Pulmonary nodules detected by thoracic computed tomography scan after exposure to asbestos: diagnostic significance.

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TITLE: PULMONARY NODULES DETECTED BY THORACIC CT SCAN AFTER EXPOSURE TO ASBESTOS: DIAGNOSTIC SIGNIFICANCE

Running head: Asbestos exposure and CT pulmonary nodules.

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SUMMARY:

Objective

The aim of the study was to analyse the relationships between CT pulmonary nodules mentioned by radiologists and cumulative exposure to asbestos or asbestos-related pleuro-pulmonary diseases, among 5,662 asbestos-exposed subjects, and the relationships between pulmonary nodules and thoracic cancer, in order to determine whether a specific surveillance strategy according to cumulative asbestos exposure, should be adopted.

Design

Standardised Incidence and Mortality Ratios for lung cancer and pleural mesothelioma were calculated among patients with and without mention of pulmonary nodules, and compared via the Comparative Morbidity Figure.

Results

A significant over-incidence of primary lung cancer and pleural mesothelioma was observed among subjects presenting with pulmonary nodule(s) (SIR respectively 1.95 [1.22; 2.95] and 11.88 [3.20; 30.41]). However, there was no significant relationship between pulmonary nodules mentioned by radiologists and cumulative asbestos exposure or between pulmonary nodules and the presence of asbestos-related benign diseases.

Conclusions

This study confirms the expected excess of lung cancer in subjects presenting with pulmonary nodules in the radiologist's diagnostic report, and shows the absence of relationship between these nodules and the level of cumulative asbestos exposure. Consequently, our study offers no argument in favour of specific surveillance modalities with regard to these nodules based on estimated cumulative asbestos exposure.

INTRODUCTION

The medical consequences of asbestos exposure essentially involve the respiratory tract and include benign pleural pathologies (localised pleural fibrosis, benign pleurisy, diffuse pleural fibrosis and round atelectasis), asbestosis (pulmonary fibrosis caused by the inhalation of asbestos fibres) and malignant diseases, among which pleural, pericardic and peritoneal mesothelioma, primary lung cancer, together with cancer of the larynx and the ovary **[1-2]**.

Primary lung cancer is the leading cause of mortality by cancer in France among men and current estimates suggest that asbestos is responsible for 10 to 14% of primary lung cancers **[3]**. When diagnosed at a sufficiently early stage (Stage I-II), and when resectable, the 5-year survival rate can reach 50 to 70% and, according to some recent publications, 80% of stage IA small-volume tumours are curable **[4]**.

Several studies have therefore been carried out to define the most efficient screening technique for early detection of lung cancer and the modalities of such screening. Some authors have proven the superiority of low radiation helical CT scan of the chest compared to conventional chest X-ray for the screening of primary lung cancer **[5-15]**. However, the pertinence of such screening has not yet been demonstrated in randomised studies, in terms of specific gain in mortality. Nevertheless, the use of chest CT scan for post-occupational surveillance is perfectly suited to benign asbestos-associated diseases, the drawback of this technique being the large number of pulmonary nodules detected.

Owing to the fact that the French legislation allows compensation for any asbestos-related disease, a 1999 French consensus conference on medical surveillance modalities for subjects having been occupationally exposed to asbestos, recommended the use of helical CT scan for diagnosing benign asbestos-related affections **[16]**. It is precisely within this context that four French regions (Aquitaine, Upper Normandy, Lower Normandy and Rhône-Alpes) were designated by the French Ministry for Employment and Solidarity's Occupational Relations

Directorate and the "Caisse Nationale d'Assurance Maladie des Travailleurs Salariés" (CNAMTS)'s Directorate for Occupational Risks **[17]**, to conduct an experimental study on the medical surveillance of retired or inactive subjects having been exposed to asbestos. Hence, from 2003 to 2005, 16,885 subjects were offered, free of charge, a medical check-up including chest CT scan. In evaluating this experimental programme, it was necessary to assess the significance to be afforded to the diagnosis of pulmonary nodule(s) by the clinical radiologist performing chest CT scan. Indeed, even if post-occupational CT scan screening mainly aims at diagnosing benign asbestos-related diseases, these examinations are associated with the detection of pulmonary nodules. Therefore, it is important to investigate the prognosis of these nodules according to cumulative asbestos exposure, in order, if necessary, to propose specific surveillance modalities based on estimated cumulative asbestos exposure.

The aim of our study was to analyse the relationships between the mention of pulmonary nodules in the diagnostic report drafted by the radiologist having performed the CT scan and cumulative exposure to asbestos or asbestos-related pleuro-pulmonary diseases (pleural plaques and/or asbestosis, and/or lung cancer, and/or mesothelioma) on CT scan examination, taking into account individual characteristics (age, sex, asbestos exposure characteristics and tobacco status), among the 5,662 subjects included in this experimental program for whom these data were available. We also investigated the relationships between pulmonary nodules and lung cancer, in order to determine whether a specific surveillance strategy according to cumulative asbestos exposure should be adopted for subjects having been exposed to asbestos dust.

MATERIALS AND METHODS

Population

As previously reported elsewhere **[17]**, included subjects had been informed of the screening campaign, either via personally addressed mail, or by television or printed media. For

inclusion in the study population, volunteer subjects required to be inactive or retired from the French general social security fund; to have completed and returned to the social security fund a self-questionnaire; to have undertaken chest CT scan according to the established protocol.

Data collection

Asbestos exposure and tobacco consumption:

As previously described elsewhere **[17]**, evaluation of asbestos exposure was performed using a standardised questionnaire, enabling occupational exposure to be coded into four exposure categories following expert analysis: "low" (passive exposure), "low intermediate", "high intermediate" and "high". The evaluation of each job period was classified according to the probability, intensity and frequency of exposure. Since no measurements of airborne levels were available, all estimations of exposure parameters were based on experts' subjectivity, i.e. semiquantification, to which weighting factors were assigned **[18, 19]**. Categories of intensity were established using the following semiquantitative scale - probability of exposure: not exposed, possible, definite; frequency: sporadic (less than 5 percent of working time), irregular (5-50 percent of working time), continuous (more than 50 percent of working time); intensity: low (less than 1 fibre/ml), medium (1-2 fibres/ml), high (2-10 fiberes/ml), very high (>10 fibres/ml). Weighting factors were attributed to each exposure category in order to calculate an exposure index: probability: null=0, possible=0.5, definite=1; frequency: sporadic=0.025, irregular=0.25, continuous=0.75; intensity: low=0.1 fibre/ml, medium=1 fibre/ml, high=10 fibres/ml and very high=100 fibres/ml. The CEI is the life-time sum of the products of probability, frequency, intensity and duration for each job period expressed in unit x years. Included patients were offered a standard clinical examination, respiratory functional exploration and chest CT scan according to a specific protocol, subject to consensual coding, and according to a grid common to the four regions involved.

Subjects were classified into three categories according to tobacco consumption: smokers, ex-smokers (defined as those who had quit smoking for at least one year), and non smokers.

Chest CT scan and chest X-rays

Subjects included in the study benefited from CT scan between 2003 and 2005. All clinical radiologists participating in the experimental study received specific training on asbestos-related diseases. Modalities for conducting chest CT scans were put forward by a group of experts comprising radiologists designated by the Société Française d'Imagerie Thoracique (French Chest Imaging Society) **[19]**.

Clinical radiologists forwarded a photocopy of their findings together with a CD-Rom or a duplicate of the examinations performed. Selected criteria for considering a subject as presenting pulmonary nodule(s) were mention of "nodule with a diameter superior to 5mm" **[15]**, or nodules noted as *"requiring surveillance"* or *"of a suspicious nature"* in chest CT scan initial diagnostic report.

Completing the initial radiologist's reading, all available CT-scan examinations underwent standard double reading (and triple reading in the case of disagreement) focused on benign asbestos-related abnormalities, by a panel of 7 expert radiologists. Standardized readings were blind to the initial interpretation by the radiologist having performed the examination, and to the level of asbestos exposure.

Collection of incidence and mortality data

This data collection relied on a dual effort:

- firstly, the identification of requests for coverage by the French social security fund for long-term cancer sufferers ("ALD30"), and for compensation of occupational affections consecutive to the inhalation of asbestos dust, specifically lung cancer and primary tumours of the pleura. The last search was performed in February 2009.

- secondly, based on a mortality study, via research and identification of deceased subjects after consultation of the RNIPP (French National Register of Physical Persons), then by determining the cause of death via consultation of the INSERM's CépiDC registry, in order to compare mortality among subjects from the cohort with that of a reference population comprising national populations and following an indirect standardisation process. This research was conducted once during the study period, late 2009, in order to obtain mortality results covering the longest possible period with regard to the date of inclusion in the cohort.

The project was approved by the Hôpital Cochin CCPPRB (Ethics Committee), and all included patients signed informed consent before participating in the study.

Statistical analysis method

Qualitative variables were compared using the "Chi-square test" or using "Fisher test" to compare proportions, and quantitative variables using the "Student test". Significant probability for these tests was defined as: $p \leq 0.05$.

The incidences of lung cancer and pleural mesothelioma were calculated from 1st January 2003 to 1st February 2009. The observed number of cases was then compared to the expected number, when the age structured incidence of the general French population estimated thanks to FRANCIM cancer registries network **[20]** was applied to the study population, via Standardised Incidence Ratios (SIR). Mortality rates were calculated from 1st January 2003 to 31st December 2009, using the Standardised Mortality Ratios (SMR) **[21]**. Finally, comparison of incidence rate and mortality rate in both healthy subjects and those presenting with nodules was performed via the Comparative Morbidity Figure (CMF).

RESULTS

The number of subjects for whom chest CT scan was considered as exploitable and for whom we had informative data on the presence or the absence of pulmonary nodules was 5,662.

The number of person-years calculated from our population was about 26,000 for incidence data, and about 30,500 for mortality data.

Among the 5,662 subjects in our cohort, 933 (16.5%) were classified in the group of subjects with pulmonary nodules identified by the initial radiologist, as defined above. More than 95% of the study population had a latency period in excess of 30 years, and only 0.67 % of the subjects had a latency period under 20 years.

Table 1 presents the characteristics of subjects included in our study for whom no pulmonary nodule, as previously defined, was observed, and those of subjects presenting with one or several mentioned pulmonary nodule(s). No significant difference was observed between these two groups, with regard to sex, age, smoking status, region of origin, asbestos exposure, presence of pleural plaques, asbestosis and/or isolated interstitial opacities on CT scan.

Table 2 presents asbestos related diseases by the four exposure categories (i.e. "low", "low intermediate", "high intermediate" and "high"). A significant relationship was observed between increasing asbestos exposure categories and prevalence of pleural plaques. In contrast, no relationship was observed between increasing asbestos exposure categories and frequency of nodules, lung cancer or mesothelioma. This relationship was at the borderline of significance for asbestosis, a low number of subjects presenting with this disease.

Table ~~2~~3 illustrates incidence data concerning primary lung cancers and pleural mesotheliomas, based on lung cancer and pleural mesothelioma requests for ALD30 long-term medical coverage or occupational disease compensations. For both sexes combined, there was a significant over-incidence of primary lung cancer among subjects presenting with one or several pulmonary nodule(s), SIR being 1.95 [1.22; 2.95] compared to French national incidence. Significant over-incidence of pleural mesothelioma was also observed in among these subjects, SIR being 11.88 [3.20; 30.41].

With regard to the analysis of mortality risk by lung cancer and pleural mesothelioma, as illustrated in **table 4**, a significantly high mortality risk by pleural mesothelioma was observed in subjects presenting with one or several pulmonary nodule(s), SMR being 7.89 [1.63-23.07].

As illustrated in **table 5**, comparison between subjects presenting with pulmonary nodule(s), and subjects without nodules, revealed that the incidence of lung cancer was significantly higher in subjects presenting with nodule(s), CMF being 4.08 [1.06; 15.77]. Yet, the incidence of pleural mesothelioma, the mortality risk associated with this type of cancer, and the mortality risk associated with lung cancer were not significantly higher in subjects presenting with nodules (CMF respectively 4.05 [0.72; 22.71], 2.48 [0.45; 13.72] and 2.58 [0.91; 7.33]).

DISCUSSION

The prevalence of pulmonary nodules noted in chest CT findings by clinical radiologists was 16.5%, i.e. 933 subjects. This figure is lower than that observed in the ELCAP study, also based on the use of helical CT scan, in which 233 subjects from a total population of 1,000 presented with a pulmonary nodule, i.e. a prevalence of 23.3%. However, suspect nodules mentioned as measuring over 5mm only as in our study concerned 42% of all nodules detected in ELCAP study, i.e. 9.8% of the total study population.

It is noteworthy that the ELCAP study population was not selected on occupational exposure to asbestos, but mainly on tobacco consumption, hence rendering difficult any direct comparison with the subjects included in this study and those in our own study **[5-7]**. Nevertheless, if we consider studies conducted specifically on populations of workers exposed to asbestos, the prevalence of pulmonary nodules is similar to that observed in our study (18.5% and 17.6% for Tiitola et al. **[22]** and Roberts et al. **[23]**, respectively). A

synergistic effect between exposure to asbestos and tobacco consumption in the occurrence of lung cancer has been reported in the literature **[24, 25]**. Consequently, we sought to identify, in our study population, the potential interaction between asbestos exposure and smoking with regard to lung cancer risk: we created a variable combining tobacco consumption categories (smokers and ex-smokers, non-smokers) and asbestos exposure levels (low, low intermediate, high intermediate and high), comprising 8 modalities. The "non-smoker with low exposure" category was considered as the reference. In this model, no significant interaction between tobacco status and asbestos exposure, for lung cancer, was observed (data not shown).

This study confirms that the diagnosis of pulmonary nodule(s) by the examining radiologist during CT scan, is not associated with asbestos cumulative exposure. As expected, there was a significant relationship between increasing asbestos exposure categories and the presence of pleural plaques. In contrast, no relationship was observed between increasing asbestos exposure categories and frequency of nodules, lung cancer or mesothelioma. This relationship was at the borderline of significance for asbestosis, probably due to the low number of subjects presenting with this disease, resulting in limited statistical power.

Furthermore, comparison between subjects presenting with or without pulmonary nodule(s) on CT scan, revealed, as expected, that the incidence of lung cancer was significantly higher in subjects presenting with nodules. In contrast, the incidence of pleural mesothelioma and the mortality risk associated with this type of cancer were not significantly higher in subjects presenting with nodules compared to subjects without nodules. These results are not surprising when considering the natural history of this type of cancer; however the low number of subjects for this affection limits the statistical power of this analysis. Incidence data concerning primary lung cancers and pleural mesotheliomas in our population study were based on requests for French social security fund, whereas data concerning expected cases were based on French national incidence relying on cancer registries. Comparison between

ALD and occupational disease data with those from cancer registries in the 4 regions with registries included in our study shows consistency in the collection of data on cases of primary lung cancer and incident pleural mesothelioma. Furthermore, the regional cancer mortality data used to calculate SMRs also proved to be comparable to those obtained when using national mortality data, generating no substantial modification to our results (indeed, for lung cancer SMR=0.78[0.36-1.49] and for pleural mesothelioma, SMR=7.32[1.51-21.38], using regional cancer mortality data).

No significant difference was observed according to the level of asbestos exposure between populations presenting with one or several nodule(s) detected on CT scan and subjects without nodules. Consequently, no dose-response relationship was demonstrated between the level of exposure to asbestos and the onset of pulmonary nodules. Therefore, our study offers no argument in favour of specific surveillance modalities with regard to these nodules based on estimated cumulative asbestos exposure.

Our study is original for several reasons. Firstly, the precise re-evaluation of asbestos exposure by industrial hygienists enabled individual cumulative exposure indexes (CEI) to be calculated. Secondly, a standardised re-reading (independent double, or even triple reading in the case of disagreement) by a committee of expert radiologists, was implemented, in order to determine the existence or the absence of tomodensitometric images of pleural or pulmonary fibrosis. Standardized readings were blind to the initial interpretation by the radiologist having performed the examination, and to the level of asbestos exposure. However, the diagnosis of pulmonary nodule(s), considered in our study, was not based on this standardised double reading, but exclusively on findings noted by clinical radiologists.

Despite the consequential population in the studied cohort (5,662 subjects), it should be noted that this population comprised exclusively voluntary individuals prepared to undergo repeated examinations, hence representing a potential recruitment bias. The studied cohort can

consequently not be considered as representative of the entire population of retired subjects exposed to asbestos.

Continued epidemiological monitoring of the entire cohort from the experimental programme should offer the opportunity to complete this initial analysis. A second campaign involving systematic CT scans is shortly due to be implemented in the same population; it will be of importance to develop a grid for reading CT scans integrating the presence of pulmonary nodules, for all clinical radiologists participating in the programme; it would also be constructive to test various measures to ensure that medical surveillance is more closely in keeping with recommendations by the Fleischner Society **[26]**, in the case of acknowledged pulmonary nodules on CT images.

CONCLUSION

In evaluating the experimental programme carried out in France for the post-occupational follow-up of individuals having been exposed to asbestos, it was necessary to quantify the significance to be afforded to the diagnosis of pulmonary nodule(s) by the clinical radiologist implementing the chest CT scan. As expected, particular attention should consequently be paid to such a mention, even when post-occupational CT scan screening mainly aims at diagnosing benign asbestos-related diseases. Indeed, despite methodological limitations, this study confirms the expected excess in lung cancer among subjects presenting with pulmonary nodules in the radiologist's diagnostic report, and demonstrates the absence of relationship between these nodules and the level of cumulative asbestos exposure. Consequently, our study offers no argument in favour of specific surveillance modalities with regard to these nodules based on estimated cumulative asbestos exposure. Within the context of current reflection on improvements in the post-occupational medical surveillance of asbestos-exposed

individuals, a standardisation of the performance and of the interpretation of chest CT scans appears mandatory.

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CONFLICT OF INTEREST

They authors declare that they have no competing interests, or other interests that might be perceived to influence the results and discussion reported in this paper.

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TABLES

Table 1 – Comparison of the characteristics of subjects presenting with one or several pulmonary nodule(s) mentioned by the radiologist on chest CT scan and subjects with no observed nodules

	Subjects with reported nodules (%)	Subjects without reported nodules (%)	p	Total
Total population	933 (16.5)	4,729 (83.5)	-	5,662
Sex:				
- Men	888 (16.4)	4,523 (83.6)	**NS***	5,411
- Women	45 (17.9)	206 (82.1)		251
Mean age in years (SD**)	62.98 (5.87)	63.03 (5,76)	**NS**	63.02 (5.78)
Tobacco consumption category				
- non-smoker	228 (15.5)	1,246 (84.5)		1,474
- ex-smoker	553 (16.4)	2,816 (83.6)	**NS**	3,369
- smoker	73 (18.2)	327 (81.7)		400
- data not available	79 (18.8)	340 (81.1)		419
Region of origin				
- Aquitaine	156 (16.7)	777 (83.3)		933
- Rhône-Alpes	416 (16.1)	2,163 (83.9)		2,579
- Upper Normandy	209 (16.9)	1,026 (83.1)	**NS**	1,235
- Lower Normandy	152 (16.6)	763 (83.4)		915
Level of asbestos exposure expressed as the CEI IH in exposure units x years				
-]0 – 2.5[	160 (17.1)	777 (82.9)		937
- [2.5 – 8.03[	176 (16.3)	903 (83.7)	**NS**	1,079
- [8.03 -31[	204 (16.7)	1,014 (83.3)		1,218
- [31 – 69.31[	202 (17.3)	965 (82.7)		1,167
- 69.31 or more	191 (15.1)	1,070 (84.9)		1,261
Presence of pleural plaques upon double (or triple) reading of CT scans:				
- Yes	178 (15.9)	942 (84.1)		1,120
- No	742 (16.7)	3,693 (83.3)	**NS**	4,435
- Data not available	13 (12.1)	94 (87.9)		107
Presence of asbestosis upon double (or triple) reading of CT scans:				
- Yes	4 (11.1)	32 (88.9)		36
- No	907 (16.7)	4,537 (83.3)	**NS**	5,444
- Data not available	22 (12.1)	160 (87.9)		182
Presence of isolated interstitial opacities upon double (or triple) reading of CT scans:				
- Yes	4 (11.1)	32 (88.9)	**NS**	36
- Undetermined/Other syndrome	64 (17.4)	303 (82.6)		367
- No	843 (16.6)	4,234 (83.4)		5,077
Data not available	22 (12.1)	160 (87.9)		182

* NS = Non Significant
** SD = Standard Deviation

Table 2 – Description of asbestos-related diseases in the four exposure categories.

	Level of asbestos exposure				p	Total
	Low (passive)	Low-intermediate	High-intermediate	High		
Reported nodules: n (%)						
- Yes	53 (16.9)	229 (16.1)	414 (17.3)	237 (15.4)	0.454	933
- No	260 (83.1)	1,194 (83.9)	1,977 (82.7)	1,298 (84.6)		4,729
Pleural plaques: n (%)						
- Yes	28 (9.0)	155 (10.9)	416 (17.4)	521 (34.9)	**<0.001**	1,120
- No	278 (88.8)	1,243 (87.3)	1,917 (80.2)	997 (64.0)		4,435
- Data not available	7 (2.2)	25 (1.8)	58 (2.4)	17 (1.1)		107
Asbestosis: n (%)						
- Yes	0 (0.0)	7 (0.5)	15 (0.6)	14 (0.9)	0.056	36
- No	304 (97.1)	1,376 (96.7)	2,281 (95.4)	1,483 (96.6)		5,444
- Data not available	9 (2.9)	40 (2.8)	95 (4.0)	38 (2.5)		182
Lung cancer: n (%)						
- Yes	2 (0.6)	12 (0.8)	18 (0.8)	18 (1.2)	0.537	50
- No	311 (99.4)	1,411 (99.2)	2,373 (99.2)	1,517 (98.8)		5,612
Mesothelioma: n (%)						
- Yes	0 (0)	0 (0)	6 (0.3)	5 (0.3)	0.162	11
- No	313 (100)	1,423 (100)	2,385 (99.7)	1,530 (99.7)		5,651

Table 3 – Number of observed and expected lung and pleural mesothelioma from 2003 to 2009 in subjects presenting with nodules mentioned by the radiologist on chest CT scan (Reference population: population of France)

	Subjects with nodules N= 933		
Anatomic site	Obs (N)	Exp (N)	SIR [95% CI*]
Lung	22	11.03	1.95 [1.22;2.95]
Pleural Mesothelioma	4	0.34	11.88 [3.20;30.40]

* SIR = Standardised Incidence Ratio
** CI = Confidence Interval

Table 4 – Mortality rate of observed and expected lung and pleural mesothelioma from 2003 to 2009 in subjects presenting with nodules mentioned by the radiologist on chest CT scan (Reference population: population of France)

	Subjects with nodules N= 933		
Anatomic site	Obs (N)	Exp (N)	SMR* [95% CI**]
Lung	9	11.33	0.79 [0.36-1.51]
Pleural Mesothelioma	3	0.38	7.89 [1.63-23.07]

* SMR = Standardised Mortality Ratio
** CI = Confidence Interval

Table 5 – Comparison of the incidence of primary lung cancer and pleural mesothelioma and of mortality associated with this type of cancers among subjects presenting with one or several pulmonary nodule(s) mentioned by the radiologist on chest CT scan, in comparison with subjects with no nodule.

	CMF* (nodule+/nodule-) [95% CI**]
Incidence of lung cancer	4.08 [1.06;15.77]
Incidence of pleural mesothelioma	4.05 [0.72;22.71]
Mortality by lung cancer	2.58 [0.91;7.33]
Mortality by pleural mesothelioma	2.48 [0.45;13.72]

* CMF = Comparative Morbidity Figure

** CI = Confidence Interval