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Head and neck cancer and asbestos exposure

Bénédicte Clin ,[1,2,3] Celine Gramond,[4] Isabelle Thaon,[5,6] Patrick Brochard,[7] Fleur Delva ,[8,9] Soizick Chammings,[10] Antoine Gislard,[11] François Laurent,[12] Christophe Paris,[13] Aude Lacourt,[4] Jean-Claude Pairon[14]

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For numbered affiliations see end of article.

Correspondence to
Professor Bénédicte Clin, CHU Caen, Caen, France;
benedicte.clin14@orange.fr

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ABSTRACT

Objectives The aim of this study was to analyse, within a French cohort of workers previously occupationally exposed to asbestos, incidence and mortality from various sites of head and neck cancers (larynx excluded) and to examine the potential link of these cancers with pleural plaques.

Methods A 10-year follow-up study was conducted in the 13 481 male subjects included in the cohort between October 2003 and December 2005. Asbestos exposure was assessed by industrial hygienist analysis of a standardised questionnaire. The final cumulative exposure index (CEI; in equivalent fibres.years/mL) for each subject was calculated as the sum of each employment period's four-level CEI. The number of head and neck cancers recorded by the National Health Insurance fund was collected in order to conduct an incidence study. Complementary analysis was restricted to men who had performed at least one chest CT scan (N=4804). A mortality study was also conducted. We used a Cox model with age as the time axis variable adjusted for smoking, time since first exposure, CEI of exposure to asbestos and pleural plaques on CT scans.

Results We reported a significant dose–response relationship between CEI of exposure to asbestos and head and neck cancers after exclusion of laryngeal cancers, in the mortality study (HR 1.03, 95% CI (1.01 to 1.06) for an increase of 10 f.years/mL) and a close to significant dose–response relationship in the incidence study (HR 1.02, 95% CI (1.00 to 1.04) for an increase of 10 f.years/mL). No statistically significant association between pleural plaques and head and neck cancer incidence was observed.

Conclusions This large-scale study suggests a relationship between asbestos exposure and head and neck cancers, after exclusion of laryngeal cancers, regardless of whether associated pleural plaques were present.

Key messages

What is already known about this subject?

⇒ With regard to asbestos exposure, the only established link with head and neck cancers concerns laryngeal cancers.

What are the new findings?

⇒ This large-scale study suggests a relationship between asbestos exposure and head and neck cancers, after exclusion of laryngeal cancers, regardless of whether associated pleural plaques were present.

How this study might affect research, practice and/or policy?

⇒ Such results could lead to changes in the medicolegal management of head and neck cancers among subjects having been occupationally exposed to asbestos.

INTRODUCTION

Head and neck cancers cover a large set of tumours concerning the upper part of the digestive and respiratory systems. They can then arise in the oral cavity (including lips), the nasopharynx, the oropharynx, the hypopharynx, the larynx, the nasal cavity, the sinuses and the salivary glands. In 90% of cases, head and neck cancers are invasive squamous cell carcinomas.[1] These carcinomas can be more or less differentiated and have histological variations listed in the WHO classification.[2] Conventional squamous cell carcinoma can be observed in all head and neck cancer locations. Other histological types (such as undifferentiated carcinomas or adenocarcinomas) mainly concern cancers of nasopharynx, sinonasal cavities or salivary glands.

Various risk factors were associated with head and neck cancer, one factor potentially being associated with several forms of cancer (for instance alcohol or smoking) or more specific to one location (wood dust). The majority of cases of head and neck cancer (notably oral and oropharyngeal cancers and laryngeal cancers) are attributed to the separate and combined use of tobacco, excessive alcohol consumption and human papillomavirus infection.[3–5] There is evidence that occupational exposure to various substances is also a risk factor.[6 7] Concerning cancers of the nasopharynx, exposure to Epstein-Barr virus, exposure to formaldehyde and wood dust, salt fish consumption and smoking are all associated risk factors. Unlike other head and neck tumours, squamous cell carcinomas account for around only half of histological types observed in cancers of the sinuses of the face and nasal cavities, 20% of which are adenocarcinomas, most often in the ethmoidal seat. Exposure to wood dust and nickel refining are established risk factors for this cancer location. Excess incidence of nasosinusial cancers has also been observed in leather workers,[8 9] in workers exposed to hexavalent chromium[10] and among textile workers (cotton).[10 11]

With regard to asbestos exposure, the only established link concerns laryngeal cancers.[12]

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Industrial use of asbestos is now prohibited in most industrialised countries; however, it is important to establish whether or not an increased risk of head and neck cancer could be linked to asbestos exposure: indeed, such a link could have consequences for both the occupational and postoccupational medical surveillance of exposed individuals, and for medicolegal compensation.

A large-scale screening programme for asbestos-related diseases was initiated in four regions of France in 2001, following a national consensus conference on clinical surveillance strategy for former asbestos workers.[13] In previous studies, pleural plaques were associated with an increasing incidence of mesothelioma[14] or of lung cancer mortality.[15] To our knowledge, no such associations have been reported for head and neck cancers. The present study was designed to examine the association between asbestos exposure, pleural plaques and the risk of various sites of head and neck cancer (after exclusion of laryngeal cancers) in a 10-year follow-up study of formerly asbestos-exposed workers.

MATERIAL AND METHODS

Study population

In 2001, four French regions (Aquitaine, Upper Normandy, Lower Normandy and Rhône-Alpes) were designated by the French Ministry for Employment and Solidarity's Professional Relations Directorate and the 'Caisse Nationale d'Assurance Maladie des Travailleurs Salariés's Directorate for Professional Risks, to conduct a feasibility study on the medical surveillance of retired or inactive subjects having been occupationally exposed to asbestos.[13] These subjects, comprising unemployed or retired asbestos-exposed workers covered by the French National Health Insurance fund, constituted the Asbestos-Related Diseases COhort (ARDCo). Enrolment took place between October 2003 and December 2005 and subjects were offered a free medical check-up including chest CT scan and pulmonary function tests.[13 16–18] The method of informing the subjects to be included in the study was based on different modalities according to the regions (this was specifically requested by the French Public Health authorities at the time of the beginning of the study). The subjects were informed of the study by individual letters based on age selection for the Aquitaine region, by individual letters based on occupational sectors for the Rhône-Alpes, by televised or written press for Lower and Upper Normandy. A total of 122 181 subjects were approached to enrol in the cohort without selection concerning the exposure and 16 885 responded and sent a completed exposure questionnaire. The ARDCo population included 14 218 recognisable subjects drawn from databases compiled by the 'Caisse Primaire d'Assurance maladie' national health insurance organisation. These subjects had been required to complete a standardised questionnaire describing all jobs held throughout their working lives as well as specific asbestos-exposing tasks. Subjects were included after confirmation of asbestos exposure from questionnaire analysis by industrial hygienists. Subjects were considered to be exposed to asbestos when they had at least one job with a non-zero exposure level based on exposure expertise by industrial hygienists. For example, the types of occupations performed by the subjects included were particularly: asbestos-based material production activities (such as fibre-cement, friction materials, asbestos textile), maintenance work on old materials in buildings, manufacture of articles containing asbestos, insulation (before 1996–year of interdiction of use of asbestos in France), refinery and petrochemical (before 1996), shipbuilding and ship repair, automotive repair, construction sites, the steel industry, electricians and tilers (tables describing the top 10 occupations (regardless of exposure) among all subjects included, excluding laryngeal cancers and among subjects presenting with head and neck cancer, excluding laryngeal cancers are available in online supplemental file 1). Available information included characteristics of civil status, social and occupational data (complete occupational calendar) and information concerning smoking status for a wide fraction of subjects. Among these 14 218 subjects, 13 481 were men (94.8%) and 737 were women (5.2%). Average age at inclusion was 60 years or less for 3332 subjects (23.4%), between 60 and 75 years for 10 490 subjects (73.8%) and 75 years or more for 396 subjects (2.8%).

Subjects for whom a CT scan was sent to regional coordinating centres constituted the Asbestos Post EXposure Survey (APEXS) population. Among these subjects, 4804 (37.7%) benefited from at least one chest CT scan in form of a CD-Rom (the films were not retained but only the CDs) and constitute the 'CT-Scan population' of the present study.

The 15 subjects having presented with cancer of the head and neck prior to inclusion have been excluded from analysis.

Data collection

Asbestos exposure

As previously described elsewhere,[16] information on the occupational exposure of individuals included in the cohort was available thanks to evaluation of individual asbestos exposure by industrial hygienists using data from a standardised questionnaire, describing all job positions occupied during the subject's occupational career, hence enabling us to calculate a cumulative exposure index (CEI).

Asbestos exposure was assessed according to occupation and industrial activities. The level of exposure was classified into four classes defined for each job occupied by each subject, comprising a four-level scale: low level (passive exposure), corresponding to a numerical value of '0.01 equivalent fibres/mL'; low-intermediate, corresponding to a numerical value of '0.1 equivalent fibres/mL'; high-intermediate, corresponding to a numerical value of '1 equivalent fibres/mL'; and high exposure, corresponding to a numerical value of '10 equivalent fibres/mL'. A CEI was then calculated for each job by multiplying this level (0.01; 0.1; 1 and 10, respectively) by the duration of each employment period (in years). The final CEI (in equivalent fibres.years/mL) for each subject was calculated as the sum of each employment period's four-level CEI. Time since first exposure to asbestos (TSFE) was defined as the time elapsed between year of start of first exposed job and the year of the index date (diagnosis of head and neck cancer, death or end of follow-up).

CT scanning

As previously explained, subjects included in the complementary study concerning the link between head and neck cancer and pleural plaques benefited from at least one readable chest CT scan on CD-ROM between 2003 and 2019 and constituted hereafter the 'CT-Scan sample'. 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).[16]

All available CT scan on CD-ROM examinations underwent standard double reading (and triple reading in the case of disagreement) and focused on benign asbestos-related abnormalities, by a panel of seven expert radiologists. Standardised readings were blind to the initial interpretation by the radiologist having performed the examination, and to the level of asbestos exposure.

Tobacco consumption

Subjects were classified into three categories according to tobacco consumption: smokers, ex-smokers (defined as those who had quit smoking for at least 1 year) and non-smokers.

Data collection for incident cancer cases and mortality from cancer

A follow-up study was conducted in subjects who had enrolled in the ARDCo and APEXS programmes. Figures for new head and neck cancers were recovered annually, from the date of enrolment to 1 July 2019, from the National Health insurance, which collects these data for medical cost coverage purposes.

A follow-up study of mortality was also organised in the study population. The vital status of each subject in the cohort was collected from the National directory for identification of physical persons up to 1 July 2019. For deceased subjects, both underlying and contributing causes of death according to death certificates available up to 31 December 2015 were then obtained from the INSERM CEPI DC.

Statistical analysis method

The variables used to characterise asbestos exposure were duration of asbestos exposure, CEI and TSFE. In the follow-up study, statistical associations between these asbestos exposure variables and head and neck cancer incidence were studied using survival regression analysis based on the Cox proportional hazards model. The time axis used was the current age in years with age at inclusion in the cohort as the origin, thus accounting for age in a non-prespecified manner, while duration of exposure to asbestos, CEI and TSFE to asbestos, were independent variables. Only TSFE to asbestos was time varying in the models. Proportionality assumption of the Cox models was checked with the Schoenfeld residuals. Unadjusted HRs and adjusted HRs for these variables, namely smoking status, CEI and TSFE to asbestos, were calculated for the risk of head and neck cancer incidence and for mortality. Multivariate analysis was based on TSFE and CEI as continuous variables. Linearity hypothesis of CEI has been checked using the package mfp (multivariable fractional polynomials). HRs for CEI were presented for an increase of 10 f.years/mL. For the complementary study in the CT-Scan sample, the role of pleural plaques was also analysed. Statistical analysis was carried out using R Studio. All statistical tests were two-sided and statistical significance was defined as $p<0.05$.

RESULTS

The ARDCo population comprised 13 481 male subjects among whom 12 729 were included for incident analysis, and 12 519 included for mortality analysis, as explained in the flow chart (online supplemental figure 1).

General characteristics of the entire population of the incidence analysis and the CT-scan population are given in table 1. The mean (SD) age was 63.2 (5.5) years; 6105 subjects (48.0%) were smokers or ex-smokers. Mean (SD) duration of asbestos exposure was 31.3 (10.4) years.

Table 1 Study population characteristics (incidence analysis)

Characteristics	All subjects (n=12 729)	CT-scan sample (n=4804)
Age at baseline (years)		
Mean±SD	63.2±5.5	63.2±5.5
<60	2772 (21.8%)	1097 (22.8%)
60–74	9627 (75.6%)	3584 (74.6%)
≥75	330 (2.6%)	123 (2.6%)
Follow-up (years)		
Median (min–max)	14.9 (0.005–16.3)	14.9 (0.15–16.3)
Smoking status at baseline		
Never smokers	2612 (20.5%)	1286 (26.8%)
Former smokers	5360 (42.1%)	2850 (59.3%)
Current smokers	745 (5.9%)	326 (6.8%)
Missing data	4012 (31.5%)	342 (7.1%)
Duration of exposure to asbestos (years)		
Mean±SD	31.3 (10.4)	31.5 (10.1)
<20	1848 (14.5%)	657 (13.6%)
20–29	2420 (19.0%)	928 (19.3%)
30–39	5528 (43.4%)	2127 (44.3%)
≥40	2933 (23.1%)	1092 (22.8%)
CEI* to asbestos (f.years/mL)		
Mean±SD	60.3 (99.4)	64.4 (101.0)
(0.01–2.84)	2555 (20.1%)	809 (16.9%)
(2.84–10.22)	2568 (20.2%)	928 (19.3%)
(10.22–31.70)	2546 (20.0%)	1028 (21.4%)
(31.70–70.80)	2570 (20.2%)	1029 (21.4%)
(70.80–490.00)	2490 (19.5%)	1010 (21.0%)
TSFE† (years)		
Mean±SD	56.6 (7.9)	57.3 (7.5)
<40	359 (2.8%)	92 (1.9%)
40–49	1898 (14.9%)	605 (12.6%)
50–59	5446 (42.8%)	2078 (43.3%)
≥60	5026 (39.5%)	2029 (42.2%)
Pleural plaque(s) (yes)	–	1234 (25.7%)
Incident cancer of head and neck (yes)	146 (1.1%)	50 (1.0%)

*CEI: cumulative exposure index to asbestos.
†TSFE: time since first exposure to asbestos until date of head and neck cancer, date of death or date of last news.

Incidence study

Of the 12 729 men included from the entire population, 146 head and neck cancers (including 44 laryngeal cancers) were recorded by the National Health Insurance fund between 2004 and 1 July 2019. In the CT-scan sample, 50 head and neck cancers (including 20 laryngeal cancers) were recorded (table 2).

Associations between smoking status, different asbestos exposure variables and the incidence of head and neck cancers are presented for the entire cohort, after exclusion of laryngeal cancers, in table 3. As expected, a significant relationship was observed, in univariate analyses, between smoking status and cancer of the head and neck.

In the entire cohort, multivariate analyses revealed a close to significant dose–effect response with CEI for head and neck cancer, even after exclusion of patients presenting with a laryngeal cancer (HR 1.02 (95% CI 1.00 to 1.04) for an increase of 10 f.years/mL) (table 3).

In the CT-scan population, univariate and multivariate analyses revealed a close to significant dose–effect response with CEI for head and neck cancer in univariate analysis and in multivariate analysis, even after exclusion of patients presenting with a laryngeal cancer (HR 1.03 (95% CI 1.00 to 1.06) for an increase of 10 f.years/mL) (table 4). No statistically significant association between pleural plaques and head and neck cancer incidence was observed (HR 1.05 (95% CI 0.45 to 2.45)) after adjustment for asbestos exposure and smoking status (table 4). In the analysis unadjusted by CEI, pleural plaques were similarly not associated with head and neck cancer (HR=1.24 (0.54 to 2.84)) (*data not shown*).

These results were similar after exclusion of the subjects for whom no information concerning tobacco consumption was available (*data not shown*).

Table 2 Characteristics of incidence of head and neck cancers

Characteristics	All subjects (n=12 729)	CT-scan population (n=4804)
Incidence of the head and neck cancers (yes)	146 (1.1%)	50 (1.0%)
C00 Lip	1 (0.7%)	–
C01 Base of tongue	5 (3.4%)	2 (4.0%)
C02 Other and unspecified parts of tongue	8 (5.5%)	2 (4.0%)
C03 Gum	1 (0.7%)	–
C04 Floor of mouth	6 (4.1%)	3 (6.0%)
C05 Palate	1 (0.7%)	1 (2.0%)
C06 Other and unspecified parts of mouth	8 (5.5%)	2 (4.0%)
C07 Parotid gland	9 (6.2%)	2 (4.0%)
C08 Other and unspecified major salivary glands	1 (0.7%)	–
C09 Tonsil	14 (9.6%)	6 (12.0%)
C10 Oropharynx	16 (11.0%)	6 (12.0%)
C11 Nasopharynx	4 (2.7%)	1 (2.0%)
C12 Piriform sinus	13 (8.9%)	4 (8.0%)
C13 Hypopharynx	4 (2.7%)	1 (2.0%)
C14 Other and ill-defined sites in the lip, oral cavity and pharynx	6 (4.1%)	–
C30 Nasal cavity and middle ear	3 (2.0%)	–
C31 Accessory of sinuses	2 (1.4%)	–
C32 Larynx	44 (30.1%)	20 (40.0%)

Mortality study

In men, a total of 37 cases of death from head and neck cancer (excluding 8 from laryngeal cancers) were registered in the follow-up study. Multivariate analyses, including smoking status as a confounding factor and TSFE, showed a close to significant dose–effect response between CEI and mortality from head and neck cancer (HR 1.03 (95% CI 1.00 to 1.05)) for an increase of 10 f.years/mL (*data not shown*) and a significant relationship, even after exclusion of cases of death from laryngeal cancer (HR 1.03 (95% CI 1.01 to 1.06)) for an increase of 10 f.years/mL (table 5).

We also conducted an analysis of the quantitatively significant group of pharyngeal cancers and observed a significant dose–response relationship between CEI of exposure to asbestos, in the incidence study (HR 1.04, 95% CI 1.01 to 1.06) for an increase of 10 f.years/mL in the entire cohort and HR 1.05, 95% CI (1.01 to 1.10 for an increase of 10 f.years/mL in the CT-scan sample) and a close to significant dose–response relationship in the mortality study (HR 1.04, 95% CI 0.99 to 1.10) (*data not shown*).

DISCUSSION

Our results support the hypothesis of a link between exposure to asbestos and the risk of cancer of the head and neck, both for incidence and mortality data, even after exclusion of laryngeal cancers. No link between these cancers and pleural plaques was observed.

The International Agency for Research on Cancer (IARC) concluded that there was limited evidence in humans for a link between asbestos exposure and cancers of the pharynx.[12] Furthermore, a meta-analysis conducted in 2006 and based on 16 cohort studies of mortality and 6 case-control studies[19] concluded that the evidence is suggestive but not sufficient to infer a causal relationship between asbestos exposure and pharyngeal cancer. Few studies have evaluated exposure–response trends, and there was no indication of higher risk associated with more extreme exposures to asbestos (HR=0.93, 95% CI 0.21 to 4.15). Concerning the six case-control studies included in this meta-analysis, four were adjusted for alcohol consumption and smoking. An hospital-based study of 206 total hypopharynx cases and 305 controls[20] was designed to assess the effects of occupational exposures to asbestos and man-made mineral fibres. The authors reported an HR of 1.80 (95% CI 1.08 to 2.99) for those ever exposed to asbestos, adjusted for smoking and alcohol consumption. In analysis focusing on magnitude of exposure, the OR was

Table 3 Incidence of head and neck cancer after exclusion of subjects with a laryngeal cancer according to asbestos exposure and smoking status in the entire cohort (Cox models, N=12 685–176 256 subjects years)

	Cancer of the head and neck after exclusion of subjects with a laryngeal cancer					
	Number		Univariate model		Final model adjusted for smoking, CEI* and TSFE†	
	N‡	C§	HR(95% CI)	P value	HR(95% CI)	P value
Smoking status (baseline)						
Never smokers	2611	14	Ref	**<0.001**	Ref	**<0.001**
Former smokers	5340	29	1.03 (0.54 to 1.94)		1.00 (0.53 to 1.89)	
Current smokers	735	18	**4.32 (2.09 to 8.94)**		**4.27 (2.07 to 8.82)**	
MD¶	3999	41	**2.04 (1.11 to 3.73)**		**2.09 (1.14 to 3.84)**	
Asbestos exposure						
Duration (years)			0.99 (0.97 to 1.01)	0.30		
(0–20)	1841	19	Ref	0.80	–	
(20–30)	2413	22	0.96 (0.51 to 1.79)		–	
(30–40)	5508	41	0.82 (0.47 to 1.45)		–	
≥40	2923	20	0.74 (0.39 to 1.43)		–	
CEI* (f.years/mL)						
For an increase of 10 f.years/mL			1.02 (0.99 to 1.03)	0.08	**1.02 (1.00 to 1.04)**	**0.04**

Bold values indicate statistical significance.
*CEI: cumulative exposure index to asbestos (f.years/mL).
†TSFE : time since first exposure (years).
‡N: overall number of subjects by category.
§C: overall number of incident cases of cancer of the head and neck (update 1 July 2019).
¶MD: missing data.

Table 4 Incidence of head and neck cancer after exclusion of subjects with a laryngeal cancer according to asbestos exposure and smoking status in the 'CT-scan sample' (Cox Models, N=4784–68 277 subjects years)

	Cancer of the head and neck after exclusion of subjects with a laryngeal cancer					
	Number		Univariate model		Final model adjusted for smoking, CEI* and TSFE†	
	N‡	C§	HR(95% CI)	P value	HR(95% CI)	P value
Smoking status (baseline)						
Never smokers	1286	10	Ref	**<0.001**	Ref	**0.03**
Former smokers	2838	12	0.54 (0.23 to 1.24)		0.52 (0.22 to 1.21)	
Current smokers	321	7	2.31 (0.83 to 6.46)		**2.21 (0.79 to 6.15)**	
MD¶	339	1	0.41 (0.05 to 3.23)		0.40 (0.05 to 3.16)	
Pleural plaque (s)						
No	3554	22	Ref	0.50	Ref	**0.91**
Yes	1230	8	1.19 (0.52 to 2.71)		1.05 (0.45 to 2.45)	
Asbestos exposure						
Duration (years)			0.99 (0.95 to 1.02)	0.44		
(0–20)	653		Ref	0.30	–	
(20–30)	925		0.58 (0.18 to 1.90)		–	
(30–40)	2118	16	0.99 (0.38 to 2.61)		–	
≥40	1088	3	0.37 (0.09 to 1.54)		–	
CEI* (f.years/mL)						
For an increase of 10 f.years/mL			**1.03 (1.00 to 1.06)**	**0.04**	**1.03 (1.00 to 1.06)**	**0.03**

Bold values indicate statistical significance.
*CEI: cumulative exposure index to asbestos (f.years/mL).
†TSFE: time since first exposure (years).
‡N: overall number of subjects by category.
§C: overall number of incident cases of cancer of the head and neck (update 1 July 2019).
¶MD: missing data.

increased in all categories, but there was little evidence of a trend with increasing exposure.

A study of 138 Swedish men with pharyngeal cancer[21] found no association of this cancer with asbestos exposure. However, in a meta-analysis including 8 case-control studies and 55 cohort studies, asbestos exposure was significantly associated with an increased risk of cancer of the oral cavity and pharynx (meta-OR=1.25 95% CI 1.10 to 1.42).[6]

More recently, in a US general population case-control study of 190 cases and 203 controls, a significant excess risk of

Table 5 Death from head and neck cancer after exclusion of death from laryngeal cancer according to asbestos exposure and smoking status in the entire cohort (Cox models, N=12 511–137 901 subjects years)

	Cancer of the head and neck after exclusion of death from laryngeal cancer					
	Number		Univariate model		Final model adjusted for smoking, CEI* and TSFE†	
	N‡	C§	HR(95% CI)	P value	HR(95% CI)	P value
Smoking status (baseline)						
Never smokers	2563	2	Ref	**0.002**	Ref	**0.0007**
Former smokers	5375	9	2.01 (0.43 to 9.35)		1.90 (0.41 to 8.81)	
Current smokers	742	9	**12.15 (2.50 to 58.93)**		**11.99 (2.49 to 57.86)**	
MD¶	3831	9	3.30 (0.71 to 15.30)		3.48 (0.75 to 16.15)	
Asbestos exposure						
Duration (years)			0.98 (0.95 to 1.02)	0.30		
(0–20)	1825	7	Ref	0.80	–	
(20–30)	2364	7	0.82 (0.28 to 2.40)		–	
(30–40)	5422	10	0.59 (0.21 to 1.63)		–	
≥40	2900	5	0.66 (0.19 to 2.22)		–	
CEI* (f.years/mL)						
For an increase to 10 f.years/mL			**1.03 (1.00 to 1.06)**	**0.03**	**1.03 (1.01 to 1.06)**	**0.02**

Bold values indicate statistical significance.
*CEI: cumulative exposure index to asbestos.
†TSFE: time since first exposure (years).
‡N: overall number of subjects by category.
§C: overall number of deaths from head and neck cancer (update 31 December 2015).
¶MD: missing data.

pharyngeal cancer was found in association with asbestos exposure in men (OR=1.41; 95% CI 1.01 to 1.97).[22] This result was also found in a prospective cohort study where asbestos exposure was associated with an HR of 2.20 (95% CI 1.08 to 4.49) for pharyngeal cancer.[23]

Concerning cancers of the nasal cavities and the sinuses, to our knowledge, no epidemiological evidence of an association with asbestos exposure has been found.

Also to our knowledge, no study has previously reported an association between head and neck cancers (after exclusion of laryngeal cancers) and asbestos exposure, with quantitative data on exposure. The strength of our study was the availability of the whole-life work history from each subject, allowing to estimate the average exposure of all workers included in the cohort, thanks to evaluation of asbestos exposure by industrial hygienists using data from a standardised questionnaire, describing all job positions occupied throughout the individual's professional career. The significant relationship between head and neck cancers (after exclusion of laryngeal cancers) and asbestos exposure is observed, despite a loss of statistical power in relation with a Berksson error[24] linked to this approach to exposure assessment.

Only a few studies, such as our own, have reported incidence data. In an incidence and mortality study conducted in a cohort of 7996 men and 584 women employed in the asbestos cement industry in Denmark,[25] the authors observed no excess incidence of cancer of the buccal cavity and pharynx (observed 13, expected 16; O/E 0.79; 95% CI 0.42 to 1.35). Another incidence and mortality study, conducted in a cohort of former workers of a crocidolite mining and milling operation in Western Australia,[26] showed a non-significantly higher incidence of upper aerodigestive cancers, cumulative exposure to asbestos not appearing to be associated with the incidence of upper aerodigestive cancers. Concerning dose–effect relationships, in a mortality study involving a cohort of miners,[27] relative risks (RR) were increased, but there was no indication of an exposure–response trend.

In our study, we were able to conduct multivariate analyses, including smoking as a confounding factor, and we also observed a significant dose–response relationship between CEI to asbestos and head and neck cancer mortality (HR 1.03 95 CI 1.01 to 1.06). These results are confirmed after analysis of sensitivity and excluding subjects for whom information concerning tobacco consumption was not available.

Furthermore, to our knowledge, no published study has studied the link between pleural plaques detected by CT scan and head and neck cancers. In our study, no association has been observed, contrary to observations in the same cohort for pleural mesothelioma and lung cancer.[14 15] A weakness of our study is the relativity low number of head and neck cancers in the CT-scan population (N=50 head and neck cancers, including 20 laryngeal cancers). Our study's strengths are its size and accurate determination of pleural plaques based on CT scans interpreted by thoracic radiology experts.

In our study, the median age for inclusion was 63. In metropolitan France in 2018, the median ages at diagnosis and death for lip, mouth and pharyngeal cancers were 62 and 65 years respectively in men and 64 and 69 years in women. For cancers of the nasal cavity, sinus appendage of the face, and ear, the median age at diagnosis in 2018 was 65 years in men and 69 years in women. For larynx cancer, the median age at diagnosis was 64 years in men and 62 years in women.[28] In this context, given the average age at diagnosis of head and neck cancers in France, a non-substantial fraction of the patients presenting with this disease was lost.

The second limitation of our study is that we could not take into account alcohol consumption which may represent a potential confounding factor. Nevertheless, this would only be a confounding factor if it was related to both the outcome (head and neck cancer) and the main exposure of interest (asbestos exposure). In a previous study looking at colon cancer, alcohol consumption was obtained from the ARDCo-Nutrition subsample of 3769 subjects and no significant relationship between CEI and alcohol consumption was observed.[29]

Even if conventional squamous cell carcinoma can be observed in all head and neck cancer locations, other histological types such as adenocarcinomas or undifferentiated cancers mainly concern the nasopharynx, sinonasal cavities or salivary glands.

Unfortunately, in our study, we did not have access to information concerning histological types of head and neck. Nevertheless, the number of incident cases would not have offered us sufficient statistical power to highlight a possible relationship between a particular localisation (pharynx or sinonasal cavities) and a particular subtype of cancer and exposure.

Our study is original for several reasons. First, it is both an incidence and a mortality study, in which occupational exposure to asbestos has been quantified. Furthermore, this study presents results that are adjusted for smoking, for CEI and for TSFE, and in which the role of alcohol consumption is unlikely.

Our study could lead to new recommendations for occupational medical surveillance of workers previously occupationally exposed to asbestos, and to new modalities concerning the potential medico-legal compensation for associated cases of head and neck cancers, other than laryngeal cancers.

CONCLUSION

We reported a dose–response effect between cumulative exposure to asbestos and the incidence and mortality of head and neck cancers, after exclusion of laryngeal cancers, in a large prospective cohort. Such results, if confirmed by other studies, could lead to changes in the medico-legal management of head and neck cancers among subjects having been occupationally exposed to asbestos.

Author affiliations
[1]CHU, Caen, France
[2]Université de Caen Normandie, Caen, France
[3]INSERM U1086 ANTICIPE, Caen, France
[4]Epicene Team, UMR U1219 - Bordeaux Population Health Research Center, Bordeaux, France
[5]INGRES, EA 7298, Université de Lorraine, Vandoeuvre les Nancy, France
[6]Centre de Consultations de Pathologie professionnelle, CHU de Nancy, Vandoeuvre les Nancy, France
[7]Université de Bordeaux, Bordeaux, France
[8]Environmental Health Platform Dedicated to Reproduction, ARTEMIS Center, Bordeaux University Hospital, Bordeaux, France
[9]Bordeaux Population Health Research Center, Inserm UMR1219-EPICENE, University of Bordeaux, Talence, France
[10]CHIC, Creteil, Île-de-France, France
[11]Service des Maladies Professionnelles, CHU, Rouen, France
[12]Radiology, Université de Bordeaux, Pessac, France
[13]CHU Rennes, Rennes, Bretagne, France
[14]Pneumologie et Pathologie Professionnelle, Centre Hospitalier Intercommunal de Créteil, Créteil Cedex, France

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ORCID iDs
Bénédicte Clin http://orcid.org/0000-0001-9138-5265
Fleur Delva http://orcid.org/0000-0001-5594-5405

REFERENCES

1 Carvalho AL, Nishimoto IN, Califano JA, *et al*. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the seer database. *Int J Cancer* 2005;114:806–16.
2 WHO. *Classification of head and neck tumours*. 4th ed. Lyon: IARC, 2017.
3 Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009;45:309–16.
4 International Agency on Research for Cancer. *Smokeless tobacco and some tobacco-specific N-nitrosamines*. Vol. 89. IARC, 2007.
5 Awan KH. Effects of tobacco use on oral health - an overview. *Ann Dent* 2011;18:18–23.
6 Paget-Bailly S, Cyr D, Luce D. Occupational exposures to asbestos, polycyclic aromatic hydrocarbons and solvents, and cancers of the oral cavity and pharynx: a quantitative literature review. *Int Arch Occup Environ Health* 2012;85:341–51.
7 Paget-Bailly S, Cyr D, Luce D. Occupational exposures and cancer of the larynx-systematic review and meta-analysis. *J Occup Environ Med* 2012;54:71–84.
8 Merler E, Baldasseroni A, Laria R, *et al*. On the causal association between exposure to leather dust and nasal cancer: further evidence from a case-control study. *Br J Ind Med* 1986;43:91–5.
9 Bonneterre V, Deschamps E, Persoons R, *et al*. Sino-Nasal cancer and exposure to leather dust. *Occup Med* 2007;57:438–43.
10 IARC. International agency for research on cancer) Working group on the evaluation of carcinogenic risks to humans. 1990. chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum* 1990;49:1–648.
11 Luce D, Gérin M, Morcet JF, *et al*. Sinonasal cancer and occupational exposure to textile dust. *Am J Ind Med* 1997;32:205–10.
12 Straif K, Benbrahim-Tallaa L, Baan R, *et al*. A review of human carcinogens--Part C: metals, arsenic, dusts, and fibres. *Lancet Oncol* 2009;10:453–4.
13 Paris C, Thierry S, Brochard P, *et al*. Pleural plaques and asbestosis: dose- and time-response relationships based on HRCT data. *Eur Respir J* 2009;34:72–9.
14 Pairon JC, Laurent F, Rinaldo M. Pleural plaques are associated with an increased risk of pleural mesothelioma. *J Natl Cancer Inst* 2013;61:11–20.
15 Pairon J-C, Andujar P, Rinaldo M, *et al*. Asbestos exposure, pleural plaques, and the risk of death from lung cancer. *Am J Respir Crit Care Med* 2014;190:1413–20.
16 Ameille J, Letourneux M, Paris C, *et al*. Does asbestos exposure cause airway obstruction, in the absence of confirmed asbestosis? *Am J Respir Crit Care Med* 2010;182:526–30.
17 Clin B, Paris C, Ameille J, *et al*. Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? *Thorax* 2011;66:985–91.
18 Clin B, Thaon I, Boulanger M, *et al*. Cancer of the esophagus and asbestos exposure. *Am J Ind Med* 2017;60:968–75.
19 Committee on Asbestos: Selected Health Effects. *Asbestos: selected cancers*. The National Academies Press, 2006: 340. ISBN: 0-309-65952-3.
20 Marchand JL, Luce D, Leclerc A, *et al*. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. *Am J Ind Med* 2000;37:581–9.
21 Gustavsson P, Jakobsson R, Johansson H, *et al*. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. *Occup Environ Med* 1998;55:393–400.
22 Langevin SM, O'Sullivan MH, Valerio JL, *et al*. Occupational asbestos exposure is associated with pharyngeal squamous cell carcinoma in men from the greater Boston area. *Occup Environ Med* 2013;70:858–63.
23 Offermans NSM, Vermeulen R, Burdorf A, *et al*. Occupational asbestos exposure and risk of oral cavity and pharyngeal cancer in the prospective Netherlands cohort study. *Scand J Work Environ Health* 2014;40:420–7.
24 Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;55:651–6.
25 Raffn E, Lynge E, Juel K, *et al*. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med* 1989;46:90–6.
26 Reid A, Ambrosini G, de Klerk N, *et al*. Aerodigestive and gastrointestinal tract cancers and exposure to crocidolite (blue asbestos): incidence and mortality among former crocidolite workers. *Int J Cancer* 2004;111:757–61.
27 Piolatto G, Negri E, La Vecchia C, *et al*. An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. *Br J Ind Med* 1990;47:810–4.
28 Defossez G, Le Guyader-Peyrou S, Uhry Z. *Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Étude partir des registres des cancers du réseau Francim*. Vol 1. Tumeurs solides, 2019.
29 Paris C, Thaon I, Hérin F, *et al*. Occupational asbestos exposure and incidence of colon and rectal cancers in French men: the asbestos-related diseases cohort (ARDCo-Nut). *Environ Health Perspect* 2017;125:409–15.