2) on pneumoconiosis] as a major criterion for asbestosis (3). Nevertheless, posteroanterior chest X-rays have a poor diagnostic value, their sensitivity having been estimated to be as low as 40–60% when compared with the results of standard chest computed tomography (CT) scans (4, 5).

High-resolution computed tomography (HRCT) of the chest has proved to be more effective than standard CT in the diagnosis of interstitial lung disease (6). Systematic use of HRCT for cohorts of people who have been exposed to asbestos revealed interstitial abnormalities consistent with asbestosis in a sizeable fraction of the asymptomatic persons whose posteroanterior chest X-rays (7–9) or pulmonary function (7, 9) were considered normal. As a result, systematic HRCT scanning with a 6-year periodicity was recommended recently in France for the diagnosis of asbestosis for people who are over 50 years of age and have had high occupational exposure to asbestos (10). Alternatively, some authors recommend HRCT only for those who have been exposed to asbestos and have radiological abnormalities of $\geq 1/0$ 1980 ILO-C or pleural plaques (11–14). Yet other authors recommend HRCT in the presence of respiratory disorders such as basilar crackles (12) or functional impairment (8, 15) even when the X-ray images can be considered normal (ie, $<1/0$ 1980 ILO-C).

In such a context, HRCT indicators need to be clarified with regard to asbestosis screening. In this study, healthy persons with a personal history of occupational asbestos exposure were systematically assessed for occupational, clinical, respiratory function, and standard X-ray criteria. They all underwent HRCT. Our goal was to identify criteria independently associated with the presence of parenchymal fibrosis in HRCT in order to define indicators for HRCT screening among people with a history of high occupational exposure to asbestos.

Participants and methods

A program for screening diseases known to be associated with occupational asbestos exposure was initiated in 1991 in the occupational disease consultation centers of the Normandy region of France, following an agreement with the French National Health Insurance Fund (“Caisse Nationale d’Assurance Maladie des Travailleurs Salariés”).

Participants

The tentative participants for this screening program included pensioners or early retirees from companies within the Normandy region in which occupational asbestos exposure was known to have been present. Most of these people had worked in a single asbestos textile and friction material factory. The rest were former employees of companies in which asbestos exposure was usually high, such as shipyards, fossil fuel power stations, and industrial insulation contractors. They all had to be free of previous involvement in systematic HRCT screening campaigns in their former companies and not known to have asbestos-related diseases prior to the time of inclusion.

The tentative participants were notified either by mail from their former employers or in local information meetings. Those who agreed to participate all gave their written informed consent. All the examinations were performed in three centers, namely, Rouen, Caen, and Flers.

Altogether 706 retired workers met the inclusion criteria for this study and were screened for asbestos-related diseases between 1 January 1991 and 31 December 1999. The participation rate widely varied by type of industry and was comprised of between a few percent (shipyards) and approximately two-thirds of the target population (energy production). All the features studied (including radiological features) were recorded for all 706 participants, except for complete interpretable functional tests, which were available for only 630 participants.

Clinical and respiratory function examinations

All the participants underwent a standard interview and clinical examination conducted by a physician. The purpose was to investigate medical history, in particular respiratory problems and smoking history, as well as to assess the presence of symptoms related to cardiorespiratory function, like cough, expectoration, dyspnea, basithoracic pain, basilar crackles, and signs of heart failure.

Conventional plethysmography (SensorMedics 6200, Yorba Linda, CA or Compact Lab Body, Jaeger, Germany) was performed in a seated position, with respect to the ATS recommendations. Total lung capacity (TLC), forced volume capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow rate at 50% of the FVC ($FEF_{50\%}$) were recorded, and FEV_1/FVC was calculated. The transfer factor of CO (T_{LCO}) was measured by the single breathholding method (MasterScreen Jaeger, Wuerzburg, Germany), and the transfer coefficient of CO (K_{CO}) was calculated using the TLC as the estimated value of alveolar volume (V_A). The participants’ predicted values were computed for respiratory function parameters using their age, gender, and height and European reference equations (16, 17) in a multiple linear regression involving all the participants. The observed-to-predicted ratios of the respiratory function parameters were

then expressed as percentages. The observed values were considered low when they were less than their corresponding predicted mean value minus the product of the residual standard deviation by 1.64, as obtained from the multiple linear regression.

Occupational exposure assessment

The methods used for the occupational exposure assessment have been described earlier in detail (18). Briefly, the occupational interview reviewed all the job positions held by the participants. For occupations implying asbestos exposure in one or several companies, dates of hire and end of assignments, as well as duration of exposure, were recorded. For the participants who had worked in the asbestos textile and friction material plant, a quantitative assessment of occupational exposure was obtained using a specific job-exposure matrix determined from airborne measurements collected annually between 1959 and 1999 in the various workshops of the plant. For all the other participants, the asbestos exposure level associated with each job was assessed using published airborne measurements available in the French database Evalutil (19), according to the calendar period of exposure and the typical reported tasks.

For all the participants, a cumulative-exposure index (CEI) was then calculated and was expressed in fibers per milliliters times years (fibers/ml \times years). It was obtained by summing the values for all job positions held, with reference to the occupational calendar established in the interview, the products of the job exposure level (in fibers per milliliter) by job duration (in years). Both the CEI and the duration of asbestos exposure were used in the statistical analysis.

Diagnosis of fibrosis from imaging

All the participants underwent a posteroanterior chest X-ray. Each X-ray was rated according to the 1980 ILO classification (2) by three independent and experienced readers from a panel of five occupational physicians (JA, PB, ML, CP, CR), who were blinded to the participants' clinical, functional and occupational characteristics. The median of the three rates was retained as the final value. Participants with small opacity profusion of grade 1/1 (1980 ILO-C) in their X-rays were considered to have asbestosis according to the ATS criteria (3), whether or not they were found to have inspiratory crackles, restrictive pattern impairment, or a low T_{LCO} . Pleural abnormalities were defined by the presence of the 1980 ILO-C criteria for circumscribed pleural plaques or diffuse pleural thickening.

CT explorations without contrast material were performed with an Elscint CT Twin tomograph (Picker International, Highland Heights, OH, USA) or a Siemens Somatom Plus tomograph (Siemens AG, Erlangen,

Germany). All the examinations included at least six high-resolution millimetric sections (200–220 mA, 130 kV, 1-mm slices, window width (WW) 1600 Hounsfield units (HU), window level (WL) –700 HU) in the prone position and full inspiration, five of which were equally spaced between the carina of the trachea and the bottom part of the costophrenic angles and the sixth being halfway between the carina of the trachea and the extreme pulmonary apices. The reading was carried out with the use of a standard grid describing the features of (i) asbestos-related pulmonary fibrosis lesions (ie, interlobular septal thickening, intralobular lines, honeycombing, subpleural curvilinear lines, and ground-glass opacity), (ii) pleural fibrosis lesions (ie, pleural plaques and diffuse pleural thickening), and (iii) pulmonary opacities associated with pleural changes (ie, parenchymal bands and rounded atelectasis), as described by several authors (20, 21). Pulmonary fibrosis was assessed from the HRCT interstitial abnormalities that persisted in the prone position. The following subjective semiquantitative grading was used: (i) grade 0: normal, without any interstitial opacity consistent with asbestos-related pulmonary fibrosis; (ii) grade 1: mild interstitial abnormalities either unilateral or, if bilateral, visible only in very limited areas (ie, less than one-third of the posterior third of each hemithorax); (iii) grade 2: bilateral interstitial abnormalities limited in extent (ie, comprised of between one and two-thirds of the posterior third of each hemithorax) but consistent with asbestos-related pulmonary fibrosis (ie, honeycombing even if alone and unilateral or at least two lesions among interlobular septal thickening, intralobular lines, and subpleural curvilinear lines); (iv) grade 3: profuse (ie, greater than two-thirds of the posterior third of each hemithorax) bilateral interstitial abnormalities visible on several slices. Only grades 2 and 3 were considered consistent with the diagnosis of pulmonary fibrosis.

As for the X-ray data, the HRCT images were independently rated by three readers from the five-reader panel, who were blinded to the participant's clinical, functional, radiographic, and occupational characteristics. Again, the median of the three rates was retained as the final rate. The interreader agreement for the diagnosis of asbestosis was moderate to substantial, as the pairwise weighted kappa coefficients were 0.54 [95% confidence interval (95% CI) 0.45–0.63], 0.58 (95% CI 0.50–0.65), and 0.61 (95% CI 0.49–0.66).

Statistical analysis

The principal-interest variable was dichotomized as the unlikely presence of pulmonary fibrosis (ie, normal examination or isolated interstitial abnormalities in the HRCT, grades 0 and 1) versus the likely presence of pulmonary fibrosis regardless of severity (ie, grades 2 and 3).

Univariate analyses were used to assess the associations between HRCT pulmonary fibrosis, so defined, and all the other categorical variables using Pearson's chi-square test or corresponding exact tests depending on the sample size. For the ordered categorical variables, Cochran's trend test or its exact version was also used. Student's t-test was used for the continuous variables. Two-sided P-values less than 0.05 were considered significant.

A multivariate analysis based on the unconditional logistic regression model was used to determine the variables independently associated with HRCT pulmonary fibrosis as a basis for defining indicators for HRCT screening. Two separate analyses were performed. In the first analysis (model I), the following five main dichotomous variables were included because of their reported association with fibrosis in previous studies (3, 8, 11–13, 15, 22): (i) basilar crackles (yes, no), (ii) the observed-to-predicted ratio for TLC (low, normal), (iii) the observed-to-predicted ratio for T_{LCO} (low, normal), (iv) small irregular opacities, and (v) pleural abnormalities in the X-ray (yes, no). In the second analysis (model II), a backward stepwise procedure was applied to all the variables that appeared to be separately associated (at the 10% level) with HRCT pulmonary fibrosis in the univariate analyses. Moreover, body mass index and smoking status were also included in models I and II because they had been reported as possible sources of interference with the diagnosis of pulmonary fibrosis in the literature (23). Finally, age and gender were adjusted for in both analyses.

The sensitivity and specificity of variables alone or in combination were computed with respect to the diagnosis of HRCT pulmonary fibrosis. All five main dichotomous variables included in model I, as well as CEI (<25 fibers/ml \times years and \geq 25 fibers/ml \times years), which was selected in model II, were considered. Crude estimates and the estimates resulting from both models were obtained. Youden's index (ie, sensitivity + specificity – 1) and the likelihood ratio [ie, sensitivity / (1 – specificity)] were computed to summarize the diagnostic value.

Data were analyzed with SPSS (SPSS Inc, release 10.0, Chicaco, IL, USA) and BMDP New System (BMDP Statistical Solutions Inc, release 7.0, Boston, MA, USA) software.

Results

The study sample included mostly men (N=630, 89%). The overall mean age was 65.2 (SD 6.1) years. Most of the participants were current or former smokers (N=447, 63%). The overall mean duration of asbestos exposure was 24.9 (SD 9.1) years and the overall mean CEI was 137.9 (SD 136.4) fibers/ml \times years. For 112 participants (16%), the CEI was <25 fibers/ml \times years. Interstitial HRCT

abnormalities consistent with pulmonary fibrosis (ie, grade 2 or 3) were found for 51 (7%) members of the entire sample. Only six (1%) participants were classified as having grade 3 pulmonary fibrosis.

The results from comparing the demographic and morphologic characteristics of the participants, as well as smoking and occupational asbestos exposure according to the existence of grades 2–3 interstitial HRCT abnormalities are shown in table 1. The participants with HRCT fibrosis were significantly older (P<0.001). Significant associations were found between the presence of HRCT fibrosis and occupational exposure to asbestos in terms of the CEI, with an odds ratio (OR) of 3.4 (95% CI 0.8–15.2) for 25–99.9 fibers/ml \times years and an OR of 6.1 (95% CI 1.5–25.9) for \geq 100 fibers/ml \times years in comparison with the CEI of \leq 25 fibers/ml \times years (P=0.002, trend test), but not with duration of exposure, for which no trend was apparent (P=0.791, trend test). No associations were noted

Table 1. Demographic and morphologic characteristics, smoking, and occupational asbestos exposure of the 706 participants according to the presence of pulmonary fibrosis as determined by high-resolution computed tomography (HRCT).

Characteristics	Subjects without HRCT fibrosis (grades 0–1)(N=655) ^a		Subjects with HRCT fibrosis (grades 2–3)(N=51) ^b		OR	95%CI
	N	%	N	%		
Age						
<60 years	108	98	3	3	1.0	.
60–69 years	400	95	22	5	2.0	0.6–6.7
\geq 70 years	147	85	26	15	6.4	1.9–21.6
P-value	P<0.001 ^a				P=0.166 ^b	
Gender						
Male	584	93	46	7	1.0	.
Female	71	93	5	7	1.1	0.4–2.9
P-value	P=0.818 ^a				.b	
Smoking						
Nonsmokers	243	94	16	6	1.0	.
Former smokers	337	92	30	8	1.4	0.7–2.5
Current smokers	75	94	5	6	1.0	0.4–2.9
P-value	P=0.597 ^a				P=0.600 ^b	
Duration of asbestos exposure						
<20 years	183	95	10	5	1.0	.
20–29 years	232	90	25	10	2.0	0.9–4.2
\geq 30 years	240	94	16	6	1.2	0.5–2.7
P-value	P=0.138 ^a				P=0.791 ^b	
Cumulative exposure index^c						
<25 fibers/ml \times years	110	98	2	2	1.0	.
25–99.9 fibers/ml \times years	241	94	15	6	3.4	0.8–15.2
\geq 100 fibers/ml \times years	304	90	34	10	6.1	1.5–25.9
P-value	P=0.008 ^a				P=0.002 ^b	

^a Comparison of subjects with and without HRCT fibrosis using Pearson's chi-square test or Fisher-Freeman-Halton's exact test, depending on the sample size for the categorical variables.

^b Cochran's trend test (asymptotic of exact version depending on the sample size) when applicable.

^c See the section on occupational exposure assessment in the text.

Table 2. Clinical characteristics of the 706 participants according to the presence of pulmonary fibrosis as determined by high-resolution computed tomography (HRCT).

Characteristic	Subjects without HRCT fibrosis (grades 0–1) (N=655)		Subjects with HRCT fibrosis (grades 2–3) (N=51)		OR	95%CI
	N	%	N	%		
Dyspnea						
No	406	94	27	6	1.0	.
Yes	249	91	24	9	1.5	0.8–2.6
P-value	P=0.201 ^a					. ^b
Basilar crackles						
No	497	94	30	6	1.0	.
Yes	158	88	21	12	2.2	1.2–4.0
P-value	P=0.007 ^a					. ^b

^a Comparison of the subjects with and without HRCT fibrosis using Pearson's chi-square test or Fisher-Freeman-Halton's exact test, depending on the sample size for the categorical variables.

^b Cochran's trend test (asymptotic or exact version depending on the sample size) when applicable.

Table 3. Radiographic characteristics of the 706 participants according to the presence of pulmonary fibrosis as determined by high-resolution computed tomography (HRCT). (ILO-C = International Labour Office Classification, TLC = total lung capacity, T_{LCO} = transfer factor of carbon monoxide, ATS = American Thoracic Society)

Characteristic	Subjects without HRCT fibrosis (grades 0–1) (N=655)		Subjects with HRCT fibrosis (grades 2–3) (N=51)		OR	95%CI
	N	%	N	%		
Small opacities in X-ray^a						
0/0	326	97	10	3	1.0	
0/1	202	92	18	8	2.9	1.3–6.4
1/0	98	87	14	13	4.7	2.0–10.8
≥1/1	29	76	9	24	10.1	3.8–26.9
P-value	P<0.001 ^b					P<0.001 ^c
Asbestosis according to the ATS criteria^d						
No	626	94	42	6	1.0	
Yes, without alterations ^e	14	78	4	22	4.3	1.3–13.5
Yes, with alterations ^e	15	75	5	25	5.0	1.7–14.4
P-value	P=0.001 ^b					P=0.001 ^c
Pleural abnormalities in X-ray^f						
No	313	95	17	5	1.0	
Yes	342	91	34	9	1.8	1.0–3.3 ^c
P-value	P=0.046 ^b					

^a According to the 1980 ILO-C for pneumoconiosis.

^b Comparison of the subjects with and without HRCT fibrosis using Pearson's chi-square test or Fisher-Freeman-Halton's exact test, depending on the sample size for the categorical variables.

^c Cochran's trend test (asymptotic or exact version depending on the sample size) when applicable.

^d ATS criteria: presence of small opacities, grade ≥1/1, according to the 1980 ILO-C in a posteroanterior chest X-ray.

^e Presence of basilar crackles, or observed TLC (or T_{LCO}), less than the difference between the predicted TLC (or T_{LCO}) and the product of the residual standard deviation by 1.64, as obtained from European multiple linear regression equations (16, 17).

^f Defined by the presence of 1980 ILO-C criteria for circumscribed pleural plaques or diffuse pleural thickening.

between HRCT pulmonary fibrosis and gender, body mass index, or smoking status.

Tables 2–4 display the observed distributions of the clinical, X-ray, and respiratory function characteristics according to the presence of HRCT pulmonary fibrosis. Fibrosis was significantly more frequent among the participants who had basilar crackles (12% versus 6%, P=0.007). A significant and positive association was found between the degree of profusion of small irregular opacities in the X-ray and the presence of fibrosis in the HRCT (P<0.001, trend test). Altogether 42 participants (6%) with grade 0/0, 0/1, or 1/0 in their X-rays, and thus considered free of fibrosis according to the ATS criteria (3), exhibited HRCT fibrosis. Conversely, out of the 38 participants who met the ATS criteria for asbestosis, only 9 were considered to have HRCT fibrosis (24%). The presence of pleural abnormalities on the X-rays according to 1980 ILO-C criteria was significantly associated with HRCT pulmonary fibrosis (P=0.046). The spirometric values were not associated with the presence of HRCT pulmonary fibrosis, except for a significant decrease in the mean predicted-to-observed TLC ratio for the participants with HRCT fibrosis (89.2 versus 94.6%, P=0.016).

Table 5 presents the results of the two multivariate analyses performed to identify factors independently associated with pulmonary fibrosis in the HRCT. As TLC and T_{LCO} were considered in both analyses, these analyses were based on the subsample of 630 participants for which respiratory function tests were available. The first analysis that considered variables reported to be associated with asbestosis in the literature (model I) only showed a significant association of HRCT pulmonary fibrosis with (i) age (OR 1.08 per year, 95% CI 1.02–1.14) and (ii) small irregular opacities of grade ≥1/0 (1980 ILO-C) for the X-ray (OR 2.9, 95% CI 1.5–5.8). No associations were found with pleural abnormalities, basilar crackles, or the observed-to-predicted TLC and T_{LCO} ratios. The second analysis (model II) selected three variables from those separately associated with HRCT pulmonary fibrosis in the univariate analysis. Namely, age (OR 1.08 per year, 95% CI 1.02–1.14), the existence of small irregular opacities of 1980 ILO-C grade ≥1/0 (OR 3.0, 95% CI 1.6–6.0), and CEI, with an OR of 2.9 (95% CI 0.6–13.5) for 25–99.9 fibers/ml × years and an OR of 6.4 (95% CI 1.5–28.4) for ≥100 in comparison with the value for <25 fibers/ml × years, appeared to be significantly and independently associated with interstitial HRCT abnormalities. Moreover, one borderline significant association was observed for the presence of basilar crackles (OR 1.8, 95% CI 0.9–3.6). No other characteristics appeared to be independently associated with HRCT pulmonary fibrosis. A significant dose–effect relationship was found between the CEI and asbestosis when the CEI was coded as a continuous variable (OR 1.004 per fibers/ml × years, 95% CI 1.002–1.005, P<0.001), after adjustment for all the other

Table 4. Functional characteristics of 630 of the 706 participants according to the presence of pulmonary fibrosis as determined in high-resolution computed tomography (HRCT).^{a, b} (FVC = forced vital capacity, TLC = total lung capacity, FEV₁ = forced expiratory volume in 1 second, FEF₅₀ = forced expiratory flow rate at a 50% of the FVC, T_{LCO} = transfer factor of carbon monoxide, K_{CO} = transfer coefficient of carbon monoxide)

	FVC		TLC		FEV ₁		FEV ₁ /FVC		FEF ₅₀		T _{LCO}		K _{CO}	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Subjects without HRCT fibrosis (grades 0–1) (N=655)	104.5	16	94.6	13	98.0	22	96.2	12	83.5	34	104.1	22	116.7	46
Subjects with HRCT fibrosis (grades 2–3) (N=51)	100.3	16	89.2	15	100.0	36	97.3	12	80.7	30	100.6	26	114.2	24
P-value ^c	0.113		0.016		0.591		0.563		0.650		0.341		0.728	

^a Complete functional tests were available only for the 630 participants for whom the functional characteristics are presented.

^b Observed-to-predicted ratio.

^c Comparison of subjects with and without HRCT fibrosis using Student's t-test for continuous variables.

significant variables. No notable changes resulted from repeating this analysis with all 706 participants included.

Table 6 displays the sensitivity and specificity of the variables included in models I and II, in isolation or in combination, with respect to the diagnosis of pulmonary fibrosis in the HRCT. The highest sensitivity (95%) was observed for a high CEI (≥ 25 fibers/ml \times years) but at the price of an extremely low specificity (18%). The highest specificity (88%) was found for a low observed-to-predicted T_{LCO} ratio, but the corresponding sensitivity was extremely low (15%). Youden's index was highest (0.33) for the presence of basilar crackles, a high CEI, small irregular opacities of grade $\geq 1/0$ for the X-ray results, a low TLC, or a low T_{LCO} (sensitivity 76%, specificity 57%). The likelihood ratio was highest (2.3) for the presence of small irregular opacities of grade $\geq 1/0$ in the X-ray alone (sensitivity 46%, specificity 80%). No single variable or combination of variables simultaneously yielded high sensitivity and specificity values.

Discussion

This study shows that interstitial pulmonary lesions detected by HRCT in participants with documented occupational asbestos exposure are independently associated with cumulative asbestos exposure (as measured by a CEI for asbestos), the presence of small interstitial abnormalities in a chest X-ray, older age, and, to a less extent, the presence of basilar crackles. It also confirms that interstitial pulmonary lesions may be present in participants whose chest X-rays can be considered normal (ie, <1/1 profusion grade according to 1980 ILO-C).

As 42 of 51 persons with HRCT interstitial abnormalities did not meet the ATS asbestosis criteria, the significance of these HRCT abnormalities relative to the diagnosis of asbestosis needs to be discussed. CT criteria for

Table 5. Multivariate analyses of associations of pulmonary fibrosis as determined by high-resolution computed tomography for 630 participants^a using two separate logistic models. (OR = odds ratio, 95% CI = 95% confidence interval, TLC = total lung capacity, T_{LCO} = transfer factor for carbon monoxide, CEI = cumulative-exposure index, BMI = body mass index)

Characteristic ^b	Model I ^c			Model II ^d		
	OR	95% CI	P-value ^e	OR	95% CI	P-value ^e
Age (years)	1.08	1.02–1.14	0.010	1.08	1.02–1.14	0.006
Small opacities $\geq 1/0$ ^f						
No	1.0	.	.	1.0	.	.
Yes	2.9	1.5–5.8	0.002	3.0	1.6–6.0	0.001
Pleural abnormalities ^f						
No	1.0
Yes	1.1	0.6–2.3	0.710	.	.	NS
Basilar crackles						
No	1.0	.	.	1.0	.	.
Yes	1.8	0.9–3.6	0.110	1.8	0.9–3.6	0.088
Low TLC ^g						
No	1.0
Yes	1.5	0.7–3.4	0.276	.	.	NS
Low T _{LCO} ^g						
No	1.0
Yes	1.2	0.4–3.6	0.785	.	.	NS
CEI (fibers/ml \times years)						
<25	.	.	.	1.0	.	.
25–99.9	.	.	.	2.9	0.6–13.5	.
≥ 100	.	.	.	6.4	1.5–28.4	0.010 ^h

^a With available respiratory function parameters.

^b In both models, gender, smoking status (non, former, current) and BMI were also included.

^c In addition to age, gender and BMI, the other five variables in this model were included because of reported associations with pulmonary fibrosis in the literature. There was no significant overall lack of fit for this model (P=0.717, Hosmer & Lemeshow's overall goodness-of-fit test). The area under the receiver operator curve (ROC) was 0.719.

^d Variables selected through a backward stepwise procedure. There was no significant overall lack of fit for this model (P=0.857, Hosmer & Lemeshow's goodness-of-fit test). The area under the ROC was 0.750.

^e Homogeneity test based on the likelihood ratio statistic.

^f According to the 1980 International Labour Office classification for pneumoconiosis.

^g Observed value less than predicted mean value minus the product of the residual standard deviation by 1.64.

^h P<0.001, trend test.

Table 6. Sensitivity and specificity relative to the diagnosis of pulmonary fibrosis as determined in high-resolution computed tomography for selected combinations of the variables in table 3 and for the 630 participants. ^a (ILO-C = Labour Office Classification, TLC = total lung capacity, T_{LCO} = transfer factor for carbon monoxide)

Variables	N	%	Sensi- tivity (%)	Speci- ficity (%)	You- den's index	Likeli- hood ratio
In isolation						
Age ≥60 years (a)	523	83.0	93	18	0.10	1.1
Small irregular opacities (b) ^b	140	22.2	46	80	0.26	2.3
Pleural abnormalities (c) ^c	337	53.5	66	47	0.13	1.3
Basilar crackles (d)	163	25.9	46	76	0.22	1.9
Low TLC (e) ^d	101	16.0	27	85	0.12	1.8
Low T _{LCO} (f) ^e	75	11.9	15	88	0.03	1.3
CEI ≥25 fibers/ml × years (g)	522	82.9	95	18	0.13	1.2
In combination						
b, d, e or f	341	54.1	80	48	0.28	1.5
b, d, e, f or c	513	81.4	95	20	0.15	1.2
g and (b, d, e or f)	283	44.9	76	57	0.33	1.8
g and (b, d, e, f or c)	390	61.9	90	40	0.30	1.5

^a With available respiratory function parameters.

^b Defined as grade ≥1/0 1980 International ILO-C for pneumoconiosis in a posteroanterior chest X-ray.

^c Defined as the presence of circumscribed plaques or diffuse pleural thickening, according to the 1980 ILO-C.

^d Defined as low if TLC was less than the predicted mean value minus the product of the residual standard deviation by 1.64.

^e Defined as low if T_{LCO} was less than the predicted mean value minus the product of the residual standard deviation by 1.64.

asbestosis were first proposed by Aberle et al (20) and then complemented by other authors (21, 24). They include subpleural curvilinear opacities, septal thickening, nonseptal lines (core lines), parenchymal bands, and honeycombing, but not ground glass opacities (25). The semiquantitative method used in our study for the assessment of interstitial pulmonary fibrosis was close to that used in previous reports (14, 21, 24, 26–28).

HRCT features of asbestosis (subpleural curvilinear opacities, septal and nonseptal lines, and honeycombing) have been shown to be associated with X-ray opacities (14), as well as with histopathological signs in the course of the disease (24, 29). However, these features may remain unnoticed in people whose asbestosis diagnosis was histologically proved (24). Moreover, although they are infrequent in healthy participants (30), HRCT abnormalities are not specific to asbestosis and can be observed in persons with other types of interstitial fibrosis or even cardiovascular diseases (31). Similarly, an excess of asbestosis diagnoses, on the basis of X-ray findings, was reported by Gaensler et al (32), who found that 5.1% of people who met the ATS criteria (3) had no pathological lesions of asbestosis, although they underlined the nonrepresentativeness of their sample.

Whereas established asbestosis has been reported to be associated with respiratory functional impairment mainly of the restrictive type (3, 12, 22), several authors have described the presence of interstitial abnormalities

on HRCT, consistent with early-stage asbestosis, in asymptomatic participants without any functional or X-ray abnormalities (7, 9). These findings suggest that early-stage HRCT abnormalities might precede functional impairment. Aberle et al (20) argued that early-stage CT abnormalities, although multifocal and bilateral by definition, may not be sufficiently widespread to have a substantial functional respiratory impact. As we observed only a slight significant TLC decrease in our patients with HRCT fibrosis, our results support this hypothesis. This issue will be addressed further in a longitudinal follow-up of the participants of our present study.

In conclusion, despite the remaining uncertainties, interstitial HRCT abnormalities of grades 2–3, observed in the participants exposed to asbestos in our study, appear consistent with a diagnosis of pulmonary fibrosis. These abnormalities may precede functional or X-ray alterations and can be interpreted as early-stage asbestosis in agreement with the findings of several other authors (20, 24). In view of our discrepant findings in terms of asbestosis diagnosis depending on whether HRCT or the ATS criteria were used, it seems warranted to discuss new criteria for asbestosis diagnosis that would include HRCT features.

We noted a significant association between HRCT fibrosis and cumulative asbestos exposure, with a clear dose-response relationship with CEI. Interestingly, we observed only two cases of HRCT pulmonary fibrosis (2%) among the 112 patients with a CEI of <25 fibers/ml × years. [The CEI values were 9.3 and 15 fibers/ml × years, respectively.] Indeed, among the 52 participants with a CEI of <25 fibers/ml × years and no symptoms or abnormal examinations, no case of HRCT asbestosis was detected. Among the remaining 60 participants with a CEI of <25 fibers/ml × years, two cases were detected, both having basilar crackles and one having small irregular opacities in the X-ray. This finding lends some support to the historical hypothesis, based on X-ray findings, of a threshold close to 25 fibers/ml × years for asbestosis occurrence (33). However, as some authors reported the existence of pulmonary fibrosis in the pathological records without any abnormalities on a CT scan (24), the presence of asbestosis in some of our patients with a CEI of <25 fibers/ml × years cannot be ruled out.

Because HRCT was carried out systematically for persons occupationally exposed to asbestos, our study allowed us to assess associations between clinical, occupational, functional, and X-ray factors and the presence of pulmonary fibrosis in HRCT, in order to identify people who could benefit the most from HRCT screening. Our findings confirm the high specificity of basilar crackles, small irregular X-ray opacities, and a low TLC or T_{LCO} for the diagnosis of HRCT pulmonary fibrosis. Unfortunately, no single criterion or combination of the criteria simultaneously produced satisfactory sensitivity and

specificity values. Similar diagnostic values were obtained with combinations including only the clinical, respiratory function, and X-ray criteria previously reported to be associated with asbestosis or with combinations including cumulative asbestos exposure as assessed by the CEI used by us (table 6).

In view of our results, there seems little justification for recommending early-stage fibrosis screening with HRCT among people with a CEI of <25 fibers/ml \times years, especially in the absence of clinical, functional, or X-ray alterations. Among patients with a CEI of ≥ 25 fibers/ml \times years, there appears to be a stronger case for HRCT screening for fibrosis, but the precise indicators remain open to discussion.

In addition to the lack of an established consensus on criteria for diagnosing asbestosis with the aid of HRCT, other potential limitations of this study deserve to be examined. First, the people included in this study made up a sample that was not representative of people occupationally exposed to asbestos in that we selected participants who were highly exposed but reached retirement age without any known asbestos-related disease. The relevance of the suggested threshold of 25 fibers/ml \times years may be dependent on this selection. Moreover, this selection led to a low prevalence of asbestosis in comparison with the findings of other studies. For instance, asbestosis prevalence, defined as the presence of small irregular opacities of grade $\geq 1/0$ (ILO-C) on a posteroanterior chest X-ray, was 19% in our study, whereas it was estimated to lie between 7.5% and 40.0% in asbestos-processing industries and between 11.5% and 60.3% in the industrial insulation sector (34). However, the prevalence of fibrosis, though highly relevant for discussion, does not affect sensitivity and specificity estimates by itself.

The lack of representativeness of our asbestosis cases may be a more critical issue. Most of the cases of fibrosis that we observed were mild, as reflected by the distribution of the ILO-C profusion stage and the generally moderate amount of functional lung impairment (tables 2–4). However, restricting our analyses to the participants most severely affected, as defined by degree of profusion of $\geq 1/1$ according to 1980 ILO-C, did not appreciably modify our results (data not shown). Therefore, our conclusions may apply as well to unselected persons with more severe asbestosis than in our sample.

A third limitation may stem from the protocol used for the HRCT examination and its interpretation. We took at least six high-resolution sections predominantly in the lower parts of the lung because of the preferential location of asbestosis in the lower lobes (3). Although the risk of underestimating the actual prevalence of asbestosis by missing very localized forms cannot be ignored totally, our procedure was consistent with the recommendations of other authors. Indeed, Aberle et al (20), Gamsu et al (24), and Bergin et al (31), as well as

a group of experts (26), all recommended using a limited number of millimetric sections, usually six, from the entire lung or under the carina, in the prone position whenever possible, according to a protocol similar to ours. Moreover, HRCT with limited three-level sections including only one section performed under the carina has been reported to depict idiopathic pulmonary fibrosis as effectively as HRCT with 10-mm increment sections (35). For future studies, and in order to improve epidemiologic knowledge on asbestosis, it would be useful to develop a standardized HRCT reading grid for asbestosis.

Our findings confirm that HRCT can detect early-stage asbestosis in people who have been highly exposed to asbestos and whose X-ray can be considered normal. It follows that the presence of ascertained interstitial abnormalities, as evidenced by HRCT, should be a prerequisite for diagnosis, in the absence of pathologic samples. Moreover, HRCT screening does not seem warranted for people with low occupational exposure (eg, CEI <25 fibers/ml \times years), especially in the absence of other asbestosis-related alterations. Additional studies are necessary so that HRCT indicators of early stage asbestosis can be better defined and so that the threshold suggested by our results can be validated. Until such indicators are precisely defined, the use of chest CT scans to monitor cohorts of exposed participants will mainly depend on more general, budgetary, and sociocultural considerations (36). HRCT-incurred irradiation, although much reduced with recent multiple-slice CT techniques, must be balanced against the prevalence of asbestosis in the population being monitored, the practical accessibility to competent specialized structures, the cost attached to periodic examinations, and the potential compensation benefits for early-stage asbestosis.

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