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AUTHOR'S CONTRIBUTION

JG performed literature review, all statistical analysis and drafted the first version of this manuscript.

Conception or design of the work was done by CP, BC, PB, JCP, AL.

Acquisition and interpretation of data was done by CP, BC, AG, FL, IT, SC, GO.

AL supervised all aspects of this manuscript.

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Abstract

Background: Occupational asbestos exposure is associated with pleural plaques (PP), a benign disease often seen as a marker of past exposure to asbestos and lung cancer. The association between these two diseases has not been formally proved, the aim of this study was to evaluate this association in the ARDCO cohort. **Methods:** ARDCO is a French multicentric cohort including workers formerly occupationally exposed to asbestos from 2003 to 2005. CT scan was performed to diagnose PP with double reading and lung cancer (incidence and mortality) was followed through health insurance data and death certificates. Cox models were used to estimate the association between PP and lung cancer adjusting for occupational asbestos-exposure (represented by cumulative exposure index, time since first exposure and time since last exposure) and smoking status. **Results:** A total of 176 cases (of 5,050 subjects) and 88 deaths (of 4,938 subjects) of lung cancer were recorded. Smoking status was identified as an effect modifier. Lung cancer incidence and mortality were significantly associated with PP only in non-smokers, respectively HR=3.13 (IC95%: 1,04; 9.35) and HR=16.83 (IC95%: 1,87; 151.24) after adjustment for age, occupational asbestos-exposure and smoking status. **Conclusions:** ARDCO study was the first to study this association considering equal asbestos-exposure and more specifically our study is the first to test smoking as an effect modifier, so comparison with scientific literature is difficult. Our results seem to consolidate the hypothesis that PP may be an independent risk factor for lung cancer but they must be interpreted with caution.

Key Message

What is already known on this topic: There is a persistent controversy related to the association between asbestos-induced pleural abnormalities and the risk of lung cancer.

What this study adds: lung cancer incidence and mortality were significantly associated with PP only in non-smokers after adjustment.

How this study might affect research, practice or policy: The finding of a higher relative risk among non-smokers than among smokers is very interesting because this phenomenon has already been highlighted in the relationship between asbestos exposure and lung cancer.

INTRODUCTION

Asbestos is a fibrous natural mineral classified as a definite carcinogen for human by the International Agency for Research on Cancer (IARC) since 1977 and whose use has been completely prohibited in France since 1997 (1). Due to the induction of numerous respiratory diseases (benign or malignant) following occupational asbestos exposure, a post-occupational monitoring has been set up since 1999 to detect asbestos-related diseases (2).

Indeed, occupational asbestos exposure is associated with several benign diseases of the pleura and lung such as asbestosis, a pulmonary fibrosis which is associated with high cumulative exposures, or pleural fibrosis, whose the most common manifestations are pleural plaques (PP) (3). More particularly, PP may also develop for relatively low level of asbestos exposure so they represent the most common benign diseases and are often considered as a marker of asbestos exposure (4, 5). The delay between the first exposure and their diagnosis generally varies from 15 to 40 years (4, 6). Prevalence varies greatly according to the occupations and characteristics of the exposure (e.g. exposure level) (4, 7) but is mainly correlated with the time since the first exposure and the cumulative exposure (8-11). In low-exposure populations, the prevalence of PP was estimated between 4.1% and 13% according to the studies and can reach nearly 60% for highly exposed occupations (12).

Occupational asbestos exposure is also associated with malignant diseases including lung cancer and mesothelioma, but also other types of cancers such as cancer of larynx and ovaries (1). More particularly asbestos exposure is the main occupational risk factor for lung cancer (13). In France, in 2015, the proportion of cases attributable to occupational asbestos exposure was estimated from 9.3% to 19.3% for men (14). Lung cancer develops on average 20 years after the first asbestos exposure and it is generally considered that under a 10-year latency no excess risk can be observed (5). Besides the time elapsed since the start of exposure, the increased risk of lung cancer also depends on the time elapsed since the end of exposure and the cumulative exposure level (5, 15).

It has been clearly established that asbestos-related interstitial fibrosis (i.e., asbestosis) is associated with an increased risk of lung cancer (16), although asbestos-related lung cancer

may occur in the absence of asbestosis (17, 18). However, there is a persistent controversy related to the association between asbestos-induced pleural abnormalities and the risk of lung cancer (19-21). In 2014, Pairon et al had shown from the ARDCO cohort, an association between the presence of pleural plaques and lung cancer mortality [20]. The evaluation of this association requires a correct PP detection, to date the most reliable tool is CT scanning, and an individual estimation of past asbestos exposure to adjust on the cumulative exposure index. The evaluation of PP-lung cancer association is a key element at a time when it's recommended to propose screening for lung cancer in population at high risk of lung cancer.

This study is a follow-up of the previously reported Pairon study which examine the association between PP and lung cancer (incidence and mortality) by carefully taking into account lifetime occupational asbestos exposure from the Asbestos related disease cohort (ARDCO), a cohort of workers formerly occupationally exposed to asbestos.

METHODS

Study population

ARDCO is a French multicentric cohort conducted from October 2003 to December 2005 in 3 French regions (Aquitaine, Rhône-Alpes and Normandie). The main objective of this cohort was to improve medical surveillance of workers formerly occupationally exposed to asbestos. Volunteer retired or unemployed workers between October 2003 and December 2005 with a previous history of occupational exposure to asbestos, affiliated to the General National Health Insurance and living at time of inclusion in one of the 3 regions participating to the study were eligible for this cohort. Subjects with knowledge of an asbestos-related disease were excluded. A free medical checkup including chest CT scan and pulmonary function tests was proposed to all study participants. The present study included all male subjects for whom a copy of their CT scan was sent to our team centers (22).

The study was approved by the hospital ethics committee. All participants received information about the study and gave their written informed consent.

Data Collection

Information related to socio-demographic characteristics (birth date, gender, place of residence…), smoking status (classified into three categories: current smokers, ex-smokers and never smokers) and complete work history were obtained using a self-administered questionnaire. For each job held during the working lifetime history, the company name, occupation title, general description of the work environment, and the start and end years were recorded.

Assessment of asbestos exposure

Occupational asbestos exposure was retrospectively assessed by industrial hygienist on the basis of the complete work history of each subject and specific questions related to performed tasks strongly entailing asbestos exposure. For each job associated with asbestos exposure, the duration (number of years), the level of exposure (low (passive exposure), low intermediate, high intermediate and high) and first years of exposure and last year of exposure were assessed. The following weighting factors were attributed for the level of exposure: low

(passive exposure): 0.01; low intermediate: 0.1; high intermediate: 1; high: 10. A cumulative exposure index (CEI) to asbestos aggregating each exposure period was calculated for each subject as the sum of the product duration x weighting factor for each exposed job (22, 23).

CT scanning

As described previously, a CT scan was proposed to each subject at baseline. All available CT scans were submitted to randomized independent double assessment (and triple assessment in the case of disagreement) focusing on benign asbestos-related abnormalities, by a panel of seven chest radiologists trained in the interpretation of asbestos-related CT abnormalities (24). These experts were blinded to the subject's cumulative asbestos exposure and to the results of the initial assessment by the radiologists who performed the CT scans (24).

Lung cancer and vital status

A follow-up study of mortality and incidence was conducted in the study population. New data are available compared to Pairon's study, we provided incidence data and there is a longer follow-up (until 2015 for mortality analyses and 2018 for incidence analyses). For mortality, vital status, date of death and cause of death where obtain from the INSERM CépiDC (Centre d'épidémiologie sur les causes de décès) which collects all death certificates. Vital status and date of death are available until 06/30/2018 and cause of death are available until 12/31/2015. For incidence, incident cases identification and diagnosis dates are annually obtained from the National Health Insurance through the determination of subjects applying for free medical care for cancer. Data are available until 11/30/2018.

Statistical Analysis

Cox proportional hazards models were employed to estimate hazard ratios (HRs) of lung cancer incidence and lung cancer mortality in relation to the presence of PP. The time axis used was the current age in years, T0 was the age at the CT scan and subjects were followed up to 11/30/2018 for incidence analyses and up to 12/31/2015 for mortality analyses. Models were adjusted for smoking status, CEI to asbestos, time since first exposure (time-dependent covariate) and time since last exposure (time-dependent covariate). Linearity hypothesis have

been checked using the package MFP (Multivariable Fractional Polynomials) and the hypothesis of proportional hazards have been checked graphically. We tested the interaction between PP and smoking status to determine if smoking status is an effect modifier in the relation between PP and lung cancer. Since smoking status was missing for about 7% of subjects, two analysis strategies were implemented: the first strategy was based on complete data analysis and the second strategy analysis was based on multiple imputation using the multiple imputation by chained equations method for smoking variable (25-27). Statistical analysis was performed with R version 3.2.3. All statistical tests were two sided, and statistical significance was defined as $P<0.05$.

RESULTS

A total of 5,520 CT scan from the 16,086 subjects of ARDCO were sent to the study centers. We excluded women, subjects considered unexposed, subjects with uninterpretable CT scans, subjects with incoherent dates (date of CT scan or date of diagnosis), subjects with incomplete work history, subjects lost at follow-up by the National Health Insurance and subjects with unknown cause of death (only for the mortality analyses). The study population consisted of 4,938 subjects for mortality analysis further called “mortality population” and 5,050 for incidence analysis further called “incidence population” (Figure 1).

A total of 1,042 subjects (21%) for incidence population and 1,038 (21%) for mortality population were diagnosed with PP. General characteristics of subjects are presented in Table 1. In incidence population, subjects with PP were older than subjects without PP (65.5 ±5.8 vs 63.0 ±5.1), were less frequently never-smokers (19.4% vs 27.5%) and more frequently ex-smokers (66.9% vs 57.4%). Similar observation could be made in mortality population.

Table 1. Study population characteristics according to the presence of pleural plaques

	Incidence population (n=5,050)				Mortality population (n=4,938)			
	Subjects without pleural plaques (n= 4,008)		Subjects with pleural plaques (n=1,042)		Subjects without pleural plaques (n=3,900)		Subjects with pleural plaques (n=1,038)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)								
Mean ± SD	63.0 ± 5.1		65.5 ± 5.8		62.8 ± 5.6		65.6 ± 6.0	
Min-Max	39.8 - 99.0		48.2 - 85.4		39.8 - 87.7		48.2 - 85.4	
Region								
Aquitaine	779	19.4	135	13.0	793	20.3	134	12.9
Normandie	1 285	32.1	533	51.2	1 344	34.5	556	53.6
Rhône-Alpes	1 944	48.5	374	35.9	1 763	45.2	348	33.5
Smoking status								
Never smokers	1 103	27.5	202	19.4	1 050	26.9	202	19.5
Ex-smokers	2 302	57.4	697	66.9	2 271	58.2	699	67.3
Current smokers	287	7.2	82	7.9	283	7.3	81	7.8
Missing data	316	7.9	61	5.9	296	7.6	56	5.4
Last employment*								
Professional, Technical and Related Workers	198	4.9	39	3.7	197	5.1	36	3.5
Administrative and Managerial Workers	89	2.2	12	1.2	86	2.2	12	1.2
Clerical and Related Workers	126	3.1	22	2.1	126	3.2	20	1.9
Sales Workers	85	2.1	18	1.7	83	2.1	19	1.8

Service Workers	49	1.2	11	1.1	54	1.4	13	1.3
Agricultural, Animal Husbandry and Forestry Workers, Fishermen and Hunters	14	0.3	2	0.2	17	0.4	2	0.2
Production and Related Workers, Transport Equipment Operators and Laborers	3 447	86.0	938	90.0	3 337	85.6	936	90.2
Outcome **								
No	3 877	96.7	997	95.7	3 844	98.6	1 006	96.9
Yes	131	3.3	45	4.3	56	1.4	32	3.1

*According major groups of International Standard Classification of Occupation 1968
**Lung cancer for incidence analysis and death from lung cancer for mortality analysis

Regarding occupational asbestos exposure (Table 2), in incidence population, duration of exposure and time since first exposure were slightly longer in subjects with PP compared to subjects without PP (33.0 ± 9.4 years *vs* 31.0 ± 10.3 and 46.7 ± 7.2 years *vs* 43.2 ± 7.3 years, respectively). The mean cumulative exposure index was two-fold higher in subjects with PP compared to subjects without PP (109.9 ± 125.5 units x years vs 55.7 ± 92.7 units x years). Similar observation could be made in mortality population.

Table 2. Occupational asbestos exposure's description of study population according the presence of pleural plaques

	Incidence population (n=5,050)				Mortality population (n=4,938)			
	Subjects without pleural plaques (n= 4,008)		Subjects with pleural plaques (n=1,042)		Subjects without pleural plaques (n= 3,900)		Subjects with pleural plaques (n=1,038)	
	n	%	n	%	n	%	n	%
Duration of exposure (years)								
< 26	1078	26.9	209	20.1	1057	27.1	204	19.7
26-34	1121	28.0	256	24.6	1097	28.1	251	24.2
35-39	961	24.0	305	29.3	930	23.9	302	29.1
> 39	848	21.2	272	26.1	816	20.9	281	27.1
Mean ± SD	31.0 ± 10.3		33.0 ± 9.4		31.0 +/- 10.3		33.1 ± 9.4	
Min-Max	1 - 55		1 - 49		1 - 55		1 - 49	
Time since the first exposure (years)								
< 40	89	2.2	6	0.6	117	3.0	9	0.9
40 - 49	586	14.6	86	8.2	899	23.1	119	11.5
50 - 59	1770	44.2	367	35.2	2049	52.5	527	50.8
≥ 60	1563	39.0	583	56.0	835	21.4	383	36.9
Mean ± SD	56.7 +/- 7.5		60.1 +/- 7.3		53.8 +/- 7.4		57.5 +/- 7.3	
Min/Max	15-87		23-85		17-84		20-82	
Time since the last exposure (years)								
< 5	1340	33.4	245	23.5	1305	33.5	253	24.4
5 - 9	873	21.8	225	21.6	832	21.3	215	20.7

9 - 16		965	24.1	288	27.6	943	24.2	280	27.0
> 16		830	20.7	284	27.3	820	21.0	290	27.9
	Mean ± SD	10.7 ± 8.8		12.3 ± 8.9		10.7 +/- 8.8		12.3 ± 8.9	
	Min/Max	0 - 52		0 - 51		0 - 52		0 - 51	
Cumulative exposure index (units x year)									
> 0 – 3.2		901	22.5	109	10.5	848	21.7	103	9.9
3.3-13.5		796	19.9	119	11.4	762	19.5	114	11.0
13.6-31.9		790	19.7	156	15.0	785	20.1	152	14.6
32-63.9		785	19.6	235	22.6	760	19.5	238	22.9
≥ 64		736	18.4	423	40.6	745	19.1	431	41.5
	Mean ± SD	55.7 ± 92.7		109.9 ± 125.5		57.3 ± 93.8		112.2 ± 126.1	
	Min/Max	0.01 - 460		0.01 - 490		0.01 - 460		0.02 - 490	
Maximum exposure level*									
Low		179	4.5	20	1.9	172	4.4	15	1.5
Low intermediate		1131	28.2	146	14.0	1057	27.1	141	13.6
High intermediate		1803	45.0	394	37.8	1768	45.3	391	37.7
High		895	22.3	482	46.3	903	23.2	491	47.3

*levels: low (< 0.1 unit x year), low intermediate (0.1 to 1 unit x year), high intermediate (1 to 10 units x year). high (> 10 units x year)

A total of 176 incident lung cancer cases were identified in the follow-up study between CT scan and 11/30/2018, 45 (4%) in subjects with PP and 131 (3%) in subjects without PP. Furthermore, 88 deaths from lung cancer were registered between CT scan and December 31st 2015, 32 (3%) in subjects with PP and 56 (1%) in subjects without PP. Probability to survive without lung cancer stratified by the PP status is presented in Figure 2, indicating that the age-related survival curve of the proportion of subjects without lung cancer was significantly different between subjects with and without pleural plaques in the mortality study (p=0.006, log rank test) and in the incidence study (p=0.04, log rank test).

Results from the Cox proportional hazards models for incidence and mortality analysis are presented in Table 3. Since the interaction term between PP and smoking status was significant for both the mortality and the incidence analysis, results are presented for each stratum of the smoking status. A statistically significant association between PP and lung cancer incidence and lung cancer mortality were observed among never-smokers (HR=3.13 95%CI =[1.04-9.35] and HR=16.83, 95% IC =[1.87-151.24], respectively). Among ex-smokers, the hazard of lung cancer (incidence and mortality) was slightly increased in subjects with PP compared to those without PP, but statistically significant only in mortality population (HR=1.48

95%CI [0.98-2.22] and HR=1.96 95%CI [1.15-3.34], for the incidence and mortality population respectively). Finally, among current smokers no statistically significant association between PP and lung cancer incidence and lung cancer mortality was observed. These results did not change after adjustment on asbestosis (data not shown).

Table 3. Association between pleural plaques and lung cancer (incidence and mortality): Cox Model

	Incidence analysis (n=5,050)			Mortality analysis (n=4,938)		
	Number of cases	HR*	95% CI	Number of cases	HR*	95% CI
Complete data	162	1.33	[0.93 ; 1.91]	79	1.91	[1.18 ; 3.07]
Never smokers	14	3.13	[1.04 ; 9.35]	5	16.83	[1.87 ; 151.24]
Ex-smokers	117	1.48	[0.98 ; 2.22]	61	1.96	[1.15 ; 3.34]
Current smokers	31	0.39	[0.12 ; 1.29]	13	0.53	[0.12 ; 2.43]
Multiple imputation[$]	176	1.25	[0.87 ; 1.78]	88	1.61	[1.01 ; 2.57]
Never smokers	-	3.12	[1.07; 9.11]	-	17.10	[1.90 ; 153.58]
Ex-smokers	-	1.35	[0.91 ; 2.01]	-	1.61	[0.97 ; 2.69]
Current smokers	-	0.38	[0.12 ; 1.27]	-	0.49	[0.11 ; 2.21]

*HR: Hazard Ratio adjusted on cumulative exposure index to asbestos, time since the first exposure, time since the last exposure and smoking status

[$] Multiple imputation: for smoking status variable based on MICE methods (Multivariate Imputation by Chained Equations)

DISCUSSION

Our study is the first one to look at smoking status as an effect modifier in the relationship between PP and lung cancer. Results from this study are in favor of a positive association between PP and lung cancer incidence or lung cancer mortality which is stronger and statistically significant in non-smokers and in ex-smokers for mortality study. However, point estimates should be interpreted with cautious due to large confidence intervals.

The finding of a higher relative risk among non-smokers than among smokers is very interesting because this phenomenon has already been highlighted in the relationship between asbestos exposure and lung cancer. In a meta-analysis and review of the literature published in 2001 and 2004 the effect of asbestos on relative risk of lung cancer was shown to be twice as high in non-smokers as in smokers because of smoking (28, 29). The absolute risk remains lower for non-smokers than for smokers. This increase in relative risk in non-smokers could be explained by a modification in the expression of various xenobiotic detoxifying enzymes between an exposure to asbestos and a co-exposure to asbestos and tobacco (30). While interesting, these results have to be replicated and interpreted cautiously because other studies did not confirm this result (31, 32) and the weak number of events for each category of smoking status lead to large confidence intervals. Moreover, only the smoking status was collected for the whole cohort, and no quantitative information was available for smoking. Thus, we were unable to look at this interaction using more precise indicator of the smoking status.

Results from this study seem to be in line with results from recent studies, which also point a significant positive association between PP and lung cancer (6, 20, 33-35). In the literature in various cell models, protooncogene expression, and several pathways activated by asbestos were elevated in lung and pleura after exposure to asbestos (36). It is not known whether dysregulation of various signaling pathways and detoxifying enzymes after exposure of cells of the respiratory tract are similar in subjects developing pleural plaques and subjects not developing pleural plaques. Comparison with previous epidemiological studies is difficult

because our study is the first one to present results according smoking status and also due to discrepancies between studies in the methodologies implemented. Indeed, previous studies used chest X-ray to diagnose PP (6, 33-35). However, it has been shown that this technique is prone to misclassifications due to its low sensitivity and specificity for the detection of pleural abnormalities (37). To date, only 2 studies used CT scan to diagnose PP (and on only a fraction of the population for Brims et al. study) and these studies come to conflicting conclusions (20, 21). Regarding past occupational asbestos exposure, most previous studies did not adjust for it in statistical analysis while it is a strong confounder in the relationship between PP and lung cancer occurrence. Thus, occupational asbestos exposure has to be carefully considered. Only four studies took into account occupational asbestos exposure but using different statistical strategies (20, 21, 35, 38) : Cullen et al.(35) and Harber et al.(38) represented occupational asbestos exposure by the duration of exposure. However, such adjustment is imperfect since levels of exposure are not taken into account and thus may lead to residual confounding by occupational asbestos exposure (39). Brims et al. represented occupational asbestos exposure by cumulative exposure and reported no significant association between PP and lung cancer (21). Finally, in a previous report, Pairon et al. represented occupational asbestos exposure by the cumulative exposure index and time since the first exposure (20) and reported a significant positive association between PP and lung cancer mortality. Here we confirm this association on a longer follow-up in mortality and we find this association in incidence with new elements on the smoking status.

Our study has some strengths and some limitations. First, to date and to our knowledge, the ARDCO cohort is the largest cohort of retirees formerly occupationally exposed to asbestos with detailed individual evaluation of exposure to asbestos and CT scan with expert reading. However, the constitution of the cohort was based on voluntary participation and the study population was restricted to subjects who agreed to return their CT scan's results which may have led to probably include subjects very concerned about their health or about asbestos exposure. This selection bias limits the extrapolation of our results to a target population from

a prediction point of view. Indeed, we have previously reported that lung cancer mortality rate and the prevalence of PP were low. These findings support the hypothesis that cohort subjects constituted a rather healthy population. In addition, since there is a dose-response relationship between asbestos exposure and PP, the low prevalence of PP in this cohort (approximately 20%) may indicate that this cohort has not been highly exposed to asbestos. In addition, we have very few subjects with asbestosis (<1%), a disease observed at high exposures, which seems to confirm a modest cumulative exposure of the cohort. This selection bias does not affect the results regarding the association between PP and lung cancer when performing internal comparison.

Over 4,800 subjects benefited of a CT scan at baseline which was interpreted by thoracic radiology experts. CT scan is the most sensitive and specific non-invasive examination to diagnose PP, thus limiting classification errors regarding to PP status (4, 5). Even if we can't exclude misclassifications regarding PP status at baseline, they should be very limited and independent of the lung cancer status which was further determined in the follow study.

Regarding asbestos exposure, an individual estimation of past asbestos exposure was performed by industrial hygienists which allowed us to quantify the past cumulative occupational asbestos exposure. Even if such method is prone to misclassification and is dependent to the quality of information reported by subjects, to date, it is considered as a gold standard in terms of retrospective assessment methods.

This study has also some limitations.

It should be acknowledged that we have only considered PP status at baseline. However, the incidence of PP is time dependent, and increases linearly without threshold with time since the first exposure (8-11). That supposes that some subjects may have developed PP after the inclusion in the study. If we consider a positive association between PP and lung cancer, then some subjects further diagnosed with lung cancer and identified as not having PP at baseline, may in fact present PP after inclusion which may lead to an underestimation of the association

between PP and lung cancer. This will be further investigated, thanks to the follow up study, where two more CT-scan campaign were implemented (2009-2010 for the second campaign and a third campaign recently).

Finally, misclassifications may also concern the lung cancer status. Indeed, lung cancer status was collected either using death certificates (mortality study) or using data from applications for free medical care for cancer or for occupational disease compensation for lung cancer. It has been shown that death certificates may bias estimations due to inaccurate completion or competing cause of death (40). In France, subjects having a lung cancer may ask for free medical care. While it is expected that most if not all of these subjects ask for this, National Insurance health system are not intended to be used for cancer cases identification. In French department (Calvados, Manche, Gironde, and Isère) there are general cancer registries which ensure exhaustiveness in cancer cases identification, cancer cases identified from National Health Insurance data were confronted to those identified from cancer registries over the period 2005-2012. On 78 cancer cases identification from either National health Insurance or cancer registries, 63 identifications were concordant (80.8%).

In conclusion, our study supports the hypothesis that there is a positive association between PP and lung cancer incidence and mortality among non-smokers, and also in mortality in ex-smokers. Further studies are needed to confirm this association and better understand the underlying biological mechanisms.

Competing Interests

No competing interests for any author

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