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Asbestos exposure, pleural plaques and digestive cancers

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Abstract

Background The aim of this study was to analyse the incidence and mortality from various digestive cancer sites and their potential link with pleural plaques, in a French cohort of workers previously occupationally exposed to asbestos.

Methods We conducted a 10-year follow-up study in 13,481 male subjects, included in the cohort between October 2003 and December 2005, for whom asbestos exposure was assessed by calculation of a cumulative exposure index (CEI) in equivalent fibres.years/mL for each subject. We conducted an incidence study and a mortality study. Complementary analysis was restricted to men who had performed at least one chest CT-scan ($N=4,794$). We used a Cox model with age as the time axis variable, adjusted for smoking, time since first exposure (TSFE), CEI to asbestos and the existence of pleural plaques on CT-scan.

Results In the incidence study, a significant dose–response relationship was observed between CEI to asbestos and oesophageal cancer (HR 1.03, 95% CI [1.01–1.06]) in the entire cohort after adjustment for TSFE and smoking status. In subjects undergoing CT-scan, a significant association between pleural plaques was observed for oesophageal cancer incidence (HR 2.80, 95% CI [1.09–7.20]) and in the mortality study, multivariate analyses showed a significant dose–effect response between CEI to asbestos and death from oesophageal cancer (HR 1.03, 95% CI [1.00–1.05]) in the entire cohort.

Conclusions This large-scale study confirms results concerning a likely relationship between asbestos exposure and oesophageal cancer, and the association between this cancer and pleural plaques after adjustment on CEI to asbestos.

Keywords Asbestos, Cancer, Digestive cancer, Oesophageal cancer, Occupational exposure, Incidence, Mortality, Pleural plaque

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Background

Until recently, the medical consequences of asbestos exposure were considered to essentially concern the respiratory tract, associating benign pleural pathologies, asbestosis and malignant pathologies (pleural and peritoneal mesothelioma, primary bronchopulmonary cancer). In an IARC monograph [1], laryngeal and ovarian cancers were also linked to asbestos exposure, with sufficient evidence in humans. Furthermore, studies focusing on occupational asbestos exposure have shown an increased risk of digestive cancers in exposed workers. Selikoff in 1964, followed by Miller in 1978, were the first authors to suggest a link between asbestos exposure and certain digestive cancers [2–5]. More recent studies focusing on occupational asbestos exposure have also shown an increased risk of digestive cancers in exposed workers [6–8], in particular for colorectal cancer [6–14] and for oesophageal cancer [15, 16]. Colorectal and stomach cancers are considered by the IARC as potentially associated with asbestos exposure, despite limited evidence in humans [17]. However, with the exception of peritoneal mesothelioma, the role of asbestos in the pathogenesis of digestive cancers remains controversial.

In 2001, following a national consensus conference on clinical surveillance strategy for former asbestos workers, a large-scale screening programme for asbestos-related diseases was initiated in four regions of France [18]. In a previous study, pleural plaques were associated with an increased incidence of mesothelioma [19] and of lung cancer mortality [20], independently of exposure to asbestos, suggesting that pleural plaques may be an independent risk factor for these cancers. To our knowledge, no study has reported that pleural plaques could also be an independent risk factor for digestive cancers.

The aim of the present study was to analyse the association between asbestos exposure, pleural plaques and the risk of various digestive cancer sites in a 10-year follow-up study of formerly asbestos-exposed workers.

Methods

Study design and population

In France, in 2001, a feasibility study on the medical surveillance of retired or inactive subjects having been occupationally exposed to asbestos, was conducted in Aquitaine, Upper Normandy, Lower Normandy and Rhône-Alpes, after designation by the French Ministry for Employment and Solidarity's Professional Relations Directorate and the 'Caisse Nationale d'Assurance Maladie des Travailleurs Salariés' (CNAM) Directorate for Professional Risks [18]. Subjects were offered and a free medical check-up including chest CT-scan and pulmonary function tests [21, 22]. The Asbestos-Related Diseases COhort (ARDCO) included 14,218 subjects (unemployed or retired asbestos-exposed workers covered by the French National Health Insurance fund), identifiable from databases compiled by the 'Caisse Primaire d'Assurance Maladie' (CPAM). These subjects completed a standardised questionnaire describing all jobs held throughout their working careers, as well as specific asbestos-exposing tasks, and were included after confirmation of asbestos exposure from questionnaire analysis by industrial hygienists. Among these 14,218 subjects, 13,481 were men (94.8%) and 737 were women (5.2%). Age at inclusion was 60 years or less for 3,332 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, 4,794 (37.7%) benefited from at least one chest CT-scan, results being forwarded in the form of a CD-Rom (only CDs were retained, not films) and constitute the 'CT-Scan population' of the present study.

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

Data collection

Asbestos exposure

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 *(Supplemental material)*, as previously described elsewhere [21].

The level of exposure, assessed according to occupation and industrial activities, was classified into four defined categories 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 cumulative exposure index (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 CEI. Time since first exposure to asbestos (TSFE) was defined as the time elapsed between the start year of the first exposed employment period and the year of the index date (diagnosis of digestive cancer, death or end of follow-up).

CT-scanning

The 'CT-Scan sample' was consisted of subjects benefited from at least one readable chest CT-scan on CD-ROM between 2003 and 2019 and 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) [21].

All available CT-scan results on CD-ROM underwent standard double reading (and triple reading in the case of disagreement), focusing 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. Pleural plaques were considered to be present in the case of circumscribed quadrangular pleural elevations with sharp borders and tissue density, sometimes calcified, with usual topography for at least some of the images [23].

Tobacco consumption

Subjects were classified into three categories according to tobacco consumption at inclusion: current smokers, former smokers (defined as those who had quit smoking since at least one year) and never 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. New cases of digestive cancer were recovered annually, from the date of enrolment to 1 July 2021, from the National Health insurance fund, which collects these data for medical cost coverage purposes. Anal margin cancers were excluded from the analysis, since their pathological characteristics are different from those of digestive cancers.

A follow-up study of mortality was also conducted in the study population. The vital status of each subject in the cohort was collected from the National directory for identification of physical persons (RNIPP) up to 1 July 2021. 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 CépiDc.

Statistical analysis method

The variables used to characterise asbestos exposure were: duration of asbestos exposure, CEI and time since first exposure (TSFE). Information on tobacco consumption was missing for 31% of subjects. In this context, we used multiple imputation based on the MICE (multiple imputation by chained equation) method. All variables included in the multivariate models (CEI, TSFE and pleural plaques) were used in the imputations' models for each model. Ten imputations were performed.

Analyses were performed on any digestive cancer site, then by specific site—excluding other sites. Due to the small number of women in this cohort (only 737, of whom 39 presenting with digestive cancer) not ensuring sufficient statistical power, the analysis was performed only in male subjects.

In the follow-up study, statistical associations between these asbestos exposure variables and digestive 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 using Schoenfeld residuals. Unadjusted hazard ratios (HRs) and adjusted HRs for these variables, namely smoking status, CEI and TSFE to asbestos, were calculated for the risk of digestive cancer incidence and for mortality. Multivariate analysis was based on TSFE and CEI as continuous variables. Linearity hypotheses of CEI were checked using the mfp package (Multivariable Fractional Polynomials). HRs for CEI were presented for an increase of 10 fibres.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 12,725 were included for incident analysis, and 12,519 included for mortality analysis, as explained in the flow chart (Fig. 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; 6,102 subjects (48.0%) were current smokers or former smokers. Mean (SD) duration of asbestos exposure was 31.3 (10.4) years.

Incidence study

In the 12,725 men included from the entire population, 685 digestive cancers were recorded by the National Health Insurance fund between 2004 and 1 July 2021. In the 'CT-scan sample', 248 digestive cancers were recorded (Table 2).

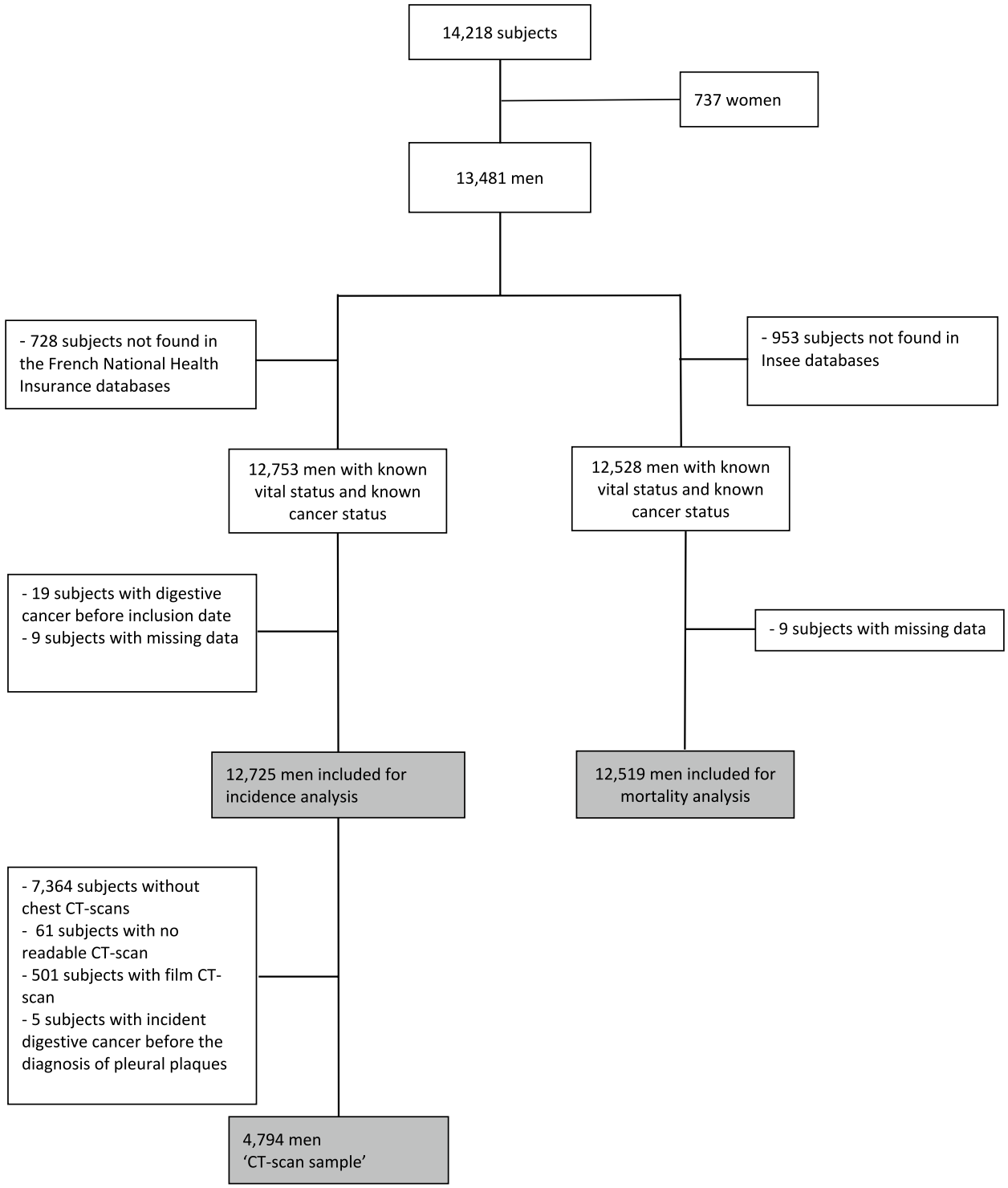

Fig. 1 Study flow chart

Associations between smoking status, different asbestos exposure variables and the incidence of digestive cancers are presented for the entire cohort, in *supplemental material*. A significant relationship was observed, in univariate and in multivariate analyses, between smoking status and digestive cancers (HR 1.31, 95% CI [1.05–1.63]

Table 1 Study population characteristics (incidence analysis)

Characteristics	All subjects ($n=12,725$)	CT-scan sample ($n=4,794$)
Age at baseline (years)		
mean ± SD[1]	63.2 ± 5.5	63.2 ± 5.4
< 60	2,767 (21.7%)	1,092 (22.8%)
60 – 74	9,627 (75.7%)	3,578 (74.6%)
≥ 75	331 (2.6%)	124 (2.6%)
Follow-up (years)		
Median [min–max]	16.7 [0.005–18.3]	16.7 [0.05–18.3]
Smoking status at baseline		
Never smokers	2,614 (20.5%)	1,286 (26.8%)
Former smokers	5,354 (42.1%)	2,841 (59.2%)
Current smokers	748 (5.9%)	324 (6.8%)
Missing data	4,009 (31.5%)	343 (7.2%)
Duration of exposure to asbestos (years)		
mean ± SD[1]	31.3 (10.4)	31.5 (10.1)
< 20	1,852 (14.6%)	657 (13.7%)
20 – 29	2,422 (19.0%)	926 (19.3%)
30 – 39	5,526 (43.4%)	2,123 (44.3%)
≥ 40	2,925 (23.0%)	1,088 (22.7%)
CEI[2] to asbestos (f.years/mL)		
mean ± SD[1]	60.2 (99.4)	64.4 (101.1)
[0.01–2.84]	2,556 (20.1%)	808 (16.8%)
[2.84–10.22]	2,569 (20.1%)	929 (19.4%)
[10.22–31.70]	2,544 (20.0%)	1,024 (21.4%)
[31.70–70.80]	2,567 (20.2%)	1,026 (21.4%)
[70.80–490.00]	2,489 (19.6%)	1,007 (21.0%)
TSFE[3] (years)		
mean ± SD[1]	57.8 (8.3)	58.6 (7.8)
< 40	344 (2.7%)	84 (1.8%)
40 – 49	1,603 (12.6%)	493 (10.3%)
50 – 59	4,910 (38.6%)	1,828 (38.1%)
≥ 60	5,868 (46.1%)	1,389 (49.8%)
Pleural plaque(s) (yes)	-	1,224 (25.5%)
Incident digestive cancer (yes)	685 (5.4%)	248 (5.2%)

[1] *SD* Standard Deviation

[2] *CEI* Cumulative exposure index to asbestos

[3] *TSFE* Time Since First Exposure to asbestos until date of digestive cancer, date of death or date of last news

for former smokers and (HR 1.46, 95% CI [1.02–2.09] for current smokers). In the entire cohort, multivariate analyses did not reveal any dose–effect response with CEI for digestive cancer, (HR 1.00, 95% CI [0.99–1.01] for an increase of 10 f.years/mL).

We also conducted analysis for each digestive cancer site. In the incidence study, we observed a significant dose–response relationship between CEI of exposure to asbestos, only for oesophageal cancer, in univariate and in multivariate analysis (HR 1.03, 95% CI [1.01–1.06]) for an increase of 10 f.years/mL in the entire cohort. The incidence of oesophageal cancer according to asbestos exposure and smoking status in the entire cohort is shown in Table 3.

The results concerning other sites, such as colon cancer, and are shown in supplementary materials. For colon or rectal cancer according to asbestos exposure and smoking status in the entire cohort, multivariate analyses did not reveal any dose–effect response with CEI (HR 1.00, 95% CI [0.99–1.01] for an increase of 10 f.years/mL). Multivariate analyses did not reveal any dose–effect response with CEI for stomach cancer (HR 0.98, 95% CI [0.95–1.01]), liver cancer (HR 0.99, 95% CI

Table 2 Characteristics of incidence of digestive cancers

Characteristics	All subjects (*n* = 12,725)	CT-scan population (*n* = 4,794)
Incidence of the digestive cancers (yes)	685 (5.4%)	248 (5.2%)
C15 Oesophagus	47 (6.9%)	19 (7.7%)
C16 Stomach	64 (9.3%)	19 (7.7%)
C17 Small intestine	8 (1.2%)	2 (0.8%)
C18 Colon	282 (41.2%)	113 (45.6%)
C19 Rectosigmoid junction	21 (3.1%)	7 (2.8%)
C20 Rectum	91 (13.3%)	32 (12.9%)
C21 Anus and anal canal	3 (0.4%)	2 (0.8%)
C22 Liver and intrahepatic bile ducts	80 (11.7%)	22 (8.9%)
C23 Gallbladder	5 (0.7%)	1 (0.4%)
C24 Other and unspecified parts of biliary tract	7 (1.0%)	1 (0.4%)
C25 Pancreas	75 (10.9%)	29 (11.7%)
C26 Other and ill-defined digestive organs	2 (0.3%)	1 (0.4%)

[0.97–1.02]) and for pancreatic cancer (HR 1.00, 95% [0.98–1.03]) for an increase of 10 f.years/mL).

In the 'CT-scan population', univariate and multivariate analyses did not reveal any significant dose–effect response with CEI for digestive cancer (HR 1.00, 95% CI [0.99–1.02] for an increase of 10 f.years/mL) *(Supplemental material)*.

No statistically significant association between pleural plaques and digestive cancer incidence was observed in the 'CT-scan sample' (HR 0.83, 95% CI [0.61–1.12]) after adjustment for asbestos exposure and smoking status *(Supplemental material)*. Nevertheless, this site-by-site analysis showed a significant association between pleural plaques and oesophageal cancer incidence (HR 2.80, 95% CI [1.09–7.20]) in this sample, after adjustment for asbestos exposure and smoking status, as shown in Table 4, describing the incidence of oesophageal cancer according to asbestos exposure and smoking status in the 'CT-scan sample'.

Complete case analyses show similar results *(data in supplemental material)*.

Mortality study

In men, a total of 282 cases of death from digestive cancer were registered in the follow-up study. In the entire cohort, multivariate analyses, including smoking status as a confounding factor and TSFE, did not reveal any significant dose–effect response between CEI and death from digestive cancer (HR 1.00, 95% CI [0.99–1.02]) for

Table 3 Incidence of oesophageal cancer according to asbestos exposure and smoking status in the entire cohort (Cox Models, *N* = 12,087 – 185,434 subjects-years)

	Oesophageal cancer					
	number		univariate model		final model adjusted for smoking, CEI[1] and TSFE[2]	
	N[3]	C[4]	HR[5] [95% CI[6]]	*p*-value	HR[5] [95% CI[6]]	*p*-value
Smoking status[7] (baseline)						
never smokers	-	-	Ref	**< 0.001**	Ref	**0.01**
former smokers	-	-	1.26 [0.53–2.97]		1.15 [0.43–3.06]	
current smokers	-	-	**4.16 [1.51–11.47]**		**3.67 [1.29–10.46]**	
Asbestos exposure						
Duration (years)			1.03 [0.99–1.06]	0.12		
[0–20]	1,766	3	Ref	0.34	-	
[20–30]	2,306	8	2.07 [0.55–7.81]		-	
[30–40]	5,249	23	2.55 [0.76–8.57]		-	
≥ 40	2,766	13	2.73 [0.77–9.72]		-	
CEI[1] (f.years/mL)						
For an increase of 10 f.years/mL			**1.03 [1.01–1.06]**	**0.002**	**1.03 [1.01–1.06]**	**0.003**

[1] *CEI* Cumulative exposure index to asbestos (f.years/mL)

[2] *TSFE* Time since first exposure (years)

[3] *N* overall number of subjects by category

[4] *C* overall number of incident cases of digestive cancer (update 1 July 2021)

[5] *HR* Hazard ratio

[6] *CI* Confidence Interval

[7] Multiple imputation for smoking status based on the MICE method

Table 4 Incidence of oesophageal cancer according to asbestos exposure and smoking status in the 'CT-scan sample' (Cox Models, *N* = 4,565 – 72,067 subjects-years)

	Oesophageal cancer					
	number		univariate model		final model adjusted for smoking, CEI[1] and TSFE[2]	
	N[3]	C[4]	HR[5] [95% CI[6]]	*p*-value	HR[5] [95% CI[6]]	*p*-value
Smoking status[7] (baseline)						
never smokers			Ref	**0.20**	Ref	0.18
former smokers			1.46 [0.38–5.67]		1.22 [0.32–4.74]	
current smokers			4.50 [0.87–23.22]		3.64 [0.69–19.25]	
Pleural plaque(s)						
No	3,393	9	Ref	**0.02**	Ref	**0.04**
Yes	1,174	10	**3.06 [1.23–7.63]**		**2.80 [1.09–7.20]**	
Asbestos exposure						
Duration (years)			1.03 [0.98–1.09]	0.24		
[0–20]	631	1	Ref	0.46	-	
[20–30]	885	2	1.46 [0.13–16.13]		-	
[30–40]	2,011	11	3.22 [0.41–24.96]		-	
≥ 40	1,038	5	2.93 [0.34–25.15]		-	
CEI[1] (f.years/mL)						
For an increase of 10 f.years/mL			1.02 [0.99–1.06]	0.19	1.01 [0.98–1.05]	0.45

[1] *CEI* Cumulative exposure index to asbestos (f.years/mL)

[2] *TSFE* Time since first exposure (years)

[3] *N* overall number of subjects by category

[4] *C* overall number of incident cases of digestive cancer (update 1 July 2021)

[5] *HR* Hazard ratio

[6] *CI* Confidence Interval

[7] Multiple imputation for smoking status based on the MICE method

an increase of 10 f.years/mL using multiple imputation based on the MICE (multiple imputation by chained equation) method *(Table in supplemental material)*.

In the analysis for each digestive cancer site in the mortality study, we only observed a significant dose–response relationship between CEI of exposure to asbestos for oesophageal cancer, in univariate (HR 1.03, 95% CI [1.00–1.05]) and in multivariate analysis (HR 1.03, 95% CI [1.00–1.05]) for an increase of 10 f.years/mL in the entire cohort (Table 5).

In the 'CT-scan population', univariate and multivariate analyses did not reveal any dose–effect response between CEI and death from digestive cancer (HR 1.00, 95% CI [0.98–1.02] for an increase of 10 f.years/mL) *(Supplemental material)*. No statistically significant association between pleural plaques and death from digestive cancer was observed (HR 1.08, 95% CI [0.66–1.75]) after adjustment for asbestos exposure and smoking status *(Supplemental material)*. No significant association between pleural plaques and oesophageal cancer incidence was observed in the 'CT-scan sample' (HR 2.58, 95% CI [0.71–9.39]) after adjustment for asbestos exposure and smoking status *(Supplemental material)*.

Discussion

This large-scale study confirms results concerning a likely relationship between asbestos exposure and oesophageal cancer, and the association between this cancer and pleural plaques after adjustment on CEI to asbestos. Indeed, in the incidence study, a significant dose–response relationship was observed between CEI to asbestos and oesophageal cancer (HR 1.03, 95% CI [1.01–1.06]) in the entire cohort after adjustment for TSFE and smoking status. Furthermore, in subjects undergoing CT-scan, a significant association between pleural plaques was observed for oesophageal cancer incidence (HR 2.80, 95% CI [1.09–7.20]) and in the mortality study, multivariate analyses showed a significant dose–effect response between CEI to asbestos and death from oesophageal cancer (HR 1.03, 95% CI [1.00–1.05]) in the entire cohort.

In a previous study conducted within the ARDCO cohort [15], we observed a significant dose–response relationship between CEI of exposure to asbestos and

Table 5 Death from oesophageal cancer according to asbestos exposure and smoking status in the entire cohort (Cox Models, *N* = 12,277 – 136,247 subjects-years)

	Oesophageal cancer					
	number		univariate model		final model adjusted for smoking, CEI[1] and TSFE[2]	
	N[3]	C[4]	HR[5] [95% CI[6]]	*p*-value	HR[5] [95% CI[6]]	*p*-value
Smoking status[7] (baseline)						
never smokers	-	-	Ref	**0.20**	Ref	0.45
former smokers	-	-	1.77 [0.58–5.43]		1.78 [0.60–5.30]	
current smokers	-	-	3.43 [0.99–11.90]		3.65 [0.99–13.53]	
Asbestos exposure						
Duration (years)			1.01 [0.97–1.04]	0.72		
[0–20]	1,790	4	Ref	0.20	-	
[20–30]	2,327	12	2.31 [0.74–7.17]		-	
[30–40]	5,316	13	1.03 [0.34–3.17]		-	
≥ 40	2,844	11	0.63 [0.52–5.17]		-	
CEI[1] (f.years/mL)						
For an increase of 10 f.years/mL			**1.03 [1.00–1.05]**	**0.04**	**1.03 [1.00–1.05]**	**0.03**

[1] *CEI* Cumulative exposure index to asbestos (f.years/mL)

[2] *TSFE* Time since first exposure (years)

[3] *N* overall number of subjects by category

[4] *C* overall number of incident cases of digestive cancer (update 1 July 2021)

[5] *HR* Hazard ratio

[6] *CI* Confidence Interval

[7] Multiple imputation for smoking status based on the MICE method

oesophageal cancer in both incidence (hazard ratio (HR) 1.26, 95% confidence interval (CI) [1.00–1.58]) and mortality (HR 1.40, 95% CI [1.12–1.75]). The results of the follow-up of this cohort, for a period of over 15 years, confirm the hypothesis of a link between exposure to asbestos and the risk of oesophageal cancer incidence, and a link between pleural plaques and oesophageal cancer. Nevertheless, no statistically significant association between pleural plaques and incidence of other digestive cancers was observed, and in the mortality analysis, no association between pleural plaques and any digestive cancer site (including oesophagus) was observed.

As previously explained, colorectal and stomach cancers are considered by the IARC as potentially associated with asbestos exposure, despite limited evidence in humans [17]. Recent studies focusing on occupational asbestos exposure have also shown an increased risk of digestive cancers in exposed workers [6–8], for colorectal cancer [6–14] and for oesophageal cancer in particular [15, 16].

The relationship between asbestos exposure and oesophageal cancer remains debated. In a cohort study of former workers of a crocidolite mine in Australia [24], no significant association between asbestos exposure and oesophageal cancer was observed (SIR: 1.11 [95% CI 0.60–2.07], SMR: 0.89 [95% CI 0.44–1.78]). Similar results were also found in asbestos exposure case control studies [25–27] showing no significantly increased risk of oesophageal cancer (relative risk (RR): 1.21 [95% CI 0.67–2.17], odds ratio (OR): 1.4 [95% CI 0.7–2.7], and OR: 1.27 [95% CI 0.77–2.10], respectively. In contrast, in a large cohort of 58,279 workers (the Netherlands Cohort Study) for whom asbestos exposure was estimated by linkage to a job-exposure matrix [8], an increase hazard ratio (2.22, 95% CI [1.00–4.94]) of oesophageal cancer was reported. Furthermore, in an incidence study conducted in a cohort of 2,024 subjects having worked in an asbestos reprocessing plant [13], the authors observed a significantly elevated incidence of oesophageal cancer (SIR = 1.63 [1.02 −2.48]). These results have been confirmed in a more recent study, conducted in the same cohort but with longer follow-up [6]. Meta-analysis, conducted in 2016 [28] concluded that high levels of exposure to asbestos may contribute towards a significantly higher risk of mortality from oesophageal cancer. More recent meta-analysis concerning the association between asbestos exposure and oesophageal cancer [16] concluded that asbestos exposure, to chrysotile in particular, was significantly and positively associated with oesophageal cancer. The association between asbestos exposure

and oesophageal cancer was determined by fixed-effect model meta-analysis in which the pooled SMR resulted from 36 SMRs of 34 studies. In a chrysotile subgroup of studies, a significantly increased pooled SMR of 1.27 (95% CI 1.07–1.51, *p*-value = 0.006) was observed.

Concerning colorectal cancer and asbestos exposure, studies mostly based on mortality cohorts have reported an association between asbestos exposure and colorectal cancer [29], mortality studies also reporting a positive association for asbestos exposure and colon and/or rectal cancer [9–11, 14]. However, other mortality cohort studies conducted in the same period did not show any association between asbestos exposure and colon and/or rectal cancer [30–34]. Incidence study results concerning an association between colon and/or rectal cancer are also discordant. For example, in 2011, a significant association between asbestos exposure and the incidence of colorectal cancer was reported among 2,024 French former textile and friction material industry workers heavily exposed to asbestos [13], whereas no significant association with colon and rectal cancer incidence rates was observed in a study among 23,285 Finnish men and 939 women involved in a large-scale screening programme of asbestos-related diseases [35]. In the cohort study of former workers of a crocidolite mine in Australia previously mentioned [24], cumulative asbestos exposure and smoking status were not associated with cancer of the colon and rectum (OR 0.97, 95% CI [0.84–1.12]). Furthermore, in this cohort, year of starting work (OR 1.01, 95% CI [0.54 –1.86]) and time since first asbestos exposure (OR 0.68, 95% CI [0.15–3.03]) were unrelated to cancer of the colon and rectum.

In a previous study conducted in the ARDCO cohort [7], a significant dose–response relationship was observed between CEI to asbestos (Hazard Risk (HR) = 1.10[1.01–1.21]), TSFE (≥ 20 and < 40 years; HR = 4.53[7.86–11.04]) and colon cancer incidence, after adjustment for smoking. Using stratified analysis on TSFE, a stronger relationship was observed for TSFE < 40 years (HR = 1.57[1.25–1.98]). Furthermore, additional data on risk factors for colorectal cancer were collected from the ARDCO-NUT subsample of 3,769 subjects in 2011. Analyses on the ARDCO-NUT subsample confirmed this association only in TSFE < 40 years strata, after adjustment for smoking and other risk factors for colon cancer. No association with rectal cancer was observed.

In the present study, no association between asbestos and colon and/or rectal cancer was found. One hypothesis to explain this lack of association is the fact that, in the study conducted in 2017 in the ARDCO cohort [7], with incidence data up to 2014, asbestos exposure could anticipate the onset of colorectal cancer, explaining the positive association found. Thus, the observed excess in subjects with relatively short latency period and the absence of effect observed after a long latency period could be linked to an "anticipation" of the cancer's occurrence in relation to the development of a disease that would otherwise have occurred later. In the present study, based on later incidence data (2021), longer follow-up may explain the absence of a significant relationship between this cancer and the history of asbestos exposure.

Unfortunately, as previously explained, due to the small number of women in this cohort (only 737), the analysis was performed only in male subjects. It is interesting to note that 39 of these women had digestive cancer, 17 of them colon cancer. In a recent study [36], the authors have reviewed the scientific literature related to asbestos-related colorectal cancer incidence and mortality rates in female. The studies included in this review reported 92 cases in total, and the colon was the primary location of the tumor in 47 cases. The authors stressed that, unfortunately, most of the scientific research is focused on males, and women are significantly under-represented.

In our study, we were able to adjust for tobacco smoking, although unfortunately using only a broad classification (never smokers, former smokers and current smokers), since no information concerning the number of pack-years was available. Unfortunately, we could not take into account alcohol consumption, which may represent a potential confounding factor. Nevertheless, it would only be a confounding factor if related to both the outcome (oesophageal cancer) and the main exposure of interest (asbestos exposure). It would be particularly interesting to collect this information when the next data collection for this cohort will be conducted. Furthermore, concerning the tobacco use, a more detailed categorization (e.g., number of pack-years) would improve the analysis and provide greater precision in the adjustment models, that's why it would also be interesting to collect this information when the next data collection for this cohort will be conducted.

Only a few studies, such as our own, reported incidence data. The strengths of this study are the large number of subjects ($n = 12{,}725$ for the entire cohort, and $n = 4{,}794$ for the 'CT-scan sample'), and the availability of precise knowledge on the occupational exposure of the individuals 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 occupational career.

Another strength is the accurate determination of pleural plaques detected on CT-scan by thoracic radiology experts. We found a significant association between pleural plaques for oesophageal cancer incidence in the 'CT-scan sample' (HR 2.80, 95% CI [1.09–7.20]). To our

knowledge, no previous study has documented the association of pleural plaques and digestive cancer, in particular oesophageal cancer, especially using CT-scan for the detection of pleural plaques. Studies have suggested that proto-oncogene expression and several pathways activated by asbestos were elevated in lung and pleura after exposure to asbestos [37]. However, to our knowledge, no author has studied the potential link between pleural accumulation of asbestos and oesophageal cancer, such as a potential initiation of asbestos-induced redox-dependent signal transduction cascades, which could be involved in the initiation of a carcinogenic responses including the oesophagus. The presence of pleural plaques may be an independent risk factor for oesophageal cancer in asbestos-exposed workers and could lead to new recommendations for occupational and post-occupational medical surveillance of retired or unemployed workers previously occupationally exposed to asbestos, particularly concerning the risk of oesophageal cancer in subjects with other associated risk factors (tobacco, alcohol consumption). Furthermore, by demonstrating that asbestos-exposed subjects with pleural plaques are at higher risk of oesophageal cancer, our results support the idea that subjects with pleural plaques may benefit from follow up, particularly when they are current or former smokers.

These findings could also lead to new modalities of medico-legal compensation for workers previously occupationally exposed to asbestos and presenting with oesophageal cancer. Indeed, whereas peritoneal mesothelioma may benefit from compensation when occupational exposure to asbestos is established, no other digestive cancer currently benefits from any such compensation in France.

Conclusion

We reported, in a large prospective cohort, a significant dose–response relationship between cumulative exposure to asbestos and oesophageal cancer. Moreover, a significant association between pleural plaques and oesophageal cancer incidence was observed after adjustment for asbestos exposure and smoking status. These results prompt the continuation of research in this field, via studies with greater statistical power, in order to confirm the observed trends. Should they be formally established, they could lead to changes in the medical surveillance of subjects presenting with pleural plaques, integrating the risk of oesophageal cancer. The question of the introduction of specific screening for esophageal cancer in asbestos-exposed workers with pleural plaques could be asked, possibly through at least the systematic search for early clinical signs. The medico-legal management of oesophageal cancer among subjects previously occupationally exposed to asbestos could also be reviewed, by adding this anatomical location to existing occupational disease tables.

Abbreviations

ARDCO	Asbestos-Related Diseases COhort
CNAM	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés
CPAM	Caisse Primaire d'Assurance Maladie
CEI	Cumulative exposure index
CI	Confidence interval
CT-scan	Computed tomography scanner
HR	Hazard ratio
IARC	International agency for research on cancer
RNIPP	National directory for identification of physical persons
SD	Standard deviation
TSFE	Time since first exposure

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Conceptualisation: BC, FD, PB, AG, CP, JCP. Methodology: BC, CG, FD, PB, CP, JCP. Writing—original draft preparation: BC, FD, JCP. Writing—review & editing: BC, CG, FD, PA, IT, PB, JB, AG, FL, IB? CP, JCP. Each author has been sufficiently involved in this work to take public responsibility for appropriate portions of its content.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the hospital ethics committee (CCPPRB Paris-Cochin n°1946 (2002), CCP Ile-de-France III, n°1946/11/02–02 (2010)). All participants received information on the study and provided their written informed consent. all experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication
"Not Applicable".

Competing interests
The authors declare no competing interests.

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