Eur Respir J 2012; 39: 1304–1312
DOI: 10.1183/09031936.00005111

Temporal patterns of occupational asbestos exposure and risk of pleural mesothelioma

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ABSTRACT: Asbestos is the primary cause of pleural mesothelioma (PM). The objective of this study was to elucidate the importance of different temporal patterns of occupational asbestos exposure on the risk of PM using case–control data in male subjects.

Cases were selected from a French case–control study conducted in 1987–1993 and the French National Mesothelioma Surveillance Program in 1998–2006. Population controls were frequency matched to cases by year of birth. Occupational asbestos exposure was evaluated with a job–exposure matrix. The dose–response relationships were estimated using restricted cubic spline functions in logistic regression models.

A total of 2,466 ever-asbestos-exposed males (1,041 cases and 1,425 controls) were used. After adjustment for intensity and total duration of occupational asbestos exposure, the risk of PM was lower for subjects first exposed after the age of 20 yrs and continued to increase until 30 yrs after cessation of exposure. The effect of total duration of exposure decreased when age at first exposure and time since last exposure increased.

These results, based on a large population-based case–control study, underline the need to take into account the temporal pattern of exposure on risk assessment.

KEYWORDS: Case–control studies, job–exposure matrix, mesothelioma, occupational exposure, restricted cubic spline, temporal pattern of asbestos exposure

Asbestos exposure is the only well-established risk factor for malignant mesothelioma, a relatively rare tumour mostly located in the pleura [1]. The incidence of pleural mesothelioma (PM) has been rising in industrialised countries over several decades, but seems to have levelled off over the last decade in several countries. However, asbestos is still used in elsewhere in the world, particularly in less-industrialised countries that frequently have inadequate safety regulations at work [2]. It is therefore important to continue to document the relationship between PM and different aspects of occupational exposure to asbestos, such as the age at first exposure, and the intensity and duration of exposure, as well as the time elapsed since the last exposure.

To our knowledge, the forms of the dose–response relationships between these important aspects of asbestos exposure and the risk of PM have never been investigated using flexible modelling. Indeed, arbitrary categorisation of the continuous exposure to asbestos variables may make the true dose–response relationship difficult to identify.

In addition, in most previous population-based studies on PM, the effects of these categorised asbestos exposure variables were estimated separately, without adjusting for other exposure aspects. This is partly due to the difficulty in simultaneously estimating several aspects of the same exposure, especially those related to time. Indeed, age at first exposure, total duration of exposure, time since last exposure and current age are perfectly multicollinear for subjects who had no interruption of occupational exposure to asbestos over their lifetime [3]. However, when investigating the impact of one component of exposure, such as the time elapsed since the last exposure, it seems important to adjust for potential confounders, such as intensity and total duration of exposure and current age.

Thus, it is not clear from previous studies how the risk of PM is affected by the different aspects of asbestos exposure parameters (intensity, total

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Received:
Jan 12 2011
Accepted after revision:
Sept 21 2011
First published online:
Nov 10 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

duration of exposure, age at first exposure and time since last exposure). The aim of the present study is to explore the quantitative relationships between these aspects of exposure and the risk of PM using flexible methods.

MATERIALS AND METHODS

Cases

Cases were recruited from a French hospital-based case–control study on PM [4], and the French National Mesothelioma Surveillance Program (NMSP) [5]. Cases from the case–control study were all newly-diagnosed with PM between January 1987 and December 1993 in different departments of all public hospitals and all main private clinics in five French regions. Cases from the NMSP were all incident PM between January 1998 and December 2006 in 22 French districts that cover a quarter of the French population (seven districts belong to the five regions mentioned above).

Controls

Controls were selected from two population-based samples from the French Institute for Public Health Surveillance (InVS), both of which included a complete job history from a structured interview of each subject. Sample A (4,758 males and 5,252 females) was selected from the French general population aged 25–74 yrs in 2007 by a quota sampling method stratified by sex, age, region and socioeconomic status. Sample B was made of 8,344 controls from 15 population-based case–control studies conducted in nearly all regions of France in 1984–2000. Controls were randomly selected from both samples A and B with frequency matching to cases on sex and birth-year within 5-yr groups.

Exposure assessment

A job exposure matrix (JEM) was used to assess occupational asbestos exposure. The JEM used was an update of the previous French asbestos JEM [6]. Industries were classified according to either the International Standard Industry Classification revision 2 [7] or the Nomenclature of French activities classification edition 1999 [8]. Occupations were defined according to the International Standard Classification of Occupation edition, 1968 [9]. The JEM was exhaustive in terms of all jobs exposed to asbestos and accounted for asbestos exposure levels changes over time [10]. Based on the judgment of industrial hygienists, it

TABLE 1 Definition of the different asbestos exposure parameters included in the job–exposure matrix (JEM) used to assess occupational asbestos exposure of subjects of a French case–control study of occupational asbestos exposure and pleural mesothelioma in 1987–2006

Asbestos exposure parameters used in the JEM	Definition	Numerical values used to calculate the MIE		
Probability of exposure % workers exposed		p_i		
Not exposed	0	0		
Possible	>0–5	0.025		
Probable	5–30	0.175		
Likely	30–70	0.5		
Definite	⩾70	0.85		
Frequency of exposure[#] % work time		f_{si} and f_{ai}		
Sporadic	>0–5	0.025		
Occasional	5–30	0.175		
Frequent	30–70	0.5		
Continuous	⩾70	0.85		
Intensity of exposure[¶] fibres per mL		**Kind of exposure[+]**		
		i_{ai}		i_{si}
		Passive	**Indirect**	**Direct**
Very low	>0–0.01	0.0005	0.0025	0.005
Low	0.01–0.1	0.005	0.025	0.05
Medium	0.1–1	0.05	0.25	0.5
High	1–10	0.5	2.5	5
Very high	⩾10	2	10	20

MIE: mean index of exposure; p_i: probability of exposure during job i; f_{si}: frequency due to specific tasks of job i; f_{ai}: frequency of exposure due to work environment contamination of job i; i_{ai}: intensity of exposure due to work environment contamination of job i; i_{si}: intensity of exposure due to due to specific tasks of job i. [#]: definition valid for the frequency of exposure due to a specific task of the job and the frequency exposure due to work environment contamination parameters; [¶]: definition valid for the intensity of exposure due to specific task of job, and the intensity exposure due to work environment contamination parameters; [+]: three types of exposure are defined (passive exposure, where workers are exposed according to diffuse contamination of buildings; indirect exposure, where workers are exposed by other workers using asbestos materials; and direct exposure, where workers are directly using asbestos materials).

includes for each job i, the starting and ending dates, the probability (p_i) of exposure during job i, the frequency (f_{si}) and intensity (i_{si}) of exposure due to specific tasks of job i, and the frequency (f_{ai}) and intensity (i_{ai}) of exposure due to work environment contamination of job i (table 1). The mean index of exposure (MIE) over lifetime was calculated as:

$$MIE = \left(\sum_{i=1}^{n} d_i p_i [(f_{si} i_{si}) + (f_{ai} i_{ai})] \right) \Big/ \sum_{i=1}^{n} d_i,$$

where n is the number of jobs exposed to asbestos over lifetime and d_i the duration of job i. For probability, frequency and intensity values, we used the numerical values indicated in the last column of table 1. Note that there was a strong weight assigned to very high exposure intensity, which resulted in high numerical values of MIE for subjects who were exposed to high levels of asbestos, even if for only a short period of time. A subject was defined as ever exposed if the probability of exposure for at least one job was different from zero.

Statistical analysis

Because our objective was to accurately investigate the effect of the quantitative time-related aspects of occupational exposure, all our analyses were restricted to subjects who were ever-exposed to asbestos (68.9% in males and 20.9% in females). In addition, because the sample size for females was too low (82 cases) to ensure adequate statistical power and accurate estimates, we restricted all the analyses to males only. All analyses were performed using unconditional logistical regression systematically including birth year and age (in years) at diagnosis for cases or interview for controls. The occupational asbestos exposure variables were age at first exposure (in years), MIE (in fibres per mL), total duration of exposure (in years) and time since last exposure (in years). Due to potential multicollinearity and correlation between age at first exposure, total duration, time since last exposure and age at interview/diagnosis, we could not simultaneously include all these variables into a single regression model [3]. Because exposure intensity and duration were potential confounders in the relationship between PM and time since last exposure or age at first exposure we have included, in model 1, MIE, total

TABLE 2 Age, year of birth and last occupation held (International Standard Classification of Occupations (ISCO) edition 1968 major group) among ever-exposed males in a case–control study of occupational asbestos exposure and pleural mesothelioma of 1,041 cases and 1,425 controls in France in 1987–2006

	Cases[#]	Controls[¶]
Age at interview/diagnosis yrs		
<50	52 (5.0)	10 (0.7)
50–54	70 (6.7)	34 (2.4)
55–59	136 (13.1)	156 (10.9)
60–64	155 (14.9)	492 (34.5)
65–69	212 (20.4)	334 (23.4)
70–74	192 (18.4)	283 (19.9)
75–79	133 (12.8)	91 (6.4)
80–84	61 (5.8)	23 (1.6)
⩾85	30 (2.9)	2 (0.2)
Year of birth		
<1920	105 (10.1)	121 (8.5)
1920–1924	133 (12.8)	187 (13.1)
1925–1929	221 (21.2)	318 (22.3)
1930–1934	217 (20.8)	367 (25.8)
1935–1939	173 (16.6)	241 (16.9)
1940–1944	92 (8.9)	90 (6.3)
1945–1949	57 (5.5)	54 (3.8)
⩾1950	43 (4.1)	47 (3.3)
Last occupation held (ISCO edition 1968 major group)		
0/1 Professional, technical and related workers	92 (8.8)	163 (11.4)
2 Administrative and managerial workers	40 (3.8)	57 (4.0)
3 Clerical and related workers	68 (6.5)	109 (7.6)
4 Sales workers	53 (5.1)	74 (5.2)
5 Service workers	47 (4.5)	89 (6.2)
6 Agricultural, animal husbandry, and forestry workers; fishermen; hunters	38 (3.6)	126 (8.8)
7/8/9 Production and related workers; transport, equipment operators and labourers	703 (67.5)	807 (56.6)

Data are presented as n (%). [#]: n=1,199; [¶]: n=2,379.

TABLE 3 Occupational asbestos exposure related characteristics of ever-exposed male subjects at the time of diagnosis/interview in a case–control study of occupational asbestos exposure and pleural mesothelioma in France in 1987–2006

	Cases[#]	Controls[¶]
Total duration of exposure yrs		
Mean±SD	27.8±12.9	24.9±14.1
Median (IQR)	32 (18–38)	28 (11–37)
Range	1–55	1–59
Age at first exposure yrs		
Mean±SD	21.0±7.0	22.6±8.1
Median (IQR)	19 (16–24)	20 (17–26)
Range	10–59	10–64
Time since last exposure yrs		
Mean±SD	16.9±13.4	17.4±14.5
Median (IQR)	14 (7–24)	13 (6–28)
Range	0–60	0–57
MIE fibres·mL^{-1}		
Mean±SD	0.61±1.43	0.21±0.44
Median (IQR)	0.12 (0.01–0.74)	0.01 (0.001–0.17)
Range	1.5×10^{-6}–16.26	3.1×10^{-7}–7.36

IQR: interquartile range; MIE: mean index of exposure. [#]: n=1,041; [¶]: n=1,425.

duration of exposure and time since last exposure and, in model 2, MIE, total duration of exposure and age at first exposure. To avoid imposing *a priori* specific functional form of the dose–response relationships between each of these continuous variables and the logit of PM, we used restricted cubic spline functions (RCS) [11]. Such functions allow the estimation of smooth and plausible dose–responses curves [11]. For each adjustment variable (age and birth year), we used three knots to ensure enough flexibility without producing an overfitting bias [11]. For each exposure variable, the number of knots was chosen to minimise the Akaike's information criterion (AIC) of the model, including this variable and the adjustment variables. Two-way interaction terms between linear spline functions were introduced in each model to test for interactions.

RESULTS

Our dataset restricted to ever-exposed males included 1,041 cases and 1,425 controls, aged mean±SD 67.0±10.0 yrs at diagnosis and 66.9±6.3 yrs at interview, respectively. The distribution of age was much more spread out in cases than in controls (table 2), which confirmed the need for a careful adjustment for age in addition to the matching factor year of birth.

Table 3 shows that cases had, on average, a MIE three-fold higher than controls (0.6 *versus* 0.2 fibres per mL), a longer total duration of exposure (27.8 *versus* 24.9 yrs) and had been exposed to asbestos earlier (21.0 *versus* 22.6 yrs). The mean time since last exposure was ~17 yrs for both cases and controls.

The effect of age at first exposure, MIE, total duration of exposure and time since last exposure were systematically significantly nonlinear (p=0.008, <0.001, <0.001 and 0.009, respectively). Based on the AIC, five-, three-, three- and four-knot RCS functions were selected for each of these variables, respectively.

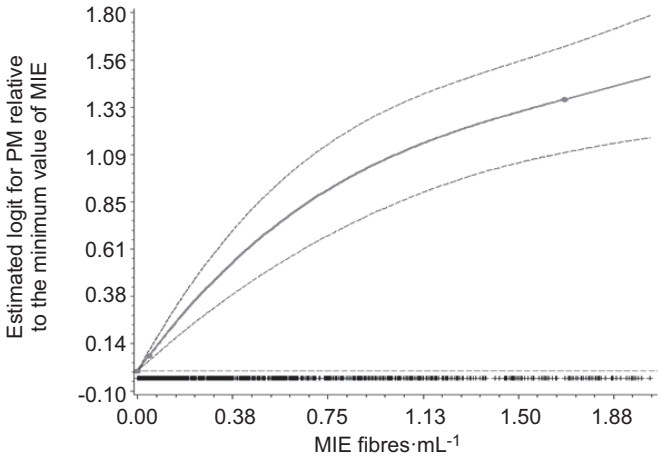

FIGURE 1. Nonlinear effect of mean index of exposure (MIE) to asbestos on the logit of pleural mesothelioma (PM). The solid curve represents logistic regression estimates using a three-knot restricted cubic spline function located at the 5th, 50th and 95th percentiles of MIE, adjusted for total duration of exposure, time since last exposure, age at diagnosis/interview and birth year. The odds ratio between two ever-exposed males with different MIE values can be derived from the exponential of the difference between the *y*-axis values corresponding to the two specific values of MIE. Dashed curves are approximate 95% pointwise confidence intervals of the estimates compared to the reference value of MIE set at its minimum value of 1.5×10^{-6} fibres per mL. The + horizontal symbols represent the observed MIE values. The *x*-axis was cut off at the 97.5th percentiles of MIE (2.02 fibres per mL) to better visualise the form of the relationship at the lower ranges.

No significant interaction was found between MIE and any other exposure variable. Figure 1 shows the estimated effect of MIE on the logit of PM, adjusted for total duration and time since last asbestos exposure, birth year and age at diagnosis/interview (model 1). The risk of PM rose sharply up to ~1 fibre mL and increased with a weaker slope thereafter. The estimated effect of MIE was almost identical when adjusted for age at first exposure (model 2) instead of time since last exposure (table 4).

We found significant interaction between total duration of exposure and time since last exposure (p<0.001 in model 1) or age at first exposure (p<0.001 in model 2). Accordingly, the effect of duration was estimated for specific values of time since last exposure (model 1, table 4) or age at first exposure (model 2, table 4). The estimated effect of exposure duration tended to decrease with increasing time since last exposure (model 1, table 4). For example, the estimated odds ratio (OR) for subjects who have been exposed during 30 yrs compared to those exposed during 1 yr only was 7.5 (95% CI 4.2–13.4) in subjects who had their last exposure 20 yrs ago *versus* 4.0 (95% CI 2.2–7.2) in subjects who had their last exposure 30 yrs ago. The estimated effect of duration also tended to decrease with increasing age at first exposure (model 2, table 4). For example, the estimated OR for subjects who had been exposed during 30 yrs compared with those exposed during 1 yr only was 6.5 (95% CI 4.3–9.8) in subjects who were first occupationally exposed to asbestos at 15 yrs of age, and of only 1.5 (95% CI 1.1–2.2) in subjects who were first exposed at 30 yrs of age.

TABLE 4 Effect of mean index of exposure (MIE) and total duration of exposure on pleural mesothelioma risk for selected strata of time since last exposure or age at first exposure, adjusted for age and birth cohort among exposed male subjects in a case–control study of occupational asbestos exposure and pleural mesothelioma in 1,041 cases and 1,425 controls in France in 1987–2006

Occupational asbestos exposure variable		Exposure value	OR (95% CI)
Model 1#			
MIE fibres per mL¶		0.1	1.2 (1.1–1.2)
		0.5	2.0 (1.6–2.4)
		1.0	2.9 (2.3–3.7)
		2.0	4.4 (3.2–5.9)
Time since last exposure of 20 yrs	Total duration of exposure yrs¶	10	1.9 (1.5–2.4)
		20	3.7 (2.3–5.9)
		30	7.5 (4.2–13.4)
		40	15.0 (8.0–27.9)
Time since last exposure of 30 yrs	Total duration of exposure yrs¶	10	1.5 (1.2–2.0)
		20	2.5 (1.5–3.9)
		30	4.0 (2.2–7.2)
		40	6.4 (3.2–12.9)
Time since last exposure of 40 yrs	Total duration of exposure yrs¶	10	1.3 (0.9–1.9)
		20	1.8 (0.9–3.7)
Model 2+			
MIE fibres per mL¶		0.1	1.2 (1.1–1.2)
		0.5	1.9 (1.6–2.3)
		1.0	2.8 (2.2–3.6)
		2.0	4.4 (3.2–6.0)
Age at first exposure of 15 yrs	Total duration of exposure yrs¶	10	1.8 (1.5–2.2)
		20	3.4 (2.4–4.9)
		30	6.5 (4.3–9.8)
		40	12.3 (9.0–16.9)
Age at first exposure of 20 yrs	Total duration of exposure yrs¶	10	1.5 (1.3–1.8)
		20	2.5 (1.9–3.3)
		30	4.0 (3.1–5.3)
		40	6.5 (6.1–6.9)
Age at first exposure of 30 yrs	Total duration of exposure yrs¶	10	1.1 (1.0–1.3)
		20	1.3 (1.0–1.8)
		30	1.5 (1.1–2.2)
		40	1.8 (1.1–3.0)

#: logistic regression model with MIE (3-knot restricted cubic spline (RCS)), total duration of exposure (three-knot RCS), time since last exposure (four-knot RCS), age (three-knot RCS), birth year (three-knot RCS) and interaction term between the linear spline of time since last exposure and the linear spline of total duration of exposure. ¶: estimated odds ratio (OR) relative to the minimum of exposure (1.5×10^{-6} fibres per mL for MIE and 1 yr for total duration of exposure). +: logistic regression model with MIE (three-knot RCS), total duration of exposure (three-knot RCS), age at first exposure (five-knot RCS), age (three-knot RCS), birth year (three-knot RCS) and interaction term between the linear spline of age at first exposure and the linear spline of total duration of exposure.

Because of the interaction with duration, the effect of time since last exposure (model 1) and age at first exposure (model 2) were estimated for two stratum of duration (fewer than or more than 30 yrs of duration, which corresponds to the median duration in all subjects). Figure 2 shows the estimated effect of time since last exposure on the logit of PM in these two strata. For all subjects, the risk of PM continued to increase during the first 30 yrs of cessation of exposure. For subjects with a duration <30 yrs, the estimated risk ceased to increase after 30 yrs of cessation of exposure. A slight decrease was even observed after 35 yrs of cessation, as was also suggested by the estimated OR in top left panel of table 5. In subjects with a longer duration of exposure, the maximum of the time elapsed since the last of exposure was 30 yrs, which did not allow us to observe the decrease in risk after 30 yrs of cessation (fig. 2 and table 5).

Figure 3 shows the estimated effect of the age at first occupational asbestos exposure in the two strata of duration. For subjects with longer duration of exposure, the estimated risk of PM flattens up to 18 yrs and sharply decreases thereafter. Thus, subjects who were first exposed at 30 yrs of age had a lower risk of PM than subjects who were first exposed at 10 yrs of age (estimated OR 0.2, 95% CI 0.0–0.7; table 5). The estimated

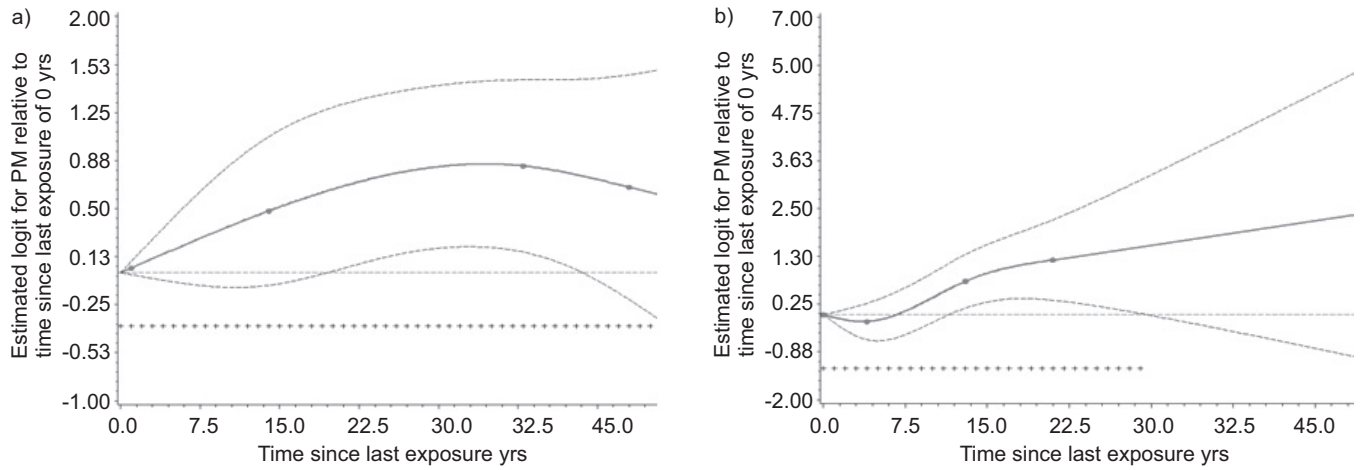

FIGURE 2. Nonlinear effect of time since last exposure on the logit of pleural mesothelioma (PM) in subjects with duration a) shorter or b) longer than the median value of 30 yrs according to model 1. The solid curve represents logistic regression estimates using a four-knot restricted cubic spline function located at the 5th, 25th, 75th and 95th percentiles of time since last exposure, adjusted for mean index of exposure, total duration of exposure, age at diagnosis/interview and birth year. Dashed curves are approximate 95% pointwise confidence intervals of the estimates compared with the reference value of time since last exposure set at its minimum value of 0 yrs. The + horizontal signs represent the observed time since last exposure values. The *x*-axis was cut off at the 97.5th percentile of time since last exposure (51 yrs) to better visualise the form of the relationship at the lower ranges.

decrease in risk was much less pronounced for subjects with shorter duration.

DISCUSSION

Our findings confirm that the risk of PM increases with increasing intensity and duration of exposure and suggest that the effect of duration decreases with increasing time since last exposure and age at first exposure. The effect of duration was weaker for subjects who had their last exposure a long time ago or their first exposure later in life. The long latency period of PM implied that the risk of PM continued to increase even after cessation of exposure. Our results suggest that the risk ceases to increase only 30 yrs after cessation of exposure. After adjustment for intensity and duration of exposure, the estimated risk of PM was lower for those exposed the first time after the age of 20 yrs.

While some previous cohort studies on asbestos cement workers found no significant effect of age at first exposure [12, 13], others

TABLE 5 Effect of time since last exposure and age at first exposure according to total duration of exposure on pleural mesothelioma risk, adjusted for age, cumulative index of exposure, total duration of exposure and birth cohort among exposed male subjects in a case–control study of occupational asbestos exposure and pleural mesothelioma in 1,041 cases and 1,425 controls in France in 1987–2006

Total duration of exposure yrs	Model 1[#]		Model 2[¶]	
	Times since last exposure yrs[+]	OR (95% CI)	Age at first exposure yrs[§]	OR (95% CI)
<30	10	1.5 (0.8–2.4)	15	1.1 (0.4–2.9)
	20	2.0 (1.0–3.9)	20	1.3 (0.4–1.3)
	30	2.4 (1.2–4.7)	25	1.0 (0.3–2.9)
	40	2.3 (1.1–4.8)	30	0.6 (0.2–2.0)
	50	1.9 (0.7–5.0)	35	0.5 (0.1–1.7)
⩾30	10	1.3 (0.72–2.4)	15	1.1 (0.3–3.8)
	20	3.1 (1.23–7.6)	20	0.7 (0.2–2.6)
	30	4.5 (0.89–22.3)	25	0.3 (0.1–1.2)
	40		30	0.2 (0.0–0.7)
	50		35	0.1 (0.0–0.5)

[#]: logistic regression model with mean index of exposure (three-knot restricted cubic spline (RCS)), total duration of exposure (three-knot RCS), time since last exposure (four-knot RCS), age (three-knot RCS), birth year (three-knot RCS) and stratified on total duration of exposure shorter/longer than 30 yrs. [¶]: logistic regression model with mean index of exposure (three-knot RCS), total duration of exposure (three-knot RCS), age at first exposure (five-knot RCS), age (three-knot RCS), birth year (three-knot RCS), and stratified on total duration of exposure class. [+]: relative to time since last exposure of 0 yrs. [§]: relative to age at first exposure of 10 yrs.

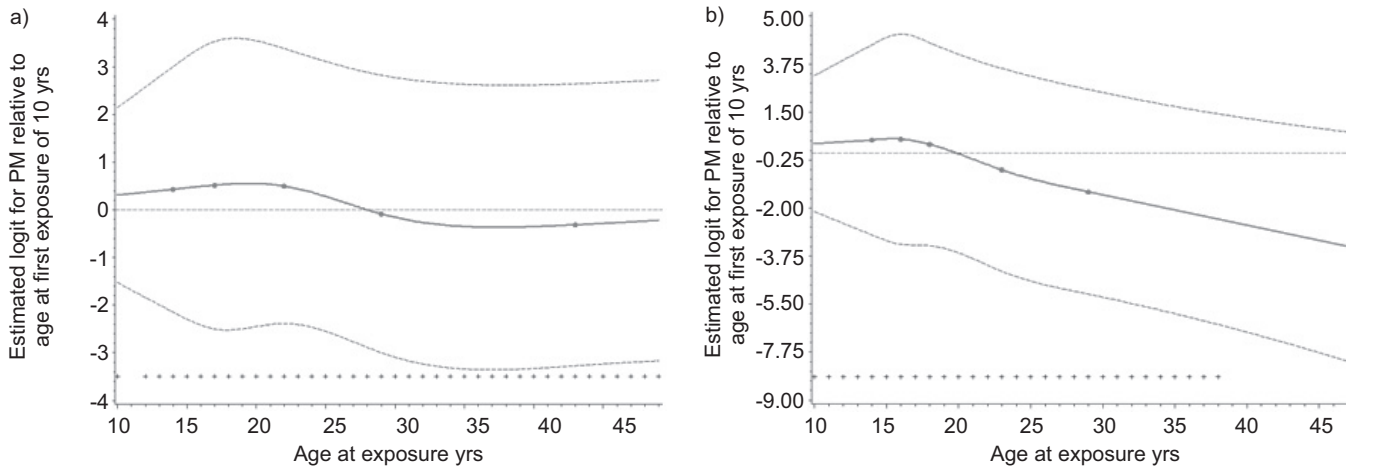

FIGURE 3. Nonlinear effect of age at first exposure on the logit of pleural mesothelioma (PM) in subjects with duration a) shorter or b) longer than the median value of 30 yrs according to model 2. The solid curve represents logistic regression estimates using a five-knot restricted cubic spline function located at the 5th, 25th, 50th, 75th and 95th percentiles of age at first exposure, adjusted for mean index of exposure, total duration of exposure, age at diagnosis/interview and birth year. Dashed curves are approximate 95% pointwise confidence intervals of the estimates compared with the reference value of age at first exposure set at its minimum value of 10 yrs. The + horizontal signs represent the observed age at first exposure values. The *x*-axis was cut off at the 97.5th percentiles of age at first exposure (49 yrs) to better visualise the form of the relationship at the lower ranges.

suggested that increasing age at first exposure decreased the risk of PM [14, 15]. In a German case–control study [16], a dose–response relationship was found for total duration of exposure, but the risk of PM did not clearly decrease with increasing time since first exposure. Some cohort studies have suggested that incidence of PM starts to increase 5–10 yrs after the beginning of exposure and continues to increase subsequently, even after cessation of exposure [17–19]. However, other studies have suggested that the trend of the incidence rate of PM starts to decline many years after first exposure, which indicates some clearance of asbestos fibres from the lung [16, 20]. A cohort study of 17,000 asbestos insulation workers indicated that the mortality rates of pleural cancer peaked 45–49 yrs after first employment and declined after 50 yrs [21]. Another cohort study of 3,434 asbestos cement workers showed a curvilinear increased of risk of death by pleural neoplasm with latency and time since cessation of exposure [13]. Reduced rates of pleural cancer many years after exposure have also been reported in other cohort studies [22–25]. In France, we observed a decline of the pleural cancer incidence between 2000 and 2005 [26]. This finding is in contradiction with previous projections for France, which predicted a peak of PM around 2020–2025 [27]. One possible explanation for the decrease in the incidence of PM was linked to the facts that chrysotile asbestos consumption in France peaked in the 1970s and that the first regulations regarding asbestos exposure at work were implemented in 1977 [26]. Another complementary explanation could be the ignorance of the decrease of the risk of PM with time since last exposure in statistical models used to predict future incidence trend of PM. Our observed slight decrease in estimated risk of PM after 30 yrs of cessation might suggest that fibres may, indeed, be removed slowly from the lung [28]. However, the sample size for such a long duration of cessation was small and the observed slight decline in risk could also result from potentially less intensive diagnostic procedures in subjects whose asbestos exposure ceased a very long time ago.

Our cases and controls came from two different sources. This allowed us to increase the statistical power for hypothesis testing, but this may have induced some potential biases. However, we believe that our pooled cases from the case–control study (1987–1993) and the NMSP (1998–2006) are representative of all French cases of PM during these two periods of time. Indeed, the NMSP cases were exhaustive incident cases in some specific but representative districts of France [5]. In addition, we observed no major distortion between the asbestos exposure distributions of the two cases series. In particular, the probability of exposure was not statistically different ($p=0.179$). Controls were also selected from two samples. The representativeness of sample B (1984–2000) with respect to the overall French male population in terms of occupations likely to be exposed to asbestos has been previously investigated, and the sample was very close to the general population for various time windows [29]. The representativeness of sample A (2007) has not yet been published. However, the quota sampling method was designed to ensure a representative sample of the general population with respect to age, region and socioeconomic status. Sample A should also be representative of the general population for occupational asbestos exposure as its prevalence depends on age, sex, region and socioeconomic status. The population source of the controls was not the same as the cases in terms of region, but our controls should be representative of the population from which the cases arose. In particular, 60% of our controls were ever-exposed to asbestos (at least one job with a probability of exposure different from zero), which is in agreement with a previous study where 67.9% of French pensioners had at least one job with a probability of exposure different from zero during their career [30]. Circumstances of occupational asbestos exposure may differ across the various time windows. However, controls were frequency matched to cases on birth year to avoid major distortion due to periods of studies. Overall, we believe that our subject's selection did not

induce major bias in the estimates of the effects of temporal patterns of occupational asbestos exposure.

Asbestos exposure was assessed using a JEM that may produce misclassification. As such misclassification is likely to be nondifferential, some effects might have been under-estimated [31]. However, in all our data sources, trained interviewers obtained work history from the subject, and previous studies found good validity and reliability of job histories obtained from such interviews [32]. There is no evidence that the recall of occupations is influenced by disease status [32]. In addition, a French study evaluated the quality of coding of job episodes collected by self-questionnaires among retired French males and found that the coding was satisfactory [33]. Moreover, for a given job, the parameters of exposure included in the JEM changed over time to account for the improvement of work environments or the change in the use of asbestos for a given job in analyses. Finally, a minor confounding factor may have been introduced in this study. Until now, asbestos has been the only established risk factor for PM, except for erionite fibres [34]. As the latter type of fibre is not present in France, confounding may have been introduced into our study by domestic or environmental asbestos exposure, as we considered only occupational asbestos exposure. Indeed, we did not have any information about possible domestic or environmental exposure to adjust for in our analyses.

Our statistical models included potentially correlated exposure variables and covariates. The strongest correlation was between duration and time since last exposure in model 1 (Pearson coefficient -0.76). All other correlation coefficients were <0.4. Strong correlation can produce inflated standard errors, which explains why the confidence intervals for the ORs of duration in model 1 were generally larger than in model 2 (table 4). However, all our estimates converged. The main limitation of our analyses is that we did not account for the time-varying pattern of intensity over the different periods of exposure for each individual. For example, for subjects who alternated periods of high and low levels of exposure, the MIE value was the same whether high levels of exposure occurred either early or later in life. This issue will be further investigated using some recent approaches [35, 36].

Despite these potential limitations, we believe that our study based on the largest population-based case–control dataset published to date and using flexible statistical methods provides new insights into the dose–response relationships between the risk of PM and temporal patterns of occupational exposure to asbestos.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors thank E. Imbernon, Director of the Occupational Health Dept at the InvS, for allowing us to use tools developed within the Occupational Health Dept, Y. Iwatsubo for allowing us to use data collected from the previous case–control study, the other members of the NMSP technical Committee (P. Astoul, S. Chammings, C. Frenay, F. Galateau-Sallé, N. Le Stang and J-C. Pairon) for allowing us to use data collected from the NMSP, J. Févotte (AgroParisTech, UMR 1290 BIOGER-CPP, Paris, France) for the use the job history samples, L. Desquilbet (AgroParisTech, UMR 1290 BIOGER-CPP) for his constructive advice about the use of the RCS_Reg SAS macro and R. Cook (Université Bordeaux Segalen, Département de Langues et Cultures et du Centre de Langues, Bordeaux, France) for her careful reading of this manuscript.

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