Pulmonary Carcinoid Tumors and Asbestos Exposure

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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 >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 two 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 >1000 AB per gram dry lung tissue, respectively, P = 0.09). Mean cumulative smoking was lower in cases than in controls (P < 0.05).

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

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

INTRODUCTION

The malignant pathologies linked to asbestos exposure include pleural, peritoneal, pericardic and/or
testicular tunica vaginalis mesothelioma, and 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%–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 composed of neuroendocrine cells. These pulmonary carcinoid tumors account for 1–2% of all lung tumors, hence the relative rarity of studies on this type of tumor (Galafre et al., 1964; Godwin and Brown, 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 (Arrigoni et al., 1972; Struyf et al., 1995; 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; Valli et al., 1994; Kayser et al., 1996; Fink et al., 2001), the etiology of carcinoid tumors, pulmonary or not, still remains unknown (Hemminki and Li, 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 two 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, and more or less than 3 years. Indeed, for each case, two 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 were required to live in the Paris region, where lung tumor resection had been performed, in order to complete an occupational questionnaire with assistance from a trained interviewer (blind to the subject’s case or control status) after hospitalization.

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 >40 years (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, and 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 prétendant 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 1 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 fibers per milliliter, based on known air-
borne levels in similar situations), and frequency of
exposure to asbestos. Since no measurements of air-
borne levels were available, all estimations of expo-
sure 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, and definite; fre-
quency: sporadic (<5% of working time), irregular
(5–50% of working time), and continuous (>50% of
working time); and intensity: low (<1 fiber ml⁻¹),
moderate (1–2 fibers ml⁻¹), high (2–10 fibers ml⁻¹),
and very high (>10 fibers ml⁻¹). Weighting factors
were attributed to each exposure category in
order to calculate an exposure index—probability:
null = 0, possible = 0.5, and definite = 1; fre-
quency: sporadic = 0.025, irregular = 0.25, and con-
tinuous = 0.75; and intensity: low = 0.1, mod-
erate = 1, high = 10, and very high = 100. The cu-
mulative exposure index is the lifetime sum of the
products of probability, frequency, intensity, and
duration for each job period expressed in unit ex-
posure × years. Expertise of this occupational ques-
tionnaire 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 Inhalées de la Ville de Paris.
Technical modalities for analysis were the same as
those routinely used by the laboratory (Pailon et al.,
1994). Each mineralogical analysis was performed
for samples of at least 10 mg of dry lung tissue. AB
concentrations were expressed as per gram of dry tis-
 sue and significant lung retention of AB was defined
in our laboratory as >1000 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 non-
trivial exposure to asbestos (Sebastien et al., 1988).

Diagnosis of cases and controls. Histological clas-
sification of pulmonary carcinoid tumors was as-
essessed using pathologic examination after lung
tumor resection. Typical and atypical pulmonary car-
inoid 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 com-
pared using the ‘Student’s t-test’ or ‘Non-parametric
Wilcoxon test’. Significant probability for these tests
was defined as P ≤ 0.05.

RESULTS

Thirty-four subjects presenting with pulmonary car-
inoid tumors were recruited (28 were aged >40 years,
Group 1A), and 56 controls aged >40 years pre-
senting with a different histological type of lung
cancer. No eligible participants refused to partici-
pate. 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 nine subjects present-
ing an atypical pulmonary carcinoid tumor was 55
years (SD = 14.4 years). No significant difference
was observed between these two populations con-
cerning age, gender, tobacco consumption, and
cumulative asbestos exposure (Table 2).

Among cases for which mineralogical analysis was
performed, five showed significant retention of AB
(≥1000 AB per gram of dry lung tissue). All controls
had mineralogical analysis of lung tissue. Five analy-
ses (9%) showed significant retention of AB.

We compared the characteristics of the 28 cases
aged >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 >40 years than in controls (P < 0.05), and re-
results of the quantification of AB tended to be higher
in cases than in controls (24 and 9% had >1000 AB
per gram dry lung tissue, respectively, P = 0.09).
Mean cumulative smoking was lower in cases than
in controls (P < 0.05). For subjects with confirmed as-
bestos exposure, the mean latency period after the be-
inning of such exposure was 44 years (SD = 6.16)
for cases and 48 years (SD = 6.63) for controls. For
subjects with mineralogical analysis ≥1000 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 pulmo-
nary carcinoid tumors. Indeed, we observed that cu-
mulative exposure to asbestos evaluated by
a practitioner specialized in occupational diseases
Mean age of cases at diagnosis was 51.1 years, which was higher in cases of carcinoid tumor aged >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 (Arrigoni et al., 1972; McCaughan et al., 1985; Struyf et al., 1995; Thomas et al., 2001). Distribution of typical and atypical pulmonary carcinoid tumors and their characteristics
(age, gender, and tobacco consumption) was also similar to previously published data (Arrigoni et al., 1972; Struyf et al., 1995; Fink et al., 2001; Thomas et al., 2001, 2008; Paillas et al., 2004).

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 from the mineralogical analysis of AB in lung tissue. Similarly to cases, they were required to live in the Paris region to allow easy access to the occupational questionnaire interview. 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 (Karjalainen et al., 1994; Mollo et al., 1995; Raffn et al., 1996; Henderson, 1997). In the study conducted by Raffn et al. (1996) 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. 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 et al., 2010). A total of 1493 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 two 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 AB of cases and controls.

CONCLUSIONS

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 from a 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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