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Pulmonary carcinoid tumors and asbestos exposure

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Abstract

Objectives

The hypothesis that asbestos exposure may have more specific associations with particular histological types of lung cancer remains controversial. The aim of this study was to analyze the relationships between asbestos exposure and pulmonary carcinoid tumors.

Methods

A retrospective case-control study was conducted in 28 cases undergoing surgery for pulmonary carcinoid tumors and aged over 40 years, and in 56 controls with lung cancer of a different histological type, matched for gender and age, from 1994 to 1999, recruited in 2 hospitals in the region of Paris. Asbestos exposure was assessed via expertise of a standardized occupational questionnaire and mineralogical analysis of lung tissue, with quantification of asbestos bodies (AB).

Results

Definite asbestos exposure was identified in 25% of cases and 14% of controls (ns). Cumulative asbestos exposure was significantly higher in cases than in controls ($p<0.05$), and results of the quantification of AB tended to be higher in cases than in controls (24% and 9% had more than 1,000 AB/g dry lung tissue, respectively, $p=0.09$). Mean cumulative smoking was lower in cases than in controls ($p<0.05$).

Conclusion

This study argues in favor of a relationship between asbestos exposure and certain pulmonary carcinoid tumors.

MESH Keywords Adult ; Aged ; Asbestos ; toxicity ; Carcinoid Tumor ; etiology ; pathology ; Case-Control Studies ; Female ; Humans ; Lung Neoplasms ; etiology ; pathology ; Male ; Middle Aged ; Occupational Diseases ; etiology ; pathology ; Occupational Exposure ; adverse effects ; analysis ; Paris ; Questionnaires ; Retrospective Studies

Author Keywords asbestos ; lung cancer ; pulmonary carcinoid tumor ; occupational exposure

INTRODUCTION

The malignant pathologies linked to asbestos exposure include pleural, peritoneal, pericardic and/or testicular tunica vaginalis mesothelioma, lung cancers, together with ovarian and laryngeal cancers (American Thoracic Society, 2004; Straif et al., 2009).

In France, lung cancer is the leading cause of mortality by cancer among men and current estimates suggest that asbestos is responsible for 5% to 15% of lung cancers (Expertise collective INSERM, 1997; Boffetta et al., 2010; Guida et al., 2011). No clinical,

histological, topographical or radiological characteristic differentiates lung cancer linked to asbestos exposure from other lung cancers (Ives et al.,1983; Lee et al., 1998; Mollo et al., 2002). Among these cancers, typical or atypical pulmonary carcinoid tumors are considered as low-grade malignant neoplasms comprised of neuroendocrine cells. These pulmonary carcinoid tumors account for 1 to 2% of all lung tumors, hence the relative rarity of studies on this type of tumor (Galofre et al., 1964; Godwin et al., 1977; Blondal et al., 1980; McCaughan et al., 1985; Fink et al., 2001). A male predominance (2/1) is observed for atypical carcinoid tumors (Quaedvlieg et al., 2001). Typical carcinoid tumors, which represent 90% of pulmonary carcinoid tumors, are characterized by neuroendocrine histological differentiation, no tumoral necrosis and rare mitoses (Davila et al., 1993; Travis et al., 2004). Age at diagnosis is generally between 35 and 50 years, whereas atypical carcinoid tumors, characterized by neuroendocrine histological differentiation, tumoral necrosis and an increase in mitotic activity, occur in older subjects, generally aged between 55 and 60 years (Struyf et al., 1995; Arrigoni et al., 1972; Thomas et al., 2001). Although certain studies suggest that tobacco smoking could be a risk factor for atypical pulmonary carcinoid tumors (McCaughan et al., 1985; Fink et al., 2001; Valli et al., 1994; Kayser et al., 1996) the etiology of carcinoid tumors, pulmonary or not, still remains unknown (Hemminki et al., 2001; Modlin et al., 2003). The aim of our study was to evaluate occupational asbestos exposure among subjects presenting with pulmonary carcinoid tumor, in order to analyze the relationships between asbestos and this type of lung cancer.

METHODS

Study population

A retrospective case-control study was conducted in subjects undergoing surgery for lung cancer, recruited in 2 hospitals in the Paris region from 1994 to 1999. Cases were subjects presenting with pulmonary carcinoid tumors and having volunteered to answer an occupational questionnaire (Group 1). A group of controls presenting with lung cancer of a different histological type was selected among subjects (Group 2), matched for gender and age, more or less 3 years. Indeed, for each case, 2 controls were randomly identified among files of subjects undergoing surgery for incident primary lung cancer (other than carcinoid), in the same hospitals and during the same period; these subjects also volunteered to answer an occupational questionnaire. To be eligible, cases and controls had to live in the Paris region,

Due to the young age profile of certain subjects suffering from carcinoid tumors and considering the latency phenomenon associated with carcinogenesis, it appeared appropriate to conduct the case-control study only in cases aged over 40 (Group 1A).

Asbestos exposure was assessed via expertise of a standardized occupational questionnaire and mineralogical analysis of lung tissue, with quantification of asbestos bodies (AB).

Lung cancer controls included 30 (53.5%) adenocarcinomas, 13 (23.2%) epidermoid carcinomas, 9 (16%) large cell carcinomas, 4 (7.3 %) other or mixed histological types.

This study was part of a larger project approved by the CCPPRB (Comité Consultatif pour la Protection des Personnes se prêtant à des Recherches Biomédicales) Créteil-Henri Mondor (authorization n°94-052). All patients received information on the study and gave their written informed consent.

Data collection

Demographic data, asbestos exposure and tobacco consumption

For each included subject, date of birth, gender and tobacco status were collected. Subjects were classified into three categories according to tobacco consumption: smokers, ex-smokers (defined as those having stopped smoking since at least one year), and non-smokers. Age at beginning of tobacco smoking, duration and cumulative tobacco smoking in pack years were also collected.

Evaluation of individual asbestos exposure was performed using data from a standardized questionnaire describing all job positions occupied throughout the individual's occupational history. The evaluation of each job period of a duration in excess of 6 months was classified according to the probability, intensity (i.e. estimated level of exposure to asbestos, in f/ml, based on known airborne levels in similar situations) and frequency of exposure to asbestos. 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 (Iwatsubo et al., 1998). Categories of intensity were established using the following semiquantitative scale - probability of exposure: not exposed, possible, probable, 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 fiber/ml), moderate (1–2 fibers/ml), high (2–10 fibers/ml), very high (>10 fibers/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, moderate=1, high=10 and very high=100. The CEI (Cumulative Exposure Index) is the life-time sum of the products of probability, frequency, intensity and duration for each job period expressed in unit exposure x years. Expertise of this occupational questionnaire was performed by a practitioner specialized in occupational diseases, blinded to case/control status.

A fragment of tumor-free dry lung tissue, sampled during lobectomy or pneumonectomy, was used for mineralogical analysis performed by the Laboratoire d'Etude des Particules Inhalees de la Ville de Paris (LEPI). Technical modalities for analysis were the same as those routinely used by the laboratory (Pairon et al., 1994). Each mineralogical analysis was performed for samples of at least 10 mg of dry lung tissue. AB concentrations were expressed per gram of dry tissue and significant lung retention of AB was defined in our laboratory as more than 1,000 AB per gram of dry lung tissue. This value was chosen as the cut-off point since it has been considered as indicative of a nontrivial exposure to asbestos (Sebastien et al., 1988).

Diagnosis of cases and controls

Histological classification of pulmonary carcinoid tumors was assessed using pathologic examination after lung tumor resection. Typical and atypical pulmonary carcinoid tumors were differentiated according the IASCL (International Association for the Study of Lung Cancer) 2004 classification (Travis et al., 2004).

Statistical analysis

Qualitative, i.e. categorical variables were compared using the "Chi-square test" or the "Fisher test" to compare proportions, and quantitative variables using the "Student's T test" or "Non parametric Wilcoxon test". Significant probability for these tests was defined as: $p \leq 0.05$.

RESULTS

Thirty-four subjects presenting with pulmonary carcinoid tumors were recruited (28 were aged over 40 years, Group 1A), and 56 controls aged over 40 years presenting with a different histological type of lung cancer.

The characteristics of these populations are described in table 1.

Among the 34 cases, 25 (74%) presented with a typical pulmonary carcinoid tumor. Mean age was 49.5 years (standard deviation, SD= 15.8 years). The mean age of the 9 subjects presenting with an atypical pulmonary carcinoid tumor was 55 years (SD=14.4 years). No significant difference was observed between these 2 populations concerning age, gender, tobacco consumption and cumulative asbestos exposure (table 2).

Among cases for which mineralogical analysis was performed, 5 showed significant retention of asbestos bodies (≥ 1,000 AB per gram of dry lung tissue).

All controls had mineralogical analysis of lung tissue. Five analyses (9%) showed significant retention of asbestos bodies.

We compared the characteristics of the 28 cases aged over 40 years with controls (Table 3). Definite asbestos exposure was identified in 25% of cases and 14.3% of controls (NS). Cumulative exposure to asbestos (mean and median) was higher in cases aged over 40 years than in controls ($p<0.05$), and results of the quantification of AB tended to be higher in cases than in controls (24% and 9% had more than 1,000 AB/g dry lung tissue, respectively, $p=0.09$). Mean cumulative smoking was lower in cases than in controls ($p<0.05$). For subjects with conformed asbestos exposure, the mean latency period after the beginning of such exposure was 44 years (SD=6.16) for cases and 48 years (SD=6.63) for controls. For subjects with mineralogical analysis ≥ 1,000 AB per gram of dry lung tissue, this mean latency was roughly similar (43 years (SD=6.82) for cases and 44 years (SD=6.74) for controls).

DISCUSSION

Our results are in favor of a relationship between occupational asbestos exposure and certain pulmonary carcinoid tumors. Indeed, we observed that cumulative exposure to asbestos evaluated by a practitioner specialized in occupational diseases was higher in cases of carcinoid tumor aged over 40 years than in controls, and results of the quantification of AB tended to be higher in cases than in controls. In contrast, mean cumulative smoking was lower in cases than in controls ($p<0.05$).

There was no significant difference between cases and controls with regard to age and gender, indicating a satisfactory match between cases and controls. Mean age of cases at diagnosis was 51.1 years, which is consistent with scientific data concerning pulmonary carcinoid tumors (McCaughan et al., 1985; Struyf et al., 1995; Arrigoni et al., 1972; Thomas et al., 2001). Distribution of typical and atypical pulmonary carcinoid tumors and their characteristics (age, gender, and tobacco consumption) were also similar to previously published data (Fink G, et al., 2001; Struyf et al., 1995; Arrigoni et al., 1972; Thomas et al., 2001; Paillas et al., 2004; Thomas et al., 2008).

Since lung cancer may be asbestos-related, the choice of subjects with lung cancer of a different histological type as controls, is subject for debate. Indeed, it may have been more appropriate to choose controls among subjects with diseases not known to have any relationship with asbestos exposure. Nevertheless, our aim was to select subjects for whom information on asbestos exposure was

available, via both data from the occupational questionnaire and mineralogical analysis of asbestos bodies in lung tissue. Similarly to cases, they had to live in the Paris region to allow easy access for an interview for the occupational questionnaire. The choice of possible populations consequently conducted to lung cancer patients. This bias was conservative and the significantly higher cumulative asbestos exposure observed in cases compared to controls enhances the plausibility of a relationship between asbestos exposure and pulmonary carcinoid tumors.

The hypothesis that certain risk factors for lung cancer, such as asbestos exposure, may have more specific associations with particular histological types still remains controversial. Occupational asbestos exposure associated with lung cancer has been suspected to be more specifically associated with adenocarcinoma; however, authors have reported that these findings are not conclusive (Henderson, 1997; Karjalainen et al., 1994; Raffn et al., 1996; Mollo et al., 1995). In the study conducted by Raffn *et al.* in a cohort of asbestos cement workers, the excess risk of lung cancer was shared almost equally between different histological types of lung cancer during the first 25 years after the start of employment, whereas the risk of adenocarcinoma increased after this point (Raffn et al., 1996). Nevertheless, another study demonstrated an excess risk of other histological types of lung cancer in subjects having been exposed to asbestos (De Klerk et al., 1996). Indeed, in the study conducted by De Klerk *et al.*, the incidence of both squamous cell carcinoma and adenocarcinoma of the lung was higher in subjects with the highest levels of exposure to crocidolite and, after adjustment for smoking characteristics, the increase in incidence of lung cancer with increasing exposure to crocidolite was greater for squamous cell carcinoma than for adenocarcinoma. A recent study analyzed possible associations between adenocarcinoma and gender, age, smoking characteristics and selected occupational carcinogens, such as asbestos, in relation to other histological types (Paris C et al., 2010). A total of 1,493 subjects presenting with lung cancer, including 489 cases of adenocarcinoma were included. No association was observed between adenocarcinoma and asbestos exposure. To date, no specific agent, such as asbestos, has been identified as being particularly significant for a specific histological type of lung cancer (Henderson, 1997) and, to our knowledge, only a few authors have studied the relationships between asbestos exposure and carcinoid tumors (Fisseler-Eckhoff et al., 1998; Neumann et al., 2008). In a descriptive study previously conducted in 1998 in Germany (Fisseler-Eckhoff et al., 1998), 28 subjects undergoing surgery for pulmonary carcinoid tumor were studied for occupational asbestos exposure and retention of AB. The authors reported that there was no evidence in support of the correlation between increased chronic asbestos load of the lungs and the development of typical carcinoid tumors of the lung. However, this study included no controls. In a further German study, based on the examination of lung tissue from 108 patients with carcinoid tumors, the authors failed to demonstrate a higher incidence of carcinoid tumors in patients exposed to asbestos, since no higher incidence of carcinoid tumors (1.3 %) in the population of the German mesothelioma register was observed, compared to the incidence in the population of all lung carcinomas (1–2%) (Neumann et al., 2008).

One of our study's limitations is the low number of cases, which impacts its statistical power. This was due to the fact that pulmonary carcinoid tumors are rare. Furthermore, eligible cases recruited in this series were all consecutive cases undergoing surgery in 2 hospitals and living in the Paris region.

Our study's strengths include the analysis of asbestos exposure by a practitioner specialized in occupational diseases, which enabled us to quantify the probability of asbestos exposure and cumulative asbestos exposure for each subject included in the cohort, and the mineralogical analysis of dry lung samples, which enabled us to precisely quantify the retention of asbestos bodies of cases and controls.

CONCLUSION

This study argues in favor of a relationship between occupational asbestos exposure and certain pulmonary carcinoid tumors. These results prompt the continuation of research in this field, with the use of additional controls free of lung cancer, in order to confirm the observed trends. Since the distribution of histological types of lung cancer can reflect underlying biological mechanisms, these results - should they be formally established - may suggest the need to study the molecular pathways involved in lung cancer and asbestos exposure.

The subject of this paper has only very rarely been previously investigated in the literature; however, the study of a potential link between asbestos and pulmonary carcinoid tumors is of major interest, both from a scientific and medico-legal point of view, with regard to modalities concerning the potential compensation for associated cases of cancer. Furthermore, considering the results of our study, clinicians should pay particular attention to the need to systematically investigate for occupational asbestos exposure in subjects presenting with any histological type of lung cancer, including pulmonary carcinoid tumor, given the potential for individual compensation as an occupational disease.

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Footnotes:

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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Table 1
Characteristics of cases and controls.

	Cases (Group 1)		Controls (Group 2)
	Total	**Age>40 years (Group 1A)**	**Age>40 years**
Number of subjects	34	28	56
Mean age (years) (SD)	51.1 (15.4)	56.6 (10.3)	57.1 (10.1)
Gender:			
- Male: n (%)	16 (47.1%)	14 (50%)	28 (50%)
- Female: n (%)	18 (52.9%)	14 (50%)	28 (50%)

SD: Standard deviation

Table 2

Comparison between subject groups presenting either with typical pulmonary carcinoid tumor or atypical pulmonary carcinoid tumor.

	Typical pulmonary carcinoid tumors	Atypical pulmonary carcinoid tumors	p-value[a]
Number of subjects	25	9	
Gender			
- Male: n (%)	11 (44.0)	5(56.0)	NS
- Female: n (%)	14 (56.0)	4 (44.0)	
Mean age (years)			
- Mean (SD)	49.5 (15.8)	55 (14.4)	
- Median	53	59	NS
- Range [min-maxi]	[19–77]	[22–71]	
Smoking status			
- non-smokers: n (%)	8 (32.0)	5 (55.5)	
- current smokers: n (%)	15 (60.0)	2 (22.25)	NS
- former smokers: n (%)	2 (8.0)	2 (22.25)	
Cumulated tobacco smoking in pack years: Mean (SD)	24.8 (30.7)	30 (29.7)	NS
Probability of asbestos exposure			
- definite: n (%)	4 (16.0)	3 (33.0)	
- probable: n (%)	1 (4.0)	0	NS
- possible: n (%)	1 (4.0)	2 (22.0)	
- null: n (%)	19 (76.0)	4 (44.0)	
Cumulative exposure index to asbestos (unit of exposure x years) in exposed subjects			
- Mean (SD)	4.9 (5.8)	1.9 (1.7)	NS
- Median	2.9	2.3	
- Range [min-maxi]	[0.01–14.30]	[0.10–3.90]	
Mineralogical analysis [b] **)**			
- ≥1000 AB/g: n (%)	4 (23.5)	1 (12.5)	NS
- < 1000 AB/g: n (%)	13 (76.5)	7 (87.5)	

AB: Asbestos Bodies
NS: Non Significant
SD: Standard Deviation
a : Chi-square or Fisher test
b Analysis not available in 9 cases because of insufficient material

Table 3

Comparison of cases for demographic data, smoking and occupational exposure to asbestos, and controls.

	Group 1A Pulmonary carcinoid tumors aged over 40 years	Group 2 Lung cancer controls	p-value[a]
Number of subjects	28	56	
Gender			
- Male: n (%)	14 (50)	28 (50.0)	NS
- Female: n (%)	14 (50)	28 (50.0)	
Mean age (SD) (years)	56.6 (10.3)	57.1 (10.1)	NS
Smoking status			NS
- non-smokers: n (%)	9 (32.1)	8 (14.3)	
- former and current smokers: n (%)	19 (67.9)	48 (85.7)	
Cumulated tobacco smoking in pack-years: mean (SD)	28.2 (30.5)	43.2 (21.1)	**<0.05**
Probability of asbestos exposure			
- definite: n (%)	7 (25.0)	8 (14.3)	
- probable: n (%)	1 (3.6)	2 (3.6)	NS
- possible: n (%)	3 (10.7)	8 (14.3)	
- null: n (%)	17 (60.7)	38 (67.8)	
Cumulative exposure index to asbestos (unit of exposure x years) in exposed subjects			
- Mean (SD)	3.5 (4.5)	0.3 (0.5)	**<0.05**
- Median	2.28	0.22	
- Range [min-maxi]	[0.01–14.25]	[0.13–2.18]	
Mineralogical analysis [b]			
- ≥ 1000 AB/g: n (%)	5 (23.8)	5 (8.9)	0.09
- < 1000 AB/g: n (%)	16 (76.2)	51 (91.1)	

AB: Asbestos Bodies
NS: Non Significant
SD: Standard Deviation
[a] : Chi-square or Fisher test
[b] Analysis not available in 7 cases because of insufficient material