



Attributable risk in men in two French case-control studies on mesothelioma and asbestos

Aude Lacourt, Patrick Rolland, Céline Gramond, Philippe Astoul, Soizick Chamming'S, Stéphane Ducamp, Catherine Frenay, Françoise Galateau-Sallé, Anabelle Gilg Soit Ilg, Ellen Imbernon, et al.

► To cite this version:

Aude Lacourt, Patrick Rolland, Céline Gramond, Philippe Astoul, Soizick Chamming'S, et al.. Attributable risk in men in two French case-control studies on mesothelioma and asbestos. *European Journal of Epidemiology*, 2010, 25 (11), pp.799-806. 10.1007/s10654-010-9502-0 . hal-00619933

HAL Id: hal-00619933

<https://hal.science/hal-00619933>

Submitted on 7 Sep 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

MESOTHELIOMA AND ASBESTOS-ATTRIBUTABLE RISK IN MEN IN TWO FRENCH CASE-CONTROL STUDIES: THE ROLE OF CONTROL SELECTION

Aude Lacourt¹, Patrick Rolland², Céline Gramond¹, Philippe Astoul³, Soizick Chamming's⁴, Stephane Ducamp^{2,6}, Catherine Frenay³, Françoise Galateau-Salle^{5,6}, Anabelle Gilg Soit Ilg^{6,7}, Ellen Imbernon^{2,7}, Nolwenn Le Stang⁶, Jean Claude Pairon^{8,9}, Marcel Goldberg⁷, Yuriko Iwatsubo⁷, Louis-Rachid Salmi¹⁰ and Patrick Brochard¹

¹ Université Victor Segalen Bordeaux 2, Laboratoire Santé Travail Environnement EA 3672, Équipe Associée en Santé Travail, Bordeaux, Institut de Santé Publique, d'Épidémiologie et de Développement, F-33076

² Institut de Veille Sanitaire, Département Santé Travail, Équipe Associée en Santé Travail, Bordeaux, F-33076

³ Hôpital Sainte Marguerite, Département des Maladies Respiratoires, Service d'Oncologie Thoracique, Marseille, F-13009

⁴ Institut Interuniversitaire de Médecine du Travail de Paris Ile de France, Paris, F-75270

⁵ Hôpital de la Cote de Nacre, Service d'Anatomie Pathologique, Caen, F-14033

⁶ Registre Multicentrique à Vocation Nationale des Mésothéliomes Pleuraux (MESONAT), Caen, F-14033

⁷ Institut de Veille Sanitaire, Département Santé Travail, Saint Maurice, F-94415

⁸ INSERM, U955, Créteil, F-94010

⁹ Université Paris-Est Créteil-Val de Marne, Faculté de Médecine, Créteil, F-94010

¹⁰ Université Victor Segalen Bordeaux 2, Centre de recherche INSERM U897 'Épidémiologie et Biostatistique', Bordeaux, F-33076, 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

ABSTRACT

Pleural mesothelioma is a primary tumor of the pleura that is mainly due to asbestos exposure. To study the relationship between mesothelioma and occupational asbestos exposure in France, two case-control studies (A and B) were conducted. A substantial difference in the attributable risk in the population (AR_p) was observed among men: 44.5% (95% CI: [32.6 – 56.4]) in study A and 83.2% (95% CI: [76.8 – 89.6]) in study B. As different exposure assessment expert methods were used, the main objective of this work was to re-estimate the AR_p among men in two case-control studies according to a common standardized exposure assessment by using a Job Exposure Matrix (JEM) and to assess the role of subjects' selection. The initial observed AR_p difference was maintained: 36.3% (95% CI: [24.3 – 50.3]) in study A and 69.7% (95% CI: 51.7 – 83.2]) in study B. Further investigations highlighted the potential selection bias introduced in both studies, especially among controls. The AR_p could be underestimated in study A and overestimated in study B. After weighting subjects according to distribution of socio-economic status in the general population for controls and according to distribution of socio-economic status of cases registered by the French National Mesothelioma Surveillance Program, re-estimated AR_p values were 52.4% in study A and 70.2% in study B. These results provide additional information to describe the relationship between pleural mesothelioma and occupational asbestos exposure, but also confirm the importance of subjects' recruitment in case control studies, particularly control selection.

KEY WORDS

Asbestos, attributable risk, case-control study, men, mesothelioma, occupational exposure.

ABBREVIATIONS

AR_p Attributable risk in the population

CEI Cumulative exposure index

CI Confidence interval

f/ml Fibers per milliliter

f/ml-years Fibers per milliliter years

ISCO International Standard Classification of Occupations edition 1968

ISIC Industrial Classification of All Economic Activities revision 2

JEM Job exposure matrix

PNSM French national mesothelioma surveillance program

INTRODUCTION

Pleural mesothelioma is a primary tumor of the pleura mainly due to asbestos exposure [1]. Exposure-response relationships mainly based on cohort studies demonstrate the general pattern of the relationship but with large differences from one study to another due to the type of industry or type of fibers [2]. As pleural mesothelioma is rare, case-control studies are a well-suited method for analyzing dose-response relationships between occupational asbestos exposure and pleural mesothelioma. Case-control studies have been performed, but all encountered methodological difficulties in recruiting cases or controls and in assessing occupational asbestos exposure. To study the relationship between pleural mesothelioma and occupational asbestos exposure in France, two large case-control studies have been conducted. A first hospital-based case-control study was conducted between 1987-1993 (hereafter called "study A") [3], and a second population-based study nested in the French National Mesothelioma Surveillance Program (PNSM) was performed between 1998-2002 (hereafter called "study B") [4]. A substantial difference in the attributable risk in the male population (AR_p) was observed: 44.5% (95% CI: [32.6-56.4]) in study A and 83.2% (95% CI: [76.8-89.6]) in study B. The results were not comparable due to different methods of asbestos exposure assessment (assessment of individual job periods of subjects in study A and overall assessment of work history of subjects in study B). Furthermore, there was a slight difference in the proportion of exposed subjects (61.2% in study A and 67.5% in study B), maybe due to different population recruitment methods (hospital population in study A and general population in study B). Therefore, the large difference in the AR_p might be explained by inadequate exposure assessment in one or other study, that could bias AR_p by inadequate exposure classification [5, 6], or by the population recruitment. This is especially so for recruitment of controls that could bias prevalence of exposure among controls and thus bias the odds ratio and AR_p .

To promote better occupational health and safety strategies, it is important to correctly estimate the AR_p related to occupational asbestos exposure. For this reason, it is essential to understand the major difference in AR_p between these studies. We made the hypothesis that one way to improve comparisons and to estimate the real difference in the AR_p between these two studies was to standardize the exposure assessment across both studies.

The main objectives of this work were to estimate the dose-response relationship between pleural mesothelioma and occupational asbestos exposure among men, to calculate the AR_p in the two case-

control studies according to a common standardized exposure assessment through the use of a job exposure matrix, and to appreciate the role of subjects' selection.

POPULATION AND METHODS

Studies A [3] and B [4] were multicenter case-control studies. Study A was a hospital-based case-control study where cases were selected in five French administrative regions. Case collection was passive through clinicians from public hospitals (departments of respiratory disease, chest surgery and oncology) and private clinics. Study B was a population-based case-control study nested within the French National Mesothelioma Surveillance Program (PNSM). Since 1998, the PNSM has recorded all incident pleural mesotheliomas in 21 French districts that cover a quarter of the French population. These districts were chosen as being representative of France with regard to the main demographic, occupational and economic characteristics. Recording of cases in study B was active and aimed at exhaustivity. Cases in both studies were alive at the time of interview. Study A and B included 460 and 371 male cases, respectively. Two controls matched for sex, age (± 5 years) and district of residence were randomly selected from the hospital population in study A and from the general population in study B using the voting rolls of the districts. In both studies, a standardized questionnaire was administered to each subject by a trained interviewer. Experts in industrial hygiene, five in study A and two in study B, assessed occupational asbestos exposure by consensus [7]. Expertise methods were different: in study A, experts assessed the subjects' jobs sorted by industry, blinded to the full career of subjects [3], and in study B, experts assessed consecutively all the jobs of each subject [4]. The socioeconomic category of the subject was determined by the last occupation and work sector before the interview and was coded using the major groups of the International Standard Classification of Occupations (ISCO edition 1968) [8] and the International Standard Industrial Classification of All Economic Activities (ISIC revision 2) [9], respectively. In addition, distribution of the economic status of the general population was obtained from the French national 1999 census in men older than 50 years, restricted to the same districts of studies A and B.

To standardize occupational exposure assessment to asbestos across both studies, we used a job exposure matrix (JEM) that includes a temporal weighting when exposure levels changed within the time-period of interest [10]. The JEM used was developed by French industrial hygienists and previously used in several studies [11, 12]. It was designed to estimate asbestos exposure in relevant jobs and includes three exposure parameters for each job: probability, frequency and intensity of

exposure. Estimates of these parameters are semi-quantitative and based on the judgment of industrial hygienists. The probability of exposure was categorized as 'not exposed', 'possible' (where exposure might have occurred) and 'definite' (undoubted exposure or highly likely exposure). The frequency of exposure was defined as 'sporadic' (less than 5 percent of work time), 'irregular' (5-50 percent of work time) and 'continuous' (more than 50 percent of work time). The intensity of exposure (expressed in fibers per milliliter (f/ml)) was categorized as 'low' (less than 0.1 f/ml), 'medium' (0.1-1 f/ml), 'high' (1-10 f/ml) and 'very high' (>10 f/ml). Industries were classified according to the ISIC revision 2 [9] and occupations according to the ISCO edition 1968 [8]. In all, the JEM included 10,692 unique exposed industry/occupation combinations. It can be consulted through Internet on the Evalutil web site (Essat 2008) [13].

We linked all subjects' job histories to the JEM. A subject was defined as 'occupationally exposed to asbestos' if the probability of exposure for at least one job was different from zero. We also characterized each subject's history by: the highest probability of any job period during lifetime work history; total duration of exposure (years); time since first exposure (latency period); age at first exposure (year); Cumulative Exposure Index (CEI) expressed in 'fibers/ml-years' (f/ml-years) and defined as the sum of the products of probability, frequency, intensity, and duration for each job period. To calculate the CEI, we attributed weighting factors used in a previous study [3] to each exposure category of these three parameters. Then, we categorized CEI as continuous variable in four CEI levels.

We estimated odds ratios and 95% confidence intervals (95% CI) by using conditional logistic regression matched for age and French districts. Because the latency period of this disease is long, we did not take into account asbestos exposure during the 20 years before the diagnosis of mesothelioma. Therefore, we calculated AR_p according to all CEI levels [14] and confidence intervals were estimated using the bootstrap method with 500 replicates [15].

We further compared for socioeconomic status controls from both studies A and B with the general population and cases with cases registered by the PNSM until December 2009. We considered that cases registered by the PNSM were representative of all French cases of mesothelioma, because the PNSM records all incident pleural tumors in 21 French districts that are representative of France regarding the main demographic, occupational and economic characteristics [4]. Then, we estimated AR_p again according to all CEI levels, after adjusting the two samples by weighting subjects according

to distribution of socio-economic status in the general population for controls and according to distribution of socio-economic status of cases registered by the PNSM. We conducted three different simulations to re-estimate the AR_p in the two studies. In simulation 1, we weighted only controls and a weight of 1 was given to cases. In simulation 2, we weighted only cases and a weight of 1 was given to controls. In simulation 3, we weighted cases and controls together. SAS 9.1[®] software was used for the analysis.

RESULTS

Study A included 460 male cases and 421 controls and study B included 371 male cases and 732 controls. In each study, cases and controls were age-matched but study A subjects were significantly younger than study B subjects (Table I). Among cases, subjects were on average 63.6 years old in study A and 68.4 years old in study B.

According to the last occupation held, cases and controls differed significantly in both studies with more blue-collar workers among cases and more professional, technical and related workers among controls. Overall, cases did not differ between studies. On the contrary, controls had more blue-collar workers in study A, and more professional, technical and related workers, and administrative and managerial workers, in study B. In addition, with regard to the last work sector, cases and controls differed significantly within each study with more cases in the manufacturing industry. Cases between both studies did not differ but there were more controls in the manufacturing industry in study A and more controls in agriculture, hunting, forestry and fishing in study B.

According to the different exposure parameters, exposure probability did not differ among cases ($p=0.47$) but did differ among controls between both studies ($p=0.01$). There were more unexposed controls in study B versus more exposed controls in study A (data not shown). Considering cumulative exposure (Table II), cases between both studies differed significantly ($p<0.01$), as there were more cases in the highest category of exposure in study B. The distribution was also different for controls within both studies ($p<0.01$). There were more unexposed controls in study B than in study A.

The exposure-response relationship between mesothelioma and asbestos was confirmed in both studies but was more pronounced in study B (Table III). Mesothelioma risk increased with the probability of exposure, duration of job exposure and cumulative exposure in both studies, and with time since first exposure only in study B. A trend was observed only in study B with age at first exposure. There was a large difference between the studies with regard to the magnitude of the odds

ratios for all exposure parameters. Odds ratios for possible exposure were 1.5 (95% CI: [1.1 - 2.1]) in study A and 3.4 (95% CI: [2.4 - 4.9]) in study B. For definite exposure, it was 2.9 (95% CI: [2.0 - 4.2]) in study A and 10.6 (95% CI: [7.2 - 15.6]) in study B. Odds ratios increased in both studies with cumulative exposure, but more than two-fold in study B (from 1.8 (95% CI: [1.2 - 2.9]) for subjects with less than 0.1 'f/ml-years' to 19.6 (95% CI: [11.3 - 34.0]) for those with more than 10 'f/ml-years') than in study A (from 1.3 (95% CI: [0.9 - 2.0]) for the lowest category to 5.3 (95% CI: [2.8 - 10.1]) for the highest).

The variation in AR_p initially observed between both studies remained. It was 36.8% (95% CI: [18.8 - 50.8]) in study A and 72.3% (95% CI: [63.8 - 78.8]) in study B, including all CEI categories (Table III).

The two sets of controls differed from the general population with regard socioeconomic status ($p < 0.01$). In study A, there were 45.8% blue-collar workers compared to 35.0% in the general population, and 15.2% controls in the "professional, technical and related workers" category compared to 29.5% in the general population. In study B, there were 32.1% blue-collar workers in the controls versus 41.1% in the general population. Cases from both studies and cases registered by the PNSM did not differ according to socioeconomic status ($p > 0.05$).

Re-estimated AR_p values were 50.1% (95% CI: [36.3 - 60.9]) in study A and 70.1% [60.6-77.3] in study B according to simulation 1 (weighted controls). When only cases were weighted (simulation 2), AR_p values were 43.0% (95% CI: [24.8 - 56.7]) in study A and 70.7% [61.1 - 77.9] in study B. When cases and controls together were weighted (simulation 3), values were 52.4% (95% CI: [37.9 - 63.5]) in study A and 70.2% [60.7 - 77.4] in study B.

DISCUSSION

The initial differences between studies still persisted after standardization of exposure assessment. AR_p for occupational asbestos exposure was 36.8% (95% CI: [18.8 - 50.8]) in study A and 72.3% (95% CI: [63.8 - 78.8]) in study B by using the JEM, so expert methods used primarily to assess occupational exposure to asbestos may not explain the variations in the AR_p .

We chose to estimate the exposure-response relationship and AR_p according to CEI levels of occupational asbestos exposure. Although this indicator is limited by retrospective exposure assessment [16], it was impossible to obtain retrospective quantitative asbestos exposure assessment in the context of case-control studies. We thought that using the CEI to assess semi-quantitative

asbestos remained an acceptable approach so we cannot explain the difference observed for AR_p values.

Several biases in both studies A and B may explain this difference. The methods of asbestos exposure assessment cannot explain the differences in the findings either, since the assessment was performed with the same JEM in both studies. JEM inevitably produce misclassifications but non-differential, so odds ratios and AR_p were under-estimated similarly in both studies [17]. However, since exposure assessment by a JEM relies on the quality of job histories, we cannot rule out differences with regard to the validity and reliability of the job histories obtained from interviews, nor to their coding quality. Some studies found good validity and reliability of job histories obtained from interviews [18-23], and there is no evidence that the recall of occupations is influenced by disease status [18, 19]. 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 [24]. Despite potential differences in data collection and coding in both studies, such differences cannot explain such large differences in estimations of AR_p .

The most likely explanation is a selection bias due to recruitment of subjects and specially controls. According to the socioeconomic status, the distribution of the general population and the distribution of the controls in both studies are different. In study B, a complementary analysis was conducted in order to compare participant controls to eligible controls who refused to participate (data not shown). There was a significant difference between participating controls and refusing controls regarding the distribution of their socioeconomic status ($p < 0.01$). There were more blue-collar workers among refusing controls and more white-collar workers among participating controls. Therefore, participating controls may have been less exposed than the general population so the exposure-response relation and AR_p may be over-estimated. Conversely, in study A, the controls seemed to be more exposed to asbestos than the general population. Indeed, study A controls were hospital controls, and even if subjects with asbestos-related disease were excluded, there were more blue-collars hospitalized, so the proportion of exposed subjects may be higher in hospital than in the general population. Thus, the exposure-response relation and AR_p may be under-estimated.

The cases in both studies seem to be equivalent with regard to probability of occupational asbestos exposure, but study A cases appear less exposed than study B cases considering cumulative occupational asbestos exposure. This can be explained by the geographical recruitment of the

subjects. Study B cases were recruited in 21 French districts representative of France regarding the main demographic, occupational and economic characteristics, while study A cases were recruited in five regions with a large proportion in the region of Ile de France, which is a less industrialized region than the rest of France. Therefore, these differences in occupational exposure to asbestos may explain the significant difference observed for AR_p values.

The three simulations confirmed this hypothesis. Simulation 1 suggests that, controls seemed to play an important role in the difference observed in the AR_p due to the large under-estimation of AR_p in study A and the slight over-estimation in study B. In simulation 2, case recruitment seemed to play a smaller role in the difference observed. In simulation 3, the estimated AR_p were close to those estimated in simulation 1, thus reflecting more the weight of the controls than the cases. These findings illustrate the potential variations in AR_p due to the selection of controls, and may account for the results observed in both studies [25].

Whatever the simulation, the differences in the AR_p initially observed still persisted. Thus, there may have been confounding factors in both studies. Until now, asbestos is the only established risk factor for mesothelioma (except for erionite fibers but these are not present in France). However, in the two studies only occupational asbestos exposure were considered, and domestic or environmental asbestos exposure could have been a possible confounding factor [26].

To date, several studies have analyzed the exposure-response relation between occupational asbestos exposure and mesothelioma [27-32], yet few have estimated the AR_p . All these studies assessed exposure by expertise, except the work by Spirtas et al. [32] (JEM), and all showed an exposure-response relation, but the magnitude of the relation differed. The main methodological difference between these studies was the mode of recruitment (hospital vs general population).

Table IV summarizes the data of these studies. To be able to compare studies according to AR_p and mode of recruitment, we needed to estimate AR_p a posteriori from data given in the articles. AR_p closer to that in study B were those estimated in studies with the same design as study B, i.e. population-based case-control studies [28, 29, 32]. The AR_p values were 88% for overall exposure, 69.8%, 85% and 83.2% for occupational exposure in Spirtas et al. [32], Howel et al [28], Rake et al. [29] and our study B, respectively. The Rödelsperger et al. study [31] gave the same results (84.6%) even if the cases were recruited from hospital records. This is in agreement with our findings in simulation 2, showing that hospital case recruitment had a lower impact on AR_p estimation. In Agudo

et al. [27], where controls but not cases came from hospitals, they observed a lower AR_p of 62%. Rees et al [30] used the same design as in our study A (hospital-based case-control study), but they found a higher AR_p close to those estimated in population-based case-control studies. This may be due to the geographical recruitment. Indeed, South Africa had mined, transported and used all varieties of asbestos fibers in large amounts. In that study, the proportion of exposed cases and controls was 96% and 60%, respectively. The proportion of exposed controls was close to that in study A and study B (68% and 57%, respectively) but the proportion of exposed cases was higher than in either study A or B (80% and 87%, respectively). This may account for the value of the estimated AR_p found in the study by Rees et al [30] despite its design.

Finally, although the true AR_p cannot be precisely determinate from our data, results of different simulations give strong arguments to estimate that the AR_p should be closer to results obtained in study B than in study A. This is in agreement with majority of recent studies.

CONCLUSION

This work confirms the hypothesis that the difference in AR_p in the two French mesothelioma case-control studies is probably due to the recruitment of the subjects, and particularly to that of the controls. Despite exposure assessment standardization using a JEM, the initial differences remained, so we were able to focus on the selection of the controls. However, selection bias cannot explain the entire difference and confounding by other type of asbestos exposure or other etiologic factor should be envisaged to explain the entire difference. Owing to the classic biases associated with hospital control selection and according the literature, the results in study B seem to be more reliable than those in study A. The dose-response relation in study A seems to be under-estimated due to over-exposure of the controls. This work throws new light on the relation between mesothelioma and asbestos exposure, and confirms the importance of subject selection and recruitment in case control studies.

ACKNOWLEDGEMENTS

The authors of this study thank the patients and their next of kin, the physicians and pathologists who made these two studies possible. They also thank R.Cooke for his careful reading of the 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 Oct; 17: 260-71.
2. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*, 2000 Dec; 44(8): 565-601.
3. Iwatsubo Y, Pairon JC, Boutin C, Menard O, Massin N, Caillaud D, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol*, 1998 Jul 15; 148(2): 133-42.
4. Goldberg M, Imbernon E, Rolland P, Gilg Soit Ilg A, Saves M, de Quillacq A, et al. The French National Mesothelioma Surveillance Program. *Occup Environ Med*, 2006 Jun; 63(6): 390-5.
5. Hsieh CC, Walter SD. The effect of non-differential exposure misclassification on estimates of the attributable and prevented fraction. *Stat Med*, 1988 Oct; 7(10): 1073-85.
6. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. *Am J Epidemiol*, 1994 Aug 15; 140(4): 303-9.
7. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent ME, et al. Validation of expert assessment of occupational exposures. *Am J Ind Med*, 2003 May; 43(5): 519-22.
8. International Standard Classification of Occupations. Genève: International labour organization. 1968.
9. International Standard Industrial Classification of all Economic Activities (Revision 2). New york: United States. 1975.
10. Goldberg M, Kromhout H, Guenel P, Fletcher AC, Gerin M, Glass DC, et al. Job exposure matrices in industry. *Int J Epidemiol*, 1993; 22 Suppl 2: S10-5.
11. 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.

12. Orlowski E, Pohlabeln H, Berrino F, Ahrens W, Bolm-Audorff U, Grossgarten K, et al. 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.
13. Audignon-Durand S, Rolland P, Orlowski E, Ducamp S, Brochard P, Goldberg M. Evalutil : une base de données d'évaluation des expositions professionnelles aux fibres. *Info Respiration*, 2006; 72: 15-6.
14. Bruzzi P, Green S, Byar D, Brinton L, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*, 1985; 122(5): 904-14.
15. Cox C. Model-based estimation of the attributable risk in case-control and cohort studies. *Stat Methods Med Res*, 2006 Dec; 15(6): 611-25.
16. Siemiatycki J, Boffetta P. Invited commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? *Am J Epidemiol*, 1998 Jul 15; 148(2): 143-7.
17. 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 Aug; 21(4): 265-71.
18. Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. *Am J Epidemiol*, 1983 Oct; 118(4): 583-91.
19. Bond GG, Bodner KM, Sobel W, Shellenberger RJ, Flores GH. Validation of work histories obtained from interviews. *Am J Epidemiol*, 1988 Aug; 128(2): 343-51.
20. Bourbonnais R, Meyer F, Theriault G. Validity of self reported work history. *Br J Ind Med*, 1988 Jan; 45(1): 29-32.
21. Eskenazi B, Pearson K. Validation of a self-administered questionnaire for assessing occupational and environmental exposures of pregnant women. *Am J Epidemiol*, 1988 Nov; 128(5): 1117-29.
22. Pershagen G, Axelson O. A validation of questionnaire information on occupational exposure and smoking. *Scand J Work Environ Health*, 1982 Mar; 8(1): 24-8.
23. Stewart WF, Tonascia JA, Matanoski GM. The validity of questionnaire-reported work history in live respondents. *J Occup Med*, 1987 Oct; 29(10): 795-800.

24. Pilorget C, Imbernon E, Goldberg M, Bonenfant S, Spyckerelle Y, Fournier B, et al. 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 Jun; 60(6): 438-43.
25. Ben-Shlomo Y, Markowe H, Shipley M, Marmot MG. Stroke risk from alcohol consumption using different control groups. *Stroke*, 1992 Aug; 23(8): 1093-8.
26. Goldberg M, Luce D. The health impact of nonoccupational exposure to asbestos: what do we know? *Eur J Cancer Prev*, 2009 Jul 16.
27. Agudo A, Gonzalez CA, Bleda MJ, Ramirez J, Hernandez S, Lopez F, et al. Occupation and risk of malignant pleural mesothelioma: A case-control study in Spain. *Am J Ind Med*, 2000 Feb; 37(2): 159-68.
28. Howel D, Arblaster L, Swinburne L, Schweiger M, Renvoize E, Hatton P. Routes of asbestos exposure and the development of mesothelioma in an English region. *Occup Environ Med*, 1997 Jun; 54(6): 403-9.
29. 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 Mar 3.
30. Rees D, Goodman K, Fourie E, Chapman R, Blignaut C, Bachmann MO, et al. Asbestos exposure and mesothelioma in South Africa. *S Afr Med J*, 1999 Jun; 89(6): 627-34.
31. Rodelsperger K, Jockel KH, Pohlabein H, Romer W, Weitowitz HJ. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med*, 2001 Mar; 39(3): 262-75.
32. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med*, 1994 Dec; 51(12): 804-11.

Table I: Demographic characteristics of subjects in two French case-control studies of occupational asbestos exposure and pleural mesothelioma at the time of diagnosis/interview.

	Study A					Study B					<i>p</i>	<i>p_{ca}</i> [†]	<i>p_{co}</i> [‡]
	Cases		Controls		<i>p</i> [*]	Cases		Controls					
	(557)		(515)			(462)		(897)					
	n	%	n	%		n	%	n	%				
Sex					0.72					0.56	0.35	0.95	
Men	460	82.6	421	81.7		371	80.3	732	81.6				
Women	97	17.4	94	18.3		91	19.7	165	18.4				
Age (Men, year)													
Mean (SD [§])	63.6	(10.4)	64.0	(10.9)	0.57	68.4	(9.4)	67.4	(9.1)	0.10	<0.01	<0.01	
Median	63		64			70		68					
Min-Max	25 - 88		29 - 93			42 - 93		42 - 89					
Last held occupation (ISCO ed 1968[¶] major group)					0.03					<0.01	0.40	<0.01	
0/1 Professional, technical and related workers	63	13.7	64	15.2		47	12.7	142	19.4				
2 Administrative and managerial workers	28	6.1	24	5.7		16	4.3	66	9.0				
3 Clerical and related worker	46	10.0	49	11.6		33	8.9	89	12.1				
4 Sales workers	37	8.0	36	8.6		23	6.2	73	10.0				
5 Service workers	26	5.7	40	9.5		20	5.4	59	8.1				
6 Agricultural, animal husbandry and forestry workers; fishermen; hunters	6	1.3	15	3.6		11	2.9	69	9.4				
7/8/9 Production and related workers, transport equipment operators and labourers	254	55.2	193	45.8		221	59.6	234	32.0				
Last held industry (ISIC rev. 2**major group)					<0.01					<0.01	0.14	<0.01	
1 Agriculture, hunting, forestry and fishing	6	1.3	11	2.6		13	3.5	69	9.4				
2 Mining and quarrying	7	1.5	6	1.4		1	0.3	2	0.3				
3 Manufacturing	203	44.1	135	32.1		164	44.2	214	29.2				
4 Electricity, gas and water	12	2.6	3	0.7		11	3.0	14	1.9				
5 Construction	66	14.4	38	9.0		51	13.7	62	8.5				
6 Wholesale and retail trade and restaurants and hotels	37	8.1	59	14.0		18	4.8	75	10.2				
7 Transport, storage and communication	38	8.3	48	11.4		37	10.0	64	8.8				
8 Financing, insurance, real estate and business services	25	5.4	31	7.4		20	5.4	57	7.8				
9 Community, social and personal services	64	13.9	89	21.2		56	15.1	175	23.9				
0 Activities not adequately defined	2	0.4	1	0.2		-	-	-	-				

* *p*-value comparing cases and controls ; † *p_{ca}*- *p*-value comparing cases of both studies; ‡ *p_{co}*- *p*-value comparing controls of both studies

§ SD: Standard deviation; || Min-Max. minimum and maximum, ¶ ISCO ed 1968: international standard classification of occupations

** ISIC rev 2. International standard Industrial Classification of all Economic Activities

Table II: Cumulative asbestos exposure of subjects in two French case-control studies of occupational asbestos exposure and pleural mesothelioma.

Results
heading,
third
paragraph

Cumulative exposure (f/ml-years*) (JEM)	Cases					Controls				
	Study A N=460		Study B N=371		p^{\dagger}	Study A N=421		Study B N=732		p
	n	%	n	%		n	%	n	%	
Not exposed	94	20.4	50	13.5	< 0.01	135	32.1	326	44.5	< 0.01
> 0 - 0.1	82	17.8	42	11.3		93	22.1	154	21.1	
> 0.1 - 1	129	28.1	93	25.1		119	28.2	132	18.0	
> 1 - 10	100	21.7	116	31.3		58	13.8	94	12.8	
> 10	55	12.0	70	18.8		16	3.8	26	3.6	

* f/ml-years. Fibers per milliliter years, † p . p-value.

Results
heading, fourth
paragraph

Table III: Dose response relation between pleural mesothelioma and occupational asbestos exposure parameters in men, 20 years of latency period, two French case-control studies of occupational asbestos exposure and pleural mesothelioma.

Occupational asbestos exposure parameters (JEM)		Study A						Study B					
		Cases (460)		Controls (421)		OR*	95% CI†	Cases (371)		Controls (732)		OR	95% CI
		n	%	n	%			n	%	n	%		
Not exposed		94	20.4	135	32.1	1.0		50	13.5	326	44.5	1.0	
Highest probability of exposure	Possible	205	44.6	202	48.0	1.5	1.0-2.1	146	39.3	289	39.5	3.5	2.4-5.0
	Definite	161	35.0	84	19.9	2.8	1.9-4.2	175	47.2	117	16.0	11.2	7.5-16.7
Duration of exposed job (years)	1 - 10	114	24.8	127	30.1	1.3	0.9-1.9	62	16.7	141	19.3	3.0	1.9-4.6
	>10 - 20	100	21.7	64	15.2	2.2	1.4-3.4	66	17.8	96	13.1	4.6	3.0-7.3
	> 20	152	33.1	95	22.6	2.4	1.6-3.6	193	52.0	169	23.1	8.6	5.8-12.6
Time since first exposure (years)	> 19 - 40	106	23.1	92	21.8	1.6	1.0-2.4	55	14.8	111	15.2	3.0	1.9-5.0
	> 40 - 50	133	28.9	91	21.6	2.0	1.3-3.0	100	27.0	117	16.0	6.3	4.1-9.6
	> 50	127	27.6	103	24.5	2.0	1.3-3.1	166	44.7	178	24.3	6.8	4.6-10.1
Age at first exposure (years)	≤ 15	97	21.1	80	19.0	1.8	1.2-2.7	103	27.7	96	13.1	7.6	5.3-11.6
	> 15 - 20	161	35.0	115	27.3	2.0	1.3-2.8	109	29.4	131	17.9	5.8	3.9-8.8
	> 20	108	23.5	91	21.6	1.7	1.2-2.6	109	29.4	179	24.5	4.3	2.9-6.3
Cumulative exposure (f/ml - years‡)	> 0 - 0.1	82	17.8	93	22.1	1.3	0.9-2.0	42	11.3	154	21.1	1.9	1.2-3.0
	> 0.1 - 1	129	28.1	119	28.2	1.5	1.0-2.2	93	25.1	132	18.0	5.0	3.4-7.6
	> 1 - 10	100	21.7	58	13.8	2.5	1.6-3.8	116	31.3	94	12.8	9.4	6.1-14.3
	> 10	55	12.0	16	3.8	4.9	2.6-9.3	70	18.8	26	3.6	21.4	12.1-37.7
AR _p § [95% CI]		36.8[18.8-50.8]						72.3 [63.8-78.8]					

* OR. Odds ratio matched for age and district, † CI. Confidence interval, ‡ f/ml-years. Fibers per milliliter years, § AR_p. Attributable risk in the population

Table IV: Summary of occupational asbestos exposure attributable risk in the population identified from several case-control studies.

Case-control studies name	Subject's recruitment		Exposure assessment	AR _p *
	Cases	Controls		
Agudo et al	Population	Hospital	Expertise	62.0%
Howel et al [†]	Population	Population	Expertise	69.8%
Rake et al	Population	Population	Expertise	85.0%
Rees et al [†]	Hospital	Hospital	Expertise	90.5%
Rödelsperger et al [†]	Hospital	Population	Expertise	84.6%
Spirtas et al	Population	Population	JEM	88.0%

* AR_p. Attributable risk in the population; AR_p estimated a posteriori from data given in the text of article

Discussion
heading,
last
paragraph