BMC Public Health

RESEARCH

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Occupational exposure to ultrafine particles and lung cancer in a population exposed to asbestos

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Abstract

Background Ultrafine particles are present in ever greater quantities in the workplace and only one epidemiological study to date has found an association with the occurrence of lung cancer.

Objective To investigate the effect of occupational exposure to ultrafine particles on the risk of lung cancer.

Methods The ARDCO is a surveillance program involving retiree workers who had been exposed to asbestos during their working life. Exposure to ultrafine particles over the complete lifetime occupational history was assessed using the French job exposure matrix MATPUF. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI).

Results There was no association between exposure to ultrafine particles and lung cancer after adjustment for smoking and exposure to asbestos and crystalline silica.

Conclusion The findings do not indicate increased risks of lung cancer for UFP after adjustment for level of exposure to asbestos, crystalline silica, and smoking status.

Clinical trial number Not applicable.

Keywords Ultrafine particles, Lung cancer, Occupational exposures, Asbestos

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Introduction

In France, primary lung cancer is the second most common cancer in men, with more than 50,000 new cases in 2023, and the primary cause of cancer mortality [1]. The prognosis is poor, with an estimated 5-year survival rate of 20% for all stages combined [1]. A large number of the pulmonary carcinogens known or suspected by the International Agency for Research on Cancer (IARC) are present in the workplace. In 1974, the IARC recognized asbestos as a definite human carcinogen. Until its prohibition in France in 1997, asbestos was used in a number of occupational settings (shipbuilding, automobile industry, construction, and public works in particular). It is estimated that approximately 25% of men over 60 years of age had at least one job that exposed them to asbestos during their career [2]. In 2017, 4.6% of lung cancers in men in the country were attributable to occupational exposure to asbestos [3].

Ultrafine particles (UFPs) are defined as those with a diameter of less than 100 nm [4]. They are emitted unintentionally, both naturally and as a result of human activity, and thus are distinguished from other nanoscale particles, such as engineered nanoparticles. Due to their main sources of emissions (thermal processes typically involving combustion, such as engines, foundries, and welding equipment and mechanical processes such as machining or sanding), UFPs are present in greater quantities in the workplace than in the general environment [5, 6]. In view of the number of sectors in which asbestos is used and UFPs are emitted, many workers may have been simultaneously exposed to these two agents in the workplace prior to the asbestos ban coming into effect.

Experimental data on nanoscale particles (mainly engineered nanoparticles) obtained over the last 20 years suggest a carcinogenic effect of nanoscale particles as a result of their inflammatory and pro-oxidant activities, which induce genotoxicity, the initiating stage of carcinogenesis [7, 8]. However, the adverse effects of engineered nanoparticles and UFPs share biological mechanisms based in particular on their high surface reactivity [9, 10]. An epidemiological study reported a significant association between occupational exposure to UFPs and the occurrence of lung cancer [11].

UFPs are a major component of a number of types of outdoor air pollution; the IARC classifies UFPs as a definite lung carcinogen for human [12]. In 2024, a large prospective cohort study found a positive association between airport-related UFP exposure and specific lung cancer histologies [13]. To date, there are no data on the effect of coexposure to asbestos and UFPs on the occurrence of lung cancer. We assessed the association between occupational exposure to UFPs and lung cancer in a population of workers exposed to asbestos.

Methods

Study population

Our study population was selected from the French ARDCO cohort followed from 2003 to 2005, which included 14,218 unemployed or retired workers from four French regions; the workers had been exposed to asbestos during their former employment. This cohort study has previously been described [14]. The ARDCO population was recruited through the media (unsolicited applications) as well as via invitations sent by mail to beneficiaries of the asbestos workers' allowance, beneficiaries of post-professional follow-up not renewed for more than 2 years, inactive workers over 55 years of age selected according to their occupational code, and early retirees according to their declared occupational category and by healthcare professionals. Subjects were considered exposed to asbestos when they had previously worked in at least one job with a non-zero exposure level based on the expert advice of industrial hygienists.

The inclusion criteria were male subjects (given the small number of women in the ARDCO population, we present the results of only men) with available details of their occupational career and codified in official job classifications. The exclusion criteria were female sex (only 737 women were included in the ARDCO study), PUF job-exposure matrix not applicable (218 subjects), prevalent cases of lung cancer (26 subjects), and subjects not found in the General Health Insurance database (for the incidence study, 707 subjects) or in the National Directory for Identification of Physical Persons (RNIPP) database (for the mortality study, 1304 subjects).

Data collection

Data on all jobs held during the career as well as the tasks performed that exposed subjects to asbestos were recovered using a self-questionnaire completed during the SPP-A/APEXS program [14]. Occupations and industries were coded according to the 1968 International Standard Classification of Occupations and the International Standard Industrial Classification (second revised edition), respectively. Information related to the age, sex, and smoking status of each subject was collected.

Lung cancer incidence and mortality

The incidence of lung cancer was evaluated using National Health Insurance data (declaration as a long-term illness or as an occupational disease) until July 1, 2021. In France, all cancers must be reported to the French National Health Insurance fund for provision of full coverage of medical costs, including treatment. Identification of incident cases and diagnosis dates are annually obtained from the National Health Insurance.

A follow-up study of mortality was also performed. In France, mortality data are available from the INSERM

CEPI DC, which collects all death certificates. The vital status of each subject in the cohort was collected from the RNIPP 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 obtained from the INSERM CEPI DC.

Exposure assessment

In the cohort all subjects were retired at the inclusion in 2003 to 2005, so cumulative exposures to asbestos, PUF and crystalline silica were calculated over the complete work history of each subject.

Asbestos exposure

An assessment of all jobs over the complete work history of each subject allowed occupational hygienists to provide an accurate estimation of the occupational asbestos exposures of the subjects in the ARDCO cohort according to exposure duration and intensity [14]. For each job period of a given subject, the level of exposure was classified as low (passive exposure), corresponding to a numerical value of 0.01 equivalent fibers/mL; low-intermediate, corresponding to 0.1 equivalent fibers/mL; high-intermediate, corresponding to 1 equivalent fibers/mL; and high, corresponding to 10 equivalent fibers/mL. We calculated the asbestos cumulative exposure index (CEI) over the working life, expressed in units of exposure-years, using the following formula: $CEI = \sum_{i=1}^{n} I_i * D_i$ where n is the number of positions held, I_i is the coefficient assigned to the exposure level of job i, and D_i is the duration of employment (years).

UFP exposure

Lifetime occupational exposure to UFPs was retrospectively assessed using a job exposure matrix (JEM) specific to UFPs, the MatPUF JEM, developed by a consortium of industrial hygienists between 2010 and 2014 [15]. Work processes generating unintentional nanoscale particles were identified by conducting a comprehensive literature review and the judgement of a panel of experts (industrial hygiene, toxicology, physics, atmospheric chemistry, and epidemiology). These work processes were linked to occupations, as defined by the ISCO (edition 1968). Next, two exposure parameters were evaluated for each occupation by two industrial hygienists—the probability and the frequency of exposure to UFPs. The probability was defined as the proportion of individuals exposed to UFPs via the implementation of work processes that generate UFPs for a given occupation on a semi-quantitative scale and was categorized as occupationally unexposed (0%), possible (>10–90%), and very probable (>90%) exposure. The frequency was defined as the proportion of time during which workers were exposed to UFPs via the implementation of work processes that generate UFPs for a given occupation (in a usually 8 h working day) on a semiquantitative scale and was categorized as sporadic (>0–5%), occasional (>5–30%), frequent (>30–70%), and permanent (>70%) exposure. The intensity of exposure was not available in the matrix. The unexposed category implies that exposure in the considered occupation was not above that of the general population. Because the nomenclatures used to code the sectors of activity are not identical in the ARDCO study and in the MatPUF matrix (ISIC and NAF 2000, respectively), a transcoding step was necessary to apply the MatPUF matrix to the ARDCO cohort data. After cross-tabulation, the data available for each job were the probability, frequency, and duration of UFP exposure for all and each of the seven chemical families of UFPs: metallic, mineral, carbonaceous, polymer, wood, PAH, and other organic (e.g., cereals, plant dust) particles.

Crystalline silica

Exposure to silica was characterized using a job-exposure matrix developed by the French Institute for Public Health Surveillance [16]. The Institute has developed the Matgene program to provide JEMs adapted to the general population in France. JEMs were drawn up by six industrial hygienists who based their assessments on available occupational measurement, economic, and statistical data, and several thousand job descriptions obtained from epidemiological studies performed in France. For each job classified in the international classifications and for different time periods, the JEM provided the probability of exposure the frequency and the intensity of exposure. Subjects were classified into three categories according to maximum probability of exposure: non-exposed, possibly exposed >0–90%, and exposed >90%. The frequency of exposure were expressed as percentages. The intensity of exposure is expressed in mg/m3 and categorized into 5 classes: non-exposed, class 1 (≥0.00–0.1 mg/m3), class 2 (≥0.1 - <0.5 mg/m3), class 3 (≥0.5 – <1 mg/m3) and class 4 (≥1 mg/m3). A silica cumulative exposure index (CEI), expressed in mg/m3-years, was calculated for each subject as follows: CEI= Σ_(i=1)^n⟦P_i*F_i*⟧ I_i*D_i where n is the number of jobs, Pi, Fi, Ii and Di are respectively the probability, the frequency, the intensity and the duration of the job i. For the intensity of exposure, the following weights were used for each class: 0 for non-exposed; 0.06 for class 1, 0.3 for class 2, 0.75 for class 3 and 5 for class 4. The duration is expressed in years.

Statistical analysis

First, we described the main characteristics of the population, asbestos exposure parameters according to UFP exposure, and exposures to asbestos, silica, and UFPs. The correlation between the different exposures (CEI

asbestos, CEI silica and PUF) are checked with a Pearson coefficient. To assess the effect of occupational exposure to UFPs, Cox proportional hazard models were used to estimate the association between occupational exposure to any and each of the seven chemical families of UFPs and lung cancer in univariate and multivariate analyses. Analyses were performed for lung cancer occurrence (incidence population) and death (mortality population) separately. Age was the main time variable in addition to age at initial inclusion in the cohort. The assumption of proportionality of risks was tested using Schöenfeld residuals [17]. The cut-off date was 31 December 2015 for the mortality analysis and 1 July 2021 for the incidence analysis (data available at this date). In the first models, the adjustment variable was smoking status at inclusion, cumulative asbestos exposure index, and cumulative silica exposure index. Analysis on lung cancer mortality were presented in supplemental file 1.

The adjustment variables were smoking status at inclusion, cumulative asbestos exposure index, and cumulative silica exposure index. Because information on smoking status was missing for more than 30% of the subjects, multiple imputation was performed using the multiple imputation by chained equation (MICE) method [18]. Correction for multiple comparisons was performed using the Bonferroni method.

Results

Figure 1 shows the selection of subjects for the study. Subjects who died between their inclusion in the SSP-APEXS program and the re-evaluation of their occupational calendar by industrial hygienists were excluded from the ARDCO cohort. The following subjects were also excluded: 423 with an incomplete work history, 1429 subjects for whom the industrial hygienists' expertise carried out during ARDCO led to a conclusion of no exposure to asbestos over the entire working career, 737 women, and 218 subjects for whom the ISCO and/or ISIC nomenclature were missing. For the study, 26 non-incident of lung cancer and 707 subjects not found in the General National Health Insurance database were excluded. In total, 12,530 subjects were included.

Table 1 shows the main characteristics of the study population. Participants ranged in age from 37 to 90 years at inclusion, and the mean age was 63.2 years. Data on smoking status were missing for more than 30% of the subjects in both the incidence study. 502 lung cancers (4.0%)) were recorded

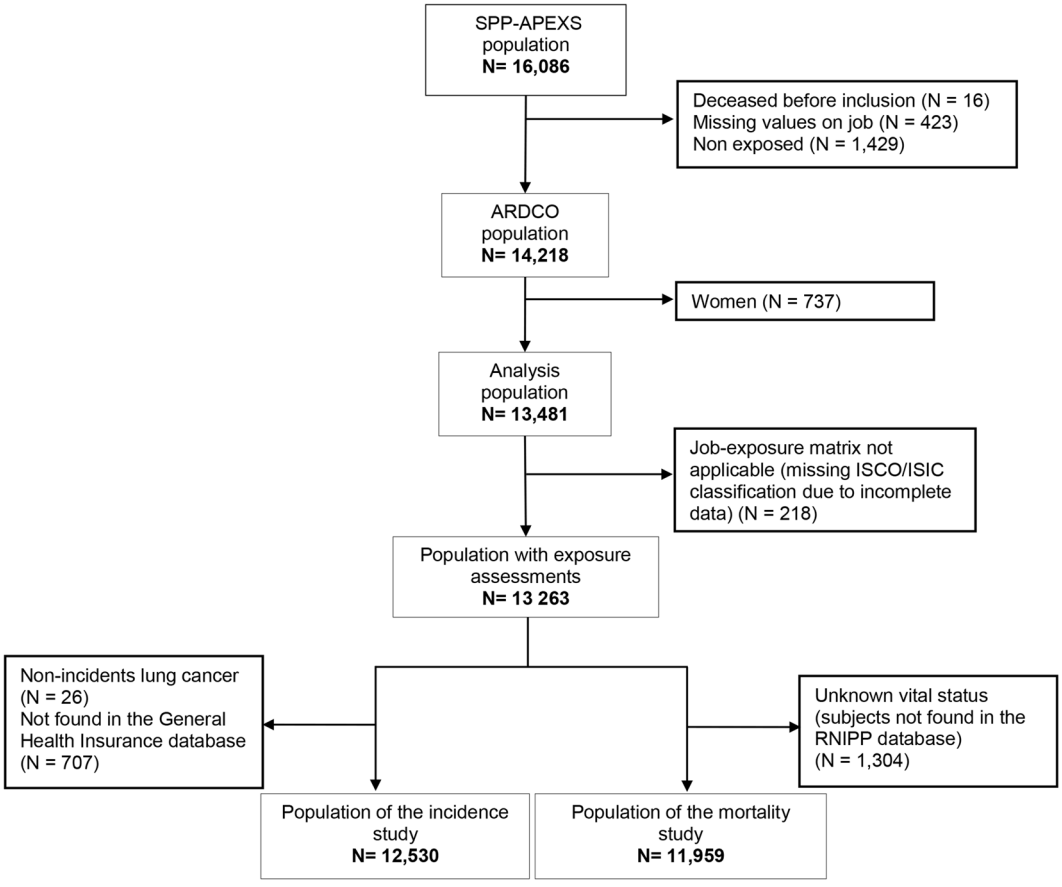

Fig. 1 Flow chart

Table 1 Main characteristics of the population (Incidence study, *N* = 12,530)

	n	%
Age (years)		
< 60 years	2718	21.7
60–75 years	9488	75.7
≥ 75 years	324	2.6
Mean ± standard deviation	63.2 (5.5)	
Min-Max	37–90	
Geographic area at inclusion		
Aquitaine	2032	16.2
Normandie	3651	29.1
Rhône-Alpes	6847	54.7
Smoking habits		
Non-smokers	2574	20.6
Ex-smokers	5268	42.0
Smokers	726	5.8
Missing values	3962	31.6
Lung cancer		
Yes	502	4.0

Table 2 lists the characteristics of asbestos, silica, and UFP exposures in the population. The average duration of exposure to asbestos was 31.4 years (range 1–55 years). Asbestos CEI was highly variable with a minimum of 0.01 units of exposure-years and a maximum of 490 units of exposure-years for a mean CEI of 60.2 units of exposure-years. The overwhelming majority of the incidence population, 12,059 subjects (96.2%), had been exposed to UFPs, with a mean exposure duration of 32.5 years. Total exposure durations ranged from 0.5 to 53 years, and almost two thirds of the subjects (7,436 or 61.7%) had a frequency-weighted exposure duration of < 20 years. The majority of subjects exposed to UFPs (11,455 subjects [95%]) had > 50% probability of exposure, including 9,730 subjects (77.6%) for whom that probability was > 90%. The results for asbestos, silica, and UFP exposures were similar in the mortality study population (supplemental file 1). No correlation greater than 0.80 was found between the various exposures (supplemental file 2).

Table 3 shows the asbestos exposure parameters according to probability of exposure to UFPs. The

Table 2 Description of exposures to asbestos and ultrafine particles (Incidence study, *N* = 12530)

	Asbestos		Silica		UFPs	
	n	%	*n*	%	*n*	%
Exposed						
No	0	0	5408	40.3	471	3.8
Yes	12,530	100.0	7482	59.7	12,059	96.2
Maximum exposure probability (%)						
> 0–90	-	-	4762	63.6	2329	19.3
≥ 90	-	-	2720	36.4	9,730	80.7
Exposure intensity				-		
Low	781	6.2	-	-	-	-
Low intermediate	3514	28.0	-	-	-	-
High intermediate	5242	41.9	-	-	-	-
High	2993	23.9	-	-	-	-
Duration of exposure (years)						
< 20 years	1804	14.4	2890	38.6	1,863	15.5
20–29 years	2362	18.9	1259	16.9	1,759	14.6
30–39 years	5454	43.5	2141	28.6	4,537	37.6
≥ 40 years	2910	23.2	1192	15.9	3,900	32.3
Mean ± standard deviation	31.4 (10.4)		24.1 (14.3)		32.5 (11.3)	
Min-Max	1–55		0.25-49		0.5–53	
Frequency-weighted exposure duration (years)						
< 20 years	-	-	-	-	7,436	61.7
20–29 years	-	-	-	-	2,403	19.9
30–39 years	-	-	-	-	1,766	14.6
≥ 40 years	-	-	-	-	454	3.8
Mean ± standard deviation	-		-		17.2 (12.0)	
Min-Max	-		-		0.002–47.48	
Cumulative asbestos exposure index f/ml-years / cumulative silica exposure index mg/m^3						
Mean ± standard deviation	60.2 (99.4)		2.1 (5.7)		-	
Median	23.0		0.42			
Min-Max	0.01–490.00		0.0003–88.65		-	

Table 3 Asbestos exposure parameters according to UFPs exposure (Incidence study, *N* = 12 530)

	Not exposed to UFPs (*N* = 471)		Exposed to UFPs > 0–90% (*N* = 2,329)		Exposed to UFPs > 90% (*N* = 9,730)	
	n	**%**	***n***	**%**	***n***	**%**
Intensity of asbestos exposure						
Low	124	26.3	225	9.7	432	4.4
Low intermediate	136	28.9	623	26.7	2,755	28.3
High intermediate	107	22.7	824	35.4	4,311	44.3
High	104	22.1	657	28.2	2,232	23.0
Duration of asbestos exposure (years)						
< 20 years	94	20.0	392	16.8	1,318	13.6
20–29 years	117	24.8	489	21.0	1,756	18.0
30–39 years	213	45.2	1,028	44.2	4,213	43.3
≥ 40 years	47	10.0	420	18.0	2,443	25.1
Mean ± standard deviation	28.2 (10.4)		30.1 (10.6)		31.9 (10.2)	
Min-Max	1–47		1–53		1–55	
Cumulative asbestos exposure index in f/ml-years						
Mean ± standard deviation	59.5 (112.1)		73.7 (112.8)		57.0 (95.0)	
Min-Max	0.02–430.0		0.01–460		0.01–490	

Table 4 Association between exposure to ultrafine particles and lung cancer (Incidence study, *N* = 12 530)

	Univariate model		Multivariate model	
	HR	**CI 95%**	**HR[1]**	**CI 95%**
Smoking status				
Non-smokers	1		1	
Ex-smokers	2.04	1.52–2.75	2.01	1.49–2.71
Smokers	4.56	3.22–6.47	4.53	3.19–6.43
CEI* asbestos for an increase of 1 f/ml-year	1.001	1.000-1.002	1.001	1.000-1.002
CEI silica for an increase of 1 mg/m^3-year	0.99	0.96–1.01	0.99	0.96–1.01
Exposed all UFPs				
No	1		1	
Yes	1.05	0.66–1.68	1.08	0.67–1.73

*Cumulative exposure index

[1]Hazard ratio adjusted for smoking status (imputed missing data with MICE method), CEI to asbestos and CEI to silica

proportion of subjects exposed to asbestos at a high intermediate level was larger in subjects exposed to UFPs. The mean duration of exposure to asbestos and the cumulative asbestos exposure index were similar for those not exposed (28.2 years and mean CEI 59.5 f/mL years, respectively) and those exposed (31.5 years and mean CEI 60.3 f/mL years) to UFPs. The asbestos exposure parameters according to UFP exposure in the mortality study (supplemental file 1) were similar to those in the incidence study.

Tables 4 and 5 summarizes the risk of lung cancer according to UFP exposure. Data were adjusted for smoking status, asbestos CEI, and silica CEI. Overall, 18 incident cases of lung cancer (i.e., 3.6%) were identified in subjects not exposed to UFPs and 484 cases (i.e., 96.4%) in those exposed to UFPs.

The largest number of incident cases of lung cancer was found in subjects exposed to carbonaceous UFPSs (416), PAH UFPs (416), and metallic UFPs (371). Only nine incident cases of lung cancer were found in subjects exposed to polymer UFPs. No excess of lung cancer was identified in association with UFP exposure (HR 1.08 [95% CI 0.67–1.73]) after adjustment. The various chemical families of UFPs yielded similar results. The association with exposure to wood UFPs, however, approached statistical significance (HR 1.16 [95% CI 0.96–1.40]). The results were close in the mortality study (Supplemental file).

Discussion

This study, based on a large cohort of subjects who had been exposed to asbestos with a follow-up of more than 20 years, suggests that occupational exposure to UFPs is not associated with an increased risk of lung cancer. The association with wood UFPs approached statistical significance.

To the best of our knowledge, no study has investigated occupational exposure to UFPs in a population exposed to asbestos. Experimental studies suggest that nanoscale particles exhibit genotoxicity, the initial stage of carcinogenesis. Exposure to these particles can cause an inflammatory reaction by triggering the secretion of cytokines and the recruitment of immune cells locally and systemically [19]. The interdependence between inflammation and oxidative stress has been confirmed [20]. During inflammation, activated phagocytic cells such as neutrophils and macrophages produce large amounts of reactive oxygen species (ROS), disrupting the pro/antioxidant

Table 5 Association between exposure to specific exposure parameters of ultrafine particles and different class of UFPs and lung cancer (Incidence study, *N* = 12 530)

		Univariate model		Multivariate model	
	Lung cancer	**HR**	**CI 95%**	**HR[1]**	**CI 95%**
Frequency-weighted exposure duration (years)					
Not exposed	18	1		1	
< 20 years	291	1.03	0.64–1.66	1.05	0.65–1.69
20–29 years	97	1.06	0.64–1.75	1.11	0.67–1.84
30–39 years	75	1.11	0.66–1.86	1.13	0.67–1.89
≥ 40 years	21	1.18	0.63–2.22	1.16	0.62–2.18
Not exposed	18	1		1	
< 15 (median)	248	1.07	0.66–1.73	1.09	0.67–1.76
≥ 15	236	1.18	0.63–2.22	1.07	0.66–1.73
Exposed to metallic UFPs					
No	131	1		1	
Yes	371	1.01	0.83–1.23	1.01	0.82–1.23
Exposed to mineral UFPs					
No	204	1		1	
Yes	298	1.04	0.87–1.24	1.06	0.88–1.27
Exposed to carbonaceous UFPs					
No	86	1		1	
Yes	416	1.12	0.89–1.42	1.12	0.89–1.42
Exposed to wood UFPs					
No	346	1		1	
Yes	156	1.15	0.95–1.39	1.16	0.96–1.40
Exposed to polymer UFPs					
No	493	1		1	
Yes	9	1.14	0.59–2.20	1.09	0.56–2.12
Exposed to PAH UFPs					
No	86	1		1	
Yes	416	1.13	0.90–1.43	1.13	0.90–1.43
Exposed to other organic UFPs					
No	455	1		1	
Yes	47	1.49	1.10–2.02	1.27	0.93–1.74

[1] Hazard ratio adjusted for smoking status (imputed missing data with MICE method), cumulative exposure index to asbestos and cumulative exposure index to silica

balance, i.e., creating oxidative stress. Moreover, the presence of nanoscale particles in contact with epithelia or after phagocytosis leads to ROS production. This is likely because of the presence of metals (e.g., iron, copper, chromium) and organic molecules (PAHs) with redox properties on the particle surface, which is particularly true for UFPs because of their main sources of emission [21]. ROS initiate an oxidation-reduction chain reaction that creates lesions in DNA (genotoxicity) such as single-strand breaks or oxidized nucleic bases [22].

DNA damage can lead to mutations (base pair substitutions, additions, deletions), which may affect genes linked to tumorigenesis (tumor suppressor genes, oncogenes) [23]. However, asbestos and nanoscale particles share mechanisms of toxicity [19, 23], namely, saturation of macrophages and induction of inefficient phagocytosis at the alveolar level, leaving to oxidative stress and chronic inflammation at the local and systemic level. During chronic exposure to these two agents, a saturation threshold of the toxicity mechanisms could be reached, due to the similar toxicity mechanisms of UFPs and asbestos, which would explain the absence of an excess risk of lung cancer in this study.

The only epidemiological data on the link between occupational exposure to UFPs and lung cancer come from a French population-based case-control study published in 2020 [11], which indicated an association between occupational exposure to UFPs and the occurrence of lung cancer in a population of 4620 men (OR 1.51 [95% CI 1.22–1.8]). Exposure to UFPs was characterized using the MatPUF matrix. Unlike the present study, however, the population of the previous study was drawn from the general population, a proportion of which had not been exposed to asbestos (data not available). A 2024 cohort study suggested an association between the long-term average outdoor ultrafine particle number concentration and lung cancer mortality [24], confirming prior reports [13, 25].

As expected, the effect of smoking on lung cancer is predominant in this cohort, and adjustment does not alter the associations between the different exposure factors and lung cancer.

The ARDCO cohort is large and has a long follow-up, promoting investigation of the association between occupational exposure to UFPs and the occurrence of lung cancer with adjustment for crystalline silica exposure. The assessment of asbestos exposure is another strength of this study. The level of exposure to asbestos over the complete working life was assessed for each subject by experts (industrial hygienists) according to a standardized method. However, there is no standardized method for measuring UFP exposure (e.g., the types of monitors and measurements, i.e., personal versus ambient) and the results (e.g., the measured parameter as mass, number, or surface area) in workplace studies. Although recommendations and standards exist, the occupational exposure data available are highly heterogeneous, hampering their use for epidemiological purposes [6, 26]. In this context, MatPUF JEM enables standardized and reproductible exposure assessment [15]. However, like other JEMs, the MatPUF JEM does not take into account the variability of exposure in the same occupation, which is likely to

lead to non-differential misclassification and a loss of power in an epidemiological study [27]. Moreover, MatPUF provides data only on the probability and frequency of exposure to UFPs. The evaluation of the parameter 'intensity' of exposure for each occupation is absent from the available version of MatPUF because of the heterogeneity of the exposure data in the literature [15]. Therefore, because it was not possible to assess a cumulative exposure index, we used the frequency-weighted exposure duration as a proxy of the cumulative dose. However, UFPs exposure is ubiquitous at the workplace and we were unable to take into account exposure to UFPs in ambient air, it is highly probable that the longest duration of exposure categories may include subjects with high intensity of exposure as well as those with low or very low intensity of exposure, leading to ORs close to 1.

This study had several other limitations that need to be discussed. First, the health insurance data for morbidity have bias in terms of the lack of completeness of reported cases. A 2013 French study showed a slight underestimate of the number of lung cancers estimated from ALD data compared to that estimated from cancer registries [28]. However, although it cannot be eliminated completely, the risk of double reporting (declaration as a long-term illness and as an occupational disease), linked to the long evolution of certain diseases, is considerably limited for lung cancer in view of its seriousness. Missing data on tobacco were also imputed, in analyses where all of the missing data were smokers or none were, the results were similar (data not shown). In addition, the large proportion of subjects exposed to UFPs (96.2%) may explain the lack of discrimination. Finally, we did not evaluate several exposure parameters that could cause residual confounding, such as exposure to welding fumes and/or radon.

Conclusion

Using the ARDCO cohort, we investigated the association between occupational exposure to UFPs and lung cancer (incidence and mortality) in more than 12,000 subjects with occupational exposure to asbestos. The findings do not indicate increased risks of lung cancer for UFP after adjustment for level of exposure to asbestos, crystalline silica, and smoking status.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22038-2.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
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Author contributions
CR performed literature review and drafted the first version of this manuscript. All statistical analysis were done by CG. Acquisition and interpretation of data were done by CR, SA, CG, IB, CG, JB, BC, AG, FL, PA, JCP and FD. FD and JCP supervised all aspects of this manuscript. CR, CG, SA, IB, IT, PA, JB, PB, CC, BC, AG, CG, FL, CP, PA, JCP, FD participated in the drafting, revision and correction of the final text.

Funding
This study was supported by the French Ministry of Labour and Social Relations; the French National Health Insurance (Occupational Risk Prevention Department); the French Agency for Food, Environmental and Occupational Health & Safety, Grant number: ANSES Grant 07-CRD-51 and EST 2006/1/43 and EST 2009/68.

Data availability
No datasets were generated or analysed during the current study.

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, no 1946/11/02–02 (2010)). All participants received information on the study and provided their written informed consent. Participants gave informed consent to participate in the study before taking part. All study procedures were performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 4 October 2024 / Accepted: 20 February 2025
Published online: 26 February 2025

References

1. Lapôtre-Ledoux B, Remontet L, Uhry Z, Dantony E, Grosclaude P, Molinié F et al. Incidence des principaux cancers en France métropolitaine en 2023 et tendances depuis 1990. BEH 12–13. 2023.
2. Goldberg M, Banaei A, Goldberg S, Auvert B, Luce D, Guéguen A. Past occupational exposure to asbestos among men in France. Scand J Work Environ Health. 2000;26:52–61.
3. Marant Micallef C, Charvat H, Houot M-T, Vignat J, Straif K, Paul A, et al. Estimated number of cancers attributable to occupational exposures in France in 2017: an update using a new method for improved estimates. J Expo Sci Environ Epidemiol. 2023;33:125–31.
4. International Organization for Standardization. Workplace atmospheres-Ultrafine, nanoparticle and nano-structured aerosols-Inhalation exposure characterization and assessment. International Organization for Standardization; 2007.
5. Manigrasso M, Protano C, Vitali M, Avino P. Where do ultrafine particles and Nano-Sized particles come from?? J Alzheimers Dis. 2019;68:1371–90.
6. Viitanen A-K, Uuksulainen S, Koivisto AJ, Hämeri K, Kauppinen T. Workplace measurements of ultrafine Particles-A literature review. Ann Work Expo Health. 2017;61:749–58.
7. Donaldson K, Poland CA, Schins RPF. Possible genotoxic mechanisms of nanoparticles: criteria for improved test strategies. Nanotoxicology. 2010;4:414–20.
8. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Lunts A, et al. Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J Toxicol Environ Health Part A. 2002;65:1531–43.
9. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113:823–39.
10. Stone V, Miller MR, Clift MJ, Elder A, Mills NL, Møller P, et al. Nanomaterials versus ambient ultrafine particles: an opportunity to exchange toxicology knowledge. Environ Health Perspect. 2017;125:106002.

11. Manangama G, Gramond C, Audignon-Durand S, Baldi I, Fabro-Peray P, Gilg Soit Ilg A, et al. Occupational exposure to unintentionally emitted nanoscale particles and risk of cancer: from lung to central nervous system - Results from three French case-control studies. Environ Res. 2020;191:110024.
12. IARC. Outdoor Air Pollution.
13. Bookstein A, Po J, Tseng C, Larson TV, Yang J, Park S-SL, et al. Association between airport ultrafine particles and lung Cancer risk: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev. 2024;33:703–11.
14. Paris C, Thierry S, Brochard P, Letourneux M, Schorle E, Stoufflet A, et al. Pleural plaques and asbestosis: dose- and time-response relationships based on HRCT data. Eur Respir J. 2009;34:72–9.
15. Audignon-Durand S, Gramond C, Ducamp S, Manangama G, Garrigou A, Delva F, et al. Development of a Job-Exposure matrix for ultrafine particle exposure: the MatPUF JEM. Ann Work Expo Health. 2021;65:516–27.
16. Févotte J, Dananché B, Delabre L, Ducamp S, Garras L, Houot M, et al. Matgéné: a program to develop job-exposure matrices in the general population in France. Ann Occup Hyg. 2011;55:865–78.
17. Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika. 1980;67:145–53.
18. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res. 2011;20:40–9.
19. Salvi S, Blomberg A, Rudell B, Kelly F, Sandström T, Holgate ST, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med. 1999;159:702–9.
20. Traboulsi H, Guerrina N, Iu M, Maysinger D, Ariya P, Baglole CJ. Inhaled pollutants: the molecular scene behind respiratory and systemic diseases associated with ultrafine particulate matter. Int J Mol Sci. 2017;18:243.
21. Leikauf GD, Kim S-H, Jang A-S. Mechanisms of ultrafine particle-induced respiratory health effects. Exp Mol Med. 2020;52:329–37.
22. Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. Redox Biol. 2019;25:101084.
23. Cheng KC, Cahill DS, Kasai H, Nishimura S, Loeb LA. 8-Hydroxyguanine, an abundant form of oxidative DNA damage, causes G----T and A----C substitutions. J Biol Chem. 1992;267:166–72.
24. Jones RR, Fisher JA, Hasheminassab S, Kaufman JD, Freedman ND, Ward MH, et al. Outdoor ultrafine particulate matter and risk of lung Cancer in Southern California. Am J Respir Crit Care Med. 2024;209:307–15.
25. Bouma F, Janssen NA, Wesseling J, van Ratingen S, Strak M, Kerckhoffs J, et al. Long-term exposure to ultrafine particles and natural and cause-specific mortality. Environ Int. 2023;175:107960.
26. Galey L, Audignon S, Brochard P, Debia M, Lacourt A, Lambert P, et al. Strategies to assess occupational exposure to airborne nanoparticles: systematic review and recommendations. Saf Health Work. 2023;14:163–73.
27. Ge CB, Friesen MC, Kromhout H, Peters S, Rothman N, Lan Q, et al. Use and reliability of exposure assessment methods in occupational case–control studies in the general population: past, present, and future. Annals Work Exposures Health. 2018;62:1047–63.
28. Uhry Z, Remontet L, Colonna M, Belot A, Grosclaude P, Mitton N, et al. Cancer incidence Estimation at a district level without a National registry: A validation study for 24 cancer sites using French health insurance and registry data. Cancer Epidemiol. 2013;37:99–114.

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