

Temporal Patterns of Occupational Asbestos Exposure and Risk of Pleural Mesothelioma

Aude Lacourt ^{1,2}, Karen Leffondré ¹, Céline Gramond ^{1,2}, Stéphane Ducamp ^{3,2}, Patrick Rolland ^{3,2}, Anabelle Gilg Soit ³ Ilg, Marie Houot ³, Ellen Imbernon ^{3,2}, Joëlle Févotte ^{3,4}, Marcel Goldberg ³ and Patrick Brochard ^{1,2}

¹ Université Bordeaux Segalen, ISPED, Centre de recherche INSERM U897 'Épidémiologie et Biostatistique', Bordeaux, France.

² Équipe Associée en Santé Travail- Essat (InVS/DST - LSTE-EA3672), Bordeaux, France.

³ Institut de Veille Sanitaire, Département Santé Travail, Saint Maurice, France.

⁴ Unité mixte de recherche épidémiologique et de surveillance en transport, travail et environnement Umrestte (UCB Lyon 1 / InVS/ Inrets), Lyon, France.

Corresponding author:

Name: Aude LACOURT

Postal address: ISPED - LSTE - ESSAT - 146 RUE LEO SAIGNAT - 33076 BORDEAUX - FRANCE

E-mail/Tel/Fax: aude.lacourt@isped.u-bordeaux2.fr - Tel.: 00 33 5 57 57 95 35 - Fax: 00 33 5 57 57 47 33

ABBREVIATIONS

PM: pleural mesothelioma

JEM: Job exposure matrix

DST: Occupational Health department

f/ml: fibres per millilitres

InVS: French Institute for Public Health Surveillance

MIE: Mean index of exposure

OR: Odds ratio

PNSM: French National Mesothelioma Surveillance Program

RCS: Restricted cubic spline

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 males.

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 years and continued to increase until 30 years 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.

KEY WORDS

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 tumor mostly located in the pleura [1]. The incidence of pleural mesothelioma (PM) has been rising in industrialized countries since several decades, and seems to have levelled off since the last decade in several countries. However, asbestos is still used in the world and particularly in less-industrialized countries which mostly 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, the intensity and the 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 categorization of the continuous exposure asbestos variables categories may make the true dose-response relationship difficult to identify.

In addition, in most previous population-based studies on PM, the effects of these categorized 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 lifetime [3]. Yet, 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 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 (PNSM) [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 PNSM were all incident PM between January 1998 and December 2006 in 22 French districts that cover a quarter of the French population (7 districts belong to the 5 regions mentioned above).

Controls

Controls were selected from two population-based samples from the French Institute for Public Health Surveillance (InVS) which both included the 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 years in 2007, by quota sampling method stratified on sex, age, region, and socio economic 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-year group.

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 the International Standard industry Classification (ISIC) revision 2 or the nomenclature of French activities (NAF) classification edition 1999. Occupations were defined according to the International Standard classification of Occupation (ISCO) edition 1968. The JEM was exhaustive in terms of all jobs exposed to asbestos and accounted for asbestos exposure levels changes over time [7]. It 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 , the frequency (f_{ai}) and intensity (i_{ai}) of exposure due to work environment contamination of job i , based on the judgment of industrial hygienists (Table 1). The mean index of exposure (MIE) over lifetime was calculated as:

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

where n is the number of jobs exposed to asbestos over lifetime; d_i the duration of job i ; and the other parameters as defined above. For probability, frequency, and intensity values, we used the numerical values indicated in the last column of Table 1. Note the strong weight assigned to very

high exposure intensity, which results in high numerical values of MIE for subjects who were exposed to high levels of asbestos even for 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.

-Insert Table 1-

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 *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 logistic 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 f/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 relation between PM and time since last exposure or age at first exposure, we have included MIE, total duration of exposure, and time since last exposure in Model 1, and MIE, total duration of exposure, and age at first exposure in Model 2. To avoid imposing a *priori* specific functional form of the dose-responses relationship between each of these continuous variables and the logit of PM, we used restricted cubic spline functions (RCS) [8]. Such functions allow the estimation of smooth and plausible dose-responses curves [8]. For each adjustment variable (age and birth year), we used three knots to ensure enough flexibility without producing over-fitting bias [8]. For each exposure variable, the number of knots was chosen to minimize 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 in average 67.0 years (Standard deviation (SD): 10.0 years) at diagnosis and 66.9 years (SD: 6.3 years) 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.

-Insert Table 2-

Table 3 shows that cases had in average a MIE three-fold higher than controls (0.6 versus 0.2 f/ml), a longer total duration of exposure (27.8 versus 24.9 years), and were earlier exposed (21.0 versus 22.6 years). The mean time since last exposure was about 17 years for both cases and controls.

-Insert Table 3-

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

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 about 1 f/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).

-Insert Figure 1 and 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 OR for subjects who have been exposed during 30 years compared to those exposed during one year only was 7.5 (95% CI: 4.2-13.4) in subjects who had their last exposure 20 years ago versus 4.0 (95%

CI: 2.2-7.2) in subjects who had their last exposure 30 years ago. The estimated effect of duration tended to decrease with increasing age at first exposure as well (Model 2, Table 4). For example, the estimated OR for subjects who had been exposed during 30 years compared to those exposed during one year only was 6.5 (95% CI: 4.3-9.8) in subjects who were first occupationally exposed to asbestos at 15 years old, and of only 1.5 (95% CI: 1.1-2.2) in subjects who were first exposed at 30 years old.

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 (less or more than 30 years 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 stratum. For all subjects, the risk of PM continued to increase during the first 30 years of cessation of exposure. For subjects with a duration lower than 30 years, the estimated risk stopped to increase after 30 years of cessation. A slight decrease was even observed after 35 years of cessation, as also suggested by the estimated OR in top left panel of Table 5. In subjects with longer duration of exposure, the maximum of the time elapsed since the last of exposure was 30 years, which did not allow us to observe the decrease in risk after 30 years of cessation (Figure 2, and Table 5).

-Insert Figure 2 and Table 5-

Figure 3 shows the estimated effect of the age at first occupational asbestos exposure, in the two stratum of duration. For subjects with longer duration of exposure, the estimated risk of PM flattens up to 18 years old and sharply decreased thereafter. Thus, subjects who started to be exposed at 30 years old had a lower risk of PM than subjects who were first exposed at 10 years old (estimated OR of 0.2, 95% CI: 0.0-0.7, Table 5). The estimated decrease in risk was much less pronounced for subjects with shorter duration.

-Insert Figure 3-

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 stops to increase only 30 years 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 years.

While some previous cohort studies on asbestos cement workers found no significant effect of age at first exposure [10, 11], others suggested that increasing age at first exposure decreased the risk of PM [12, 13]. In a German case-control study (17), 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 suggested that incidence of PM starts to increase 5-10 years after the beginning of exposure and continues to increase subsequently, even after cessation of exposure. [14-16]. However, other studies suggested that the trend of the incidence rate of PM starts to decline many years after first exposure, which indicates some clearance of asbestos fibers from the lung [17, 18]. A cohort study of 17,000 asbestos insulation workers indicated that the mortality rates of pleural cancer peaked 45-49 years after first employment and declined after 50 years [19]. 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 [11]. Reduced rates of pleural cancer many years after exposure have also been reported in other cohort studies [20-23]. In France, we observed a decline of the pleural cancer incidence between 2000 and 2005 [24]. This finding is in contradiction with previous projections for France which predicted a peak of PM around 2020-2025 [25]. One possible explanation for the decrease of the incidence of PM was linked to the chrysotile asbestos consumption in France that peaked in the 1970s and the implementation of the first regulations regarding asbestos exposure at work in 1977 [24]. Other 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 years of cessation may suggest that, indeed, fibers may be removed slowly from the lung [9]. However, the sample size for such 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.

Both 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 PNSM (1998-2006) are representative of all French cases of PM during these two periods of time. Indeed, the PNSM 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 exposed to asbestos has been previously investigated, and the sample was very close to the general population for various time windows [26]. 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 socio-economic status. Sample A should also be representative of the general population for occupational asbestos exposure since its prevalence depends on age, sex, region, and socio-economic status. The population source of the controls was not the same than 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 retirees had at least one job with a probability of exposure different from zero during their career [27]. 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. Since such misclassification is likely to be non-differential, some effects might have been under-estimated [28]. 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 [29]. There is no evidence that the recall of occupations is influenced by disease status [29]. In addition, a French study evaluated the quality of coding of job episodes collected by self-

questionnaires among retired French men and found that the coding was satisfactory [30]. Moreover, for a given job, the parameters of exposure included in the JEM changed over calendar 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 is the only established risk factors for PM except for erionite fibers [31]. Since this kind of fibers is not present in France, confounding may have been introduced in this study only by domestic or environmental asbestos exposure as we only considered 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 of -0.76). All other correlation coefficients were lower than 0.4. Strong correlation can produce inflated standard errors, which explains why the CIs 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 early or later in life. This issue will be further investigated using some recent approaches [32, 33].

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

ACKNOWLEDGEMENTS

The authors thank Ellen Imbernon, director of the Occupational Health department at National Institute for Public Health Surveillance to permit us to use tools developed within the Occupational Health department, Yuriko Iwatsubo to permit us to use data collected from the previous case-control study, the other members of the PNSM technical Committee (Philippe Astoul, Soizick Chamming's, Catherine Frenay, Françoise Galateau-Sallé, Nolwenn Le Stang, Jean-Claude Pairon) to permit us to use data collected from the PNSM, Joelle Févotte for the use the job history

samples, Loïc Desquilbet for his constructive advice about the use of the RCS_Reg SAS macro and Ray cook for her careful reading of this manuscript.

REFERENCES

1. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960; 17: 260-271.
2. Frost G, Harding AH, Darnton A, McElvenny D, Morgan D. Occupational exposure to asbestos and mortality among asbestos removal workers: a Poisson regression analysis. *Br J Cancer* 2008; 99(5): 822-829.
3. Leffondre K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: a comparison of different approaches. *Am J Epidemiol* 2002; 156(9): 813-823.
4. Iwatsubo Y, Pairon JC, Boutin C, Menard O, Massin N, Caillaud D, Orlowski E, Galateau-Salle F, Bignon J, Brochard P. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol* 1998; 148(2): 133-142.
5. Goldberg M, Imbernon E, Rolland P, Gilg Soit Ilg A, Saves M, de Quillacq A, Frenay C, Chamming's S, Arveux P, Boutin C, Launoy G, Pairon JC, Astoul P, Galateau-Salle F, Brochard P. The French National Mesothelioma Surveillance Program. *Occup Environ Med* 2006; 63(6): 390-395.
6. Orlowski E, Pohlabeln H, Berrino F, Ahrens W, Bolm-Audorff U, Grossgarten K, Iwatsubo Y, Jockel KH, Brochard P. Retrospective assessment of asbestos exposure--II. At the job level: complementarity of job-specific questionnaire and job exposure matrices. *Int J Epidemiol* 1993; 22 Suppl 2: S96-105.
7. Goldberg M, Kromhout H, Guenel P, Fletcher AC, Gerin M, Glass DC, Heederik D, Kauppinen T, Ponti A. Job exposure matrices in industry. *Int J Epidemiol* 1993; 22 Suppl 2: S10-15.
8. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010.

9. Berry G, Pooley F, Gibbs A, Harris JM, McDonald JC. Lung fiber burden in the Nottingham gas mask cohort. *Inhal Toxicol* 2009; 21(2): 168-172.
10. Finkelstein MM. The exposure-response relationship for mesothelioma among asbestos-cement factory workers. *Toxicol Ind Health* 1990; 6(6): 623-627.
11. Magnani C, Ferrante D, Barone-Adesi F, Bertolotti M, Todesco A, Mirabelli D, Terracini B. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med* 2008; 65(3): 164-170.
12. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL, Benichou J. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994; 51(12): 804-811.
13. Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer* 2009.
14. Newhouse ML, Berry G. Predictions of mortality from mesothelial tumours in asbestos factory workers. *Br J Ind Med* 1976; 33(3): 147-151.
15. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. *Br J Cancer* 1982; 45(1): 124-135.
16. Price B, Ware A. Mesothelioma: risk apportionment among asbestos exposure sources. *Risk Anal* 2005; 25(4): 937-943.
17. Barone-Adesi F, Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Long-term mortality from pleural and peritoneal cancer after exposure to asbestos: Possible role of asbestos clearance. *Int J Cancer* 2008; 123(4): 912-916.

18. Berry G. Prediction of mesothelioma, lung cancer, and asbestosis in former Wittenoom asbestos workers. *Br J Ind Med* 1991; 48(12): 793-802.
19. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-1987. *Ann N Y Acad Sci* 1991; 643: 1-14.
20. Berry G. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. *Inhal Toxicol* 1999; 11(2): 111-130.
21. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. *Occup Environ Med* 2006; 63(12): 852-855.
22. Pira E, Pelucchi C, Buffoni L, Palmas A, Turbiglio M, Negri E, Piolatto PG, La Vecchia C. Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer* 2005; 92(3): 580-586.
23. Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med* 1986; 10(5-6): 479-514.
24. Le Stang N, Belot A, Gilg Soit Ilg A, Rolland P, Astoul P, Bara S, Brochard P, Danzon A, Delafosse P, Grosclaude P, Guizard AV, Imbernon E, Lapotre-Ledoux B, Ligier K, Molinie F, Pairon JC, Sauleau EA, Tretarre B, Velten M, Bossard N, Goldberg M, Launoy G, Galateau-Salle F. Evolution of pleural cancers and malignant pleural mesothelioma incidence in France between 1980 and 2005. *Int J Cancer* 2010; 126(1): 232-238.
25. Banaei A, Auvert B, Goldberg M, Gueguen A, Luce D, Goldberg S. Future trends in mortality of French men from mesothelioma. *Occup Environ Med* 2000; 57(7): 488-494.
26. Goldberg M, Banaei A, Goldberg S, Auvert B, Luce D, Gueguen A. Past occupational exposure to asbestos among men in France. *Scand J Work Environ Health* 2000; 26(1): 52-61.

27. Imbernon E, Goldberg M, Spyckerell Y, Bonenfant S, Fournier B. Utilisation d'une matrice emplois-exposition pour l'identification des expositions professionnelles à l'amiante. *Rev Epidemiol Sante Publique* 2004; 52(1): 7-17.
28. Bouyer J, Dardenne J, Hemon D. Performance of odds ratios obtained with a job-exposure matrix and individual exposure assessment with special reference to misclassification errors. *Scand J Work Environ Health* 1995; 21(4): 265-271.
29. Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. *Am J Epidemiol* 1983; 118(4): 583-591.
30. Pilorget C, Imbernon E, Goldberg M, Bonenfant S, Spyckerelle Y, Fournier B, Steinmetz J, Schmaus A. Evaluation of the quality of coding of job episodes collected by self questionnaires among French retired men for use in a job-exposure matrix. *Occup Environ Med* 2003; 60(6): 438-443.
31. Baris YI, Grandjean P. Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite. *J Natl Cancer Inst* 2006; 98(6): 414-417.
32. Leffondre K, Wynant W, Cao Z, Abrahamowicz M, Heinze G, Siemiatycki J. A weighted Cox model for modelling time-dependent exposures in the analysis of case-control studies. *Stat Med* 2010; 29(7-8): 839-850.
33. Richardson DB, MacLehose RF, Langholz B, Cole SR. Hierarchical latency models for dose-time-response associations. *Am J Epidemiol* 2011; 173(6): 695-702.

Table 1: Definition of the Different Asbestos Exposure Parameters Include 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, 1987-2006.

| Asbestos exposure parameters used in the JEM | Definition | Numerical values used to calculate the mean index of exposure (MIE) | | |
|--|--|---|----------|---------------------------------------|
| Probability of exposure | Expressed in percent of workers exposed in the considered job code | 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 ^a | Expressed in percent of 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 ^b | Expressed in f/ml | Kind of exposure ^c | | |
| | | Environment work exposure (i_{ai}) | | Specific direct exposure (i_{si}) |
| | | Passive | Indirect | |
| 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 |

Abbreviations: JEM, Job Exposure Matrix; f/ml, fibers per milliliter

^a definition valid for the frequency of exposure due to specific task of the job and the frequency exposure due to work environment contamination parameters.

^b definition valid for the intensity of exposure due to specific task of job, and the intensity exposure due to work environment contamination parameters.

^c Three kind of exposure are defined:

- Passive exposure: workers are exposed according to diffuse contamination of buildings;
- Indirect exposure: workers are exposed by other workers using asbestos materials;
- Direct exposure: workers use directly asbestos materials.

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

| | Cases (1,199) | | Controls (2,379) | | |
|---|--|----------|-----------------------------|----------|------|
| | n | % | n | % | |
| Age at interview-diagnosis (years) | | | | | |
| < 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 |

Abbreviations: ISCO, international standard classification of occupations

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: 1,041 cases and 1,425 controls, France, 1987-2006.

| | Cases (1,041) | Controls (1,425) |
|---|-----------------------------|-----------------------------|
| Total duration of exposure (years) | | |
| Mean (SD) | 27.8 (12.9) | 24.9 (14.1) |
| Median | 32 | 28 |
| Q1-Q3* | 18-38 | 11-37 |
| Range | 1-55 | 1-59 |
| Age at first exposure (years) | | |
| Mean (SD) | 21.0 (7.0) | 22.6 (8.1) |
| Median | 19 | 20 |
| Q1-Q3* | 16-24 | 17-26 |
| Range | 10-59 | 10-64 |
| Time since last exposure (years) | | |
| Mean (SD) | 16.9 (13.4) | 17.4 (14.5) |
| Median | 14 | 13 |
| Q1-Q3* | 7-24 | 6-28 |
| Range | 0-60 | 0-57 |
| MIE (f/ml) | | |
| Mean (SD) | 0.61 (1.43) | 0.21 (0.44) |
| Median | 0.12 | 0.01 |
| Q1-Q3* | 0.01-0.74 | 0.001-0.17 |
| Range | 1.5×10^{-6} -16.26 | 3.1×10^{-7} -7.36 |

Abbreviations: SD, standard deviation; Q1-Q3, Lower quartile-upper quartile; MIE, Mean Index of Exposure; f/ml, fibers per milliliter.

Table 4: Effect of mean index of exposure 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: 1,041 cases and 1,425 controls, France, 1987-2006.

| Model 1 ^a | | | | Model 2 ^b | | | |
|---|---|------|----------|--|---|------|----------|
| Occupational asbestos exposure variable | Exposure value | OR | 95% CI | Occupational asbestos exposure variables | Exposure value | OR | 95% CI |
| MIE (f/ml) ^c | 0.1 | 1.2 | 1.1-1.2 | MIE (f/ml) ^c | 0.1 | 1.2 | 1.1-1.2 |
| | 0.5 | 2.0 | 1.6-2.4 | | 0.5 | 1.9 | 1.6-2.3 |
| | 1.0 | 2.9 | 2.3-3.7 | | 1.0 | 2.8 | 2.2-3.6 |
| | 2.0 | 4.4 | 3.2-5.9 | | 2.0 | 4.4 | 3.2-6.0 |
| Time since last exposure of 20 years | Total duration of exposure (years) ^c | | | Age at first exposure of 15 years | Total duration of exposure (years) ^c | | |
| | 10 | 1.9 | 1.5-2.4 | | 10 | 1.8 | 1.5-2.2 |
| | 20 | 3.7 | 2.3-5.9 | | 20 | 3.4 | 2.4-4.9 |
| | 30 | 7.5 | 4.2-13.4 | | 30 | 6.5 | 4.3-9.8 |
| | 40 | 15.0 | 8.0-27.9 | | 40 | 12.3 | 9.0-16.9 |
| Time since last exposure of 30 years | Total duration of exposure (year) ^c | | | Age at first exposure of 20 years | Total duration of exposure (years) ^c | | |
| | 10 | 1.5 | 1.2-2.0 | | 10 | 1.5 | 1.3-1.8 |
| | 20 | 2.5 | 1.5-3.9 | | 20 | 2.5 | 1.9-3.3 |
| | 30 | 4.0 | 2.2-7.2 | | 30 | 4.0 | 3.1-5.3 |
| | 40 | 6.4 | 3.2-12.9 | | 40 | 6.5 | 6.1-6.9 |
| Time since last exposure of 40 years | Total duration of exposure (years) ^c | | | Age at first exposure of 30 years | Total duration of exposure (years) ^c | | |
| | 10 | 1.3 | 0.9-1.9 | | 10 | 1.1 | 1.0-1.3 |
| | 20 | 1.8 | 0.9-3.7 | | 20 | 1.3 | 1.0-1.8 |
| | - | - | - | | 30 | 1.5 | 1.1-2.2 |
| | - | - | - | | 40 | 1.8 | 1.1-3.0 |

Abbreviations: OR, odds ratio; CI, confidence interval; MIE, mean index of exposure.

^a Model 1: logistic regression model with mean index of exposure (3-knot restricted cubic spline (RCS)), total duration of exposure (3-knot RCS), time since last exposure (4-knot RCS), age (3-knot RCS), birth year (3-knot RCS), and interaction term between the linear spline of time since last exposure and the linear spline of total duration of exposure.

^b Model 2: logistic regression model with mean index of exposure (3-knot RCS), total duration of exposure (3-knot RCS), age at first exposure (5-knot RCS), age (3-knot RCS), birth year (3-knot RCS), and interaction term between the linear spline of age at first exposure and the linear spline of total duration of exposure.

^c Estimated odds ratio relative to the minimum of exposure (1.5×10^{-6} f/ml for MIE and one year for total duration of exposure).

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, 1,041 cases and 1,425 controls, France, 1987-2006.

| Total duration of exposure (years) | Model 1 ^a | | | | Model 2 ^b | | | |
|------------------------------------|--|-----|-----------|---------|--|-----|---------|---------|
| | Times since last exposure (years) ^c | OR | 95% CI | P Value | Age at first exposure (years) ^d | OR | 95% CI | P Value |
| <30 | 10 | 1.5 | 0.8-2.4 | 0.034 | 15 | 1.1 | 0.4-2.9 | 0.004 |
| | 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 | 0.002 | 15 | 1.1 | 0.3-3.8 | <0.001 |
| | 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 | |

Abbreviations: OR, odds ratio; CI, confidence interval.

^a Model 1: logistic regression model with mean index of exposure (3-knot restricted cubic spline (RCS)), total duration of exposure (3-knot RCS), time since last exposure (4-knot RCS), age (3-knot RCS), birth year (3-knot RCS), and stratified on total duration of exposure shorter/longer than 30 years.

^b Model 2: logistic regression model with mean index of exposure (3-knot RCS), total duration of exposure (3-knot RCS), age at first exposure (5-knot RCS), age (3-knot RCS), birth year (3-knot RCS), and stratified on total duration of exposure class.

^c Relative to time since last exposure of 0 years.

^d Relative to age at first exposure of 10 years.

Figure 1: Nonlinear effect of mean index of exposure (MIE) to asbestos on the logit of pleural mesothelioma. The solid curve represents logistic regression estimates using a 3-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 OR 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} f/ml. The "+" horizontal signs represent the observed MIE values. The X-axis was cut off at the 97.5th percentiles of MIE (2.02 f/ml) to better visualize the form of the relationship at the lower ranges.

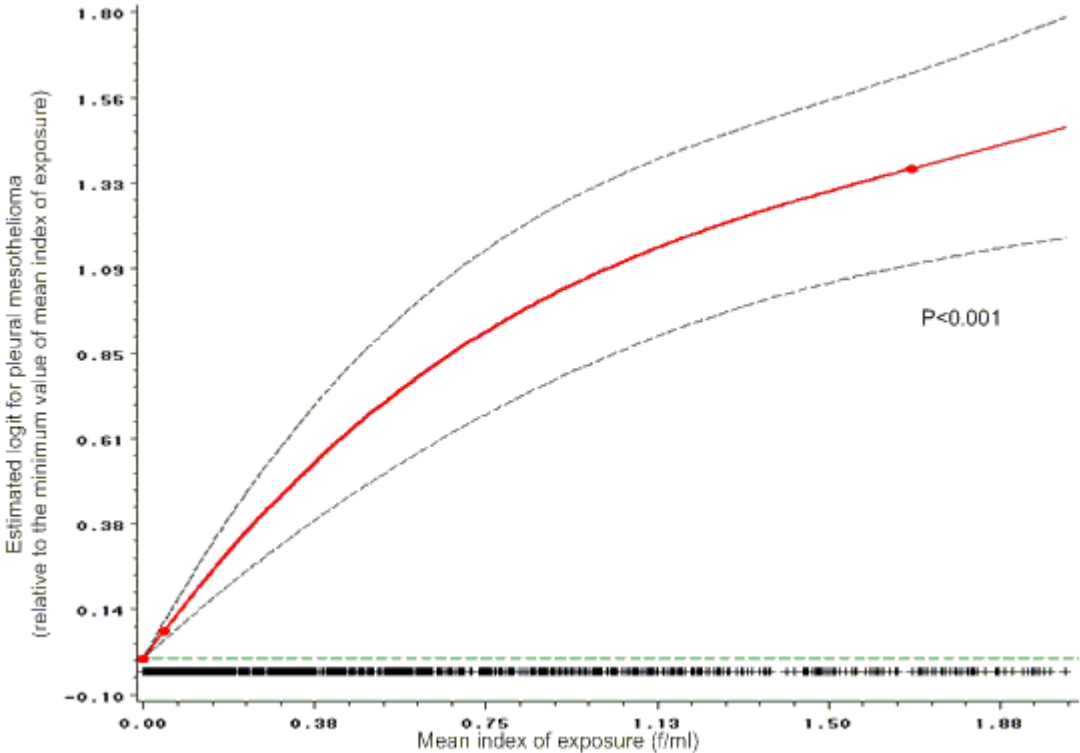


Figure 2: Nonlinear effect of time since last exposure on the logit of pleural mesothelioma in subjects with duration shorter (left panel) or longer (right panel) than the median value of 30 years according to model 1. The solid curve represents logistic regression estimates using a 4-knot restricted cubic spline function located at the 5th, 25th, 75th, 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 to the reference value of time since last exposure set at its minimum value of 0 year. 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 years) to better visualize the form of the relationship at the lower ranges.

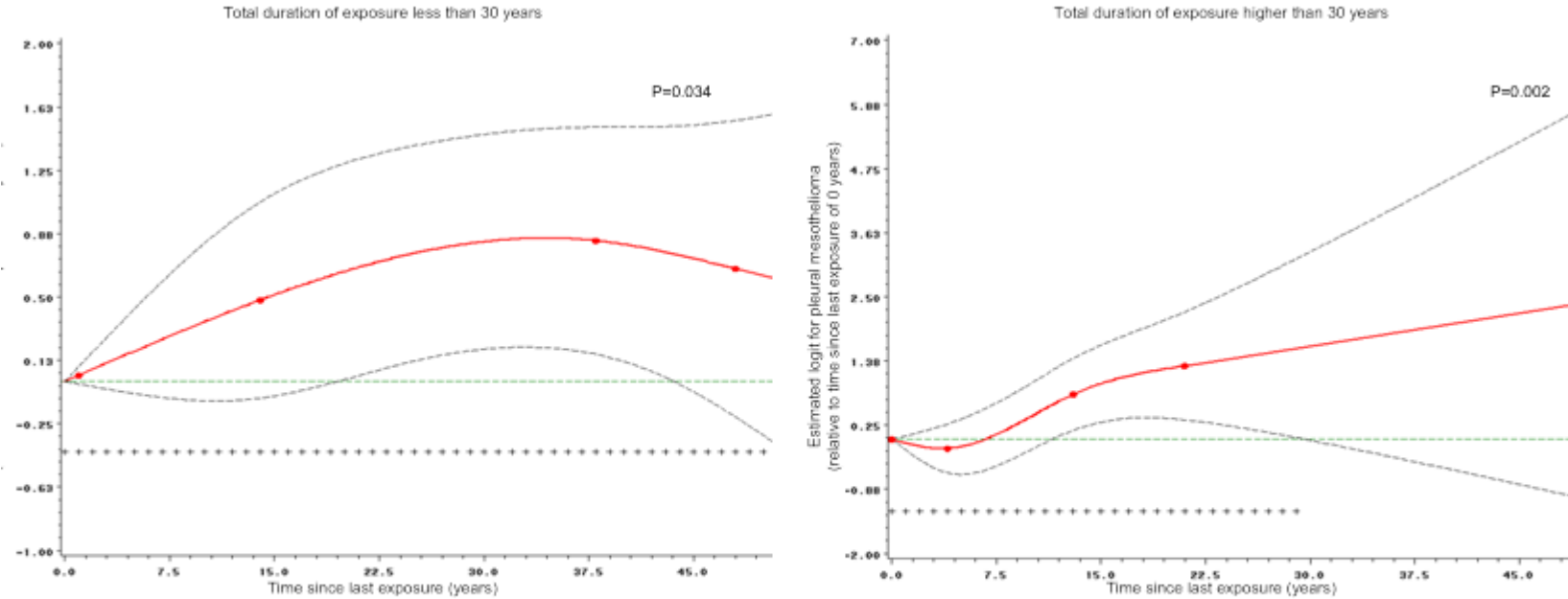


Figure 3: Nonlinear effect of age at first exposure on the logit of pleural mesothelioma in subjects with duration shorter (left panel) or longer (right panel) than the median value of 30 years according to model 2. The solid curve represents logistic regression estimates using a 5-knot restricted cubic spline function located at the 5th, 25th, 50th, 75th, 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 to the reference value of age at first exposure set at its minimum value of 10 years. 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 years) to better visualize the form of the relationship at the lower ranges.

