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Occupation and Risk of Malignant Pleural Mesothelioma: A Case–Control Study in Spain

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Background *The association of mesothelioma and asbestos exposure is well known, but some data suggest that probably many people are still being exposed to asbestos without knowing it.*
Methods *Between 1993 and 1996, 132 cases (77% males) of histologically confirmed malignant pleural mesothelioma and 257 controls, residents in two provinces of Spain (Barcelona and Cádiz), were interviewed. They were classified according to their probability and intensity of occupational asbestos exposure by a panel of industrial hygienists, based on a detailed occupational history.*
Results *Age and sex-adjusted odds ratio (OR) for the highest probability of exposure to asbestos was 13.2 (95% confidence interval 6.4–27.3), and 27.1 (9.28–79.3) for high intensity. A dose–response trend was observed for both, probability and intensity. Overall, 61% of cases and 42% of controls had ever worked in an occupation with risk of asbestos exposure, with an OR of 2.59 (1.60–4.22). In our population 62% of cases could be attributed to occupational asbestos exposure.*
Conclusion *A high risk of pleural mesothelioma due to occupational asbestos exposure is confirmed, but there is still a sizeable proportion for which no evidence of occupational exposure was found. Most of these cases could be due to other sources of asbestos exposure, mainly domestic or environmental.* Am. J. Ind. Med. 37:159–168, 2000. *© 2000 Wiley-Liss, Inc.*

KEY WORDS: mesothelioma; asbestos; case–control studies

INTRODUCTION

Malignant mesothelioma is a relatively rare tumor normally located in pleura. The highest incidence of cancer of the pleura in Europe is found in registries from Northern Italy for both sexes, with age-adjusted rates of around 4 per 100,000 for men and from 0.5 to 0.9 in women [Parkin et al., 1992]. Other European countries with relatively high rates are UK, the Netherlands, Denmark, and Switzerland. The average age-adjusted incidence rate for Spanish registries is 0.41 for men and 0.13 for women. Recent studies in the USA [Price, 1997] and UK [Peto et al., 1995] suggest that incidence and mortality are still rising. The overall upward trend is primarily because of the increased rates in men 75 years and over. According to these results, mesothelioma deaths in males will continue to increase for at least 15–25 years more.

There is strong evidence supporting the causal association between mesothelioma and occupational exposure to asbestos. Nevertheless, some data suggest that many people are still being exposed to asbestos without knowing it.

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Mesothelioma is almost always fatal, and primary prevention is the only way to reduce mortality. Given the long latency period of the disease, primary prevention today can reduce the frequency of mesothelioma in the future. In recent years, it has been shown that mesothelioma risk is no longer confined to workers in the asbestos industry and there is a small proportion of cases for which no evidence of exposure to asbestos exists [Huncharek, 1992]. Although the association of mesothelioma and occupational exposure with asbestos is well known, the proportion of cases caused by such exposure is quite different across populations. Furthermore, accurate assessment of occupational exposure is necessary to undertake research on non-occupational causes of the disease.

We conducted a case–control study in two provinces in Spain, Barcelona and Cadiz, within the framework of a European study on environmental asbestos exposure and mesothelioma [Mollo and Magnani, 1995]. Both areas have known or suspected sources of asbestos exposure and relatively high mortality rates for pleural cancer within Spain [GEMEBA, 1993; López-Abente et al., 1996]. In Spain, there has been a decrease in the importation and number of enterprises using asbestos; however, in 1991 the estimated number of workers exposed to asbestos was 60,488 [INHST, 1992]. The permitted level of asbestos in Spain was fixed at 1 fiber/mL or less in 1984, and the industrial use of blue asbestos was prohibited in 1987 [Castejón et al., 1987]. The concentration of asbestos fibers went down from a mean level of 2.4 fiber/mL in 1984 to 0.22 in 1991 [INHST, 1992]. In this paper, we present the results on the risk associated with occupational asbestos exposure. We also tried to quantify the proportion of cases in our populations that can be attributed to such exposure, and to identify the main occupations and activities related to an increased risk of mesothelioma.

SUBJECTS AND METHODS

Cases

The study base consisted of residents in the provinces of Barcelona and Cádiz between 1/1/1993 and 12/31/1996. Potential cases were all subjects from the study base, newly diagnosed with primary malignant mesothelioma of the pleura, and histologically confirmed. All hospitals with pathology departments in the study area participated in the ascertainment of cases. They were identified by pathologists and specialists from other departments involved in the diagnosis of pleural mesothelioma in any of the 30 hospitals in the study area. A referent pathologist obtained a complete protocol of diagnosis procedures and the necessary histological material to perform histochemical and inmunological examinations to confirm the diagnosis. To ensure total ascertainment of cases, a systematic review of clinical documentation and pathology files from each hospital was carried out periodically.

Controls

Two controls per case were selected according to sex and age of cases (frequency matched), among patients admitted to the participating hospitals in each province. Population controls were discarded because the low participation rate observed in the pilot phase (below 50%). Selecting controls from the same hospital where their matched case had been diagnosed was deemed unsuitable when investigating environmental exposures, as the choice of the hospital may be related to the place of residence. In order to avoid the bias that this procedure could have produced, we used a two-step selection. First, a control group was selected from a random sample of the population; this group determined the age, sex, and municipality of residence for the control series. Then, patients with the same age and sex distribution were selected from the participating hospitals in the study area. The particular hospital where each patient was selected was the nearest to the residential address of its corresponding 'population' control. Patients admitted with conditions associated with asbestos exposure were excluded as potential controls. A detailed discussion of this procedure has been presented elsewhere [Agudo and González in press].

Information

Cases and controls were interviewed at the hospital by trained interviewers (four in Barcelona and two in Cádiz). For 44% of cases who had died by the time of the interview, information was collected from relatives at home. Out of the 59 cases where a relative was interviewed, in 29 cases it was the spouse, in 25 a son or daughter, and only for five cases information was gathered from another relative or a friend. All controls but one were interviewed at the hospital, and answers were always provided by the subject. A structured questionnaire was used covering the following items: demographic characteristics, smoking habit, past exposures to radiation, occupational history, occupations of parents and other cohabitants, and residential history, including description of dwellings and their environment.

Assessment of Occupational Exposure to Asbestos

Several approaches were used to assess occupational exposure to asbestos. Firstly, a complete occupational history was collected. All the occupations held for at least 6 months by the subject were recorded in chronological order. The age at the beginning and end of each period, as well as the main characteristics of the job and of the company, were reported. Occupations and activities were coded *a posteriori* by an expert according to the International Standard Classification of Occupations (ISCO) [ILO, 1969] and Classification of Economical Activities of the European Community (NACE) [EUROSTAT, 1993]. In addition to the occupational history described above, job-specific modules were also asked for each job from a list of 33 occupations or industrial activities, potentially associated with asbestos exposure in Spain, in which the subject could have been employed. They were designed to get a standardized and more exhaustive description of each job and work environment.

Secondly, the exposure to asbestos was evaluated by a panel of industrial hygienists, blinded to the case or control condition of the subject being evaluated. Based on the information collected in the occupational history and specific modules, each occupational period was classified into six categories according to its probability of asbestos exposure: no exposure, low probability, exposure possible (intermediate probability), exposure highly probable, sure (or almost sure) exposure, and unknown. It was also classified according to its intensity, taking into account the estimated concentration of asbestos fibers in the work environment and conditions of the job. The lowest or background level was applied to a job or activity with no recognizable source of asbestos pollution; otherwise the job was assigned to one of the three levels of increasing intensity of exposure, or to the unknown category. The probability of exposure to asbestos assigned to an individual was the maximum probability recorded in any of the jobs where the subject had been employed; among those jobs that determined the subject's probability, the maximum intensity recorded was the intensity of exposure assigned to the individual.

Finally, both approaches were combined by computing a score for each occupation based on the probability assigned by the panel. For each occupational period (at the level of three digits ISCO classification), a score of 0 was given to the no exposure level; for low probability of exposure the score was 1, for possible exposure 2, for high probability 3, and sure exposure had a score of 4. The score for an occupation was the average obtained for all the occurrences in this occupation. Jobs classified with unknown probability were excluded from this procedure. Occupations with an average score of ≥ 1 were considered at risk of exposure to asbestos.

Analysis

Estimation of relative risk was done by means of unconditional logistic regression [Breslow and Day, 1980]. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated for each indicator of exposure analyzed. Taking into account the stratified sampling of the design, terms for sex, age, and center were always included in the model. When the risk for a particular occupational or industrial activity group was assessed, the reference category was formed by the nonexposed to this group. For the assessment of risk associated with levels of occupational exposure to asbestos (probability and/or intensity), each level of exposure was compared to the baseline category. The OR for occupations at risk of exposure to asbestos according to the score were estimated by comparing subjects from each occupation with a reference category formed by the individuals who had never been employed in any of these occupations. Estimation of population attributable risk proportion (PARP) and the corresponding 95% CI were calculated by using the estimates of the adjusted relative risk obtained by logistic regression and the proportion of exposed cases [Greenland, 1987]. The reliability of the occupational exposure to asbestos derived from information collected from relatives was assessed by interviewing the spouse or a son or daughter of 18 of the 59 deceased cases for which information had been previously obtained directly from the subject. Both classifications were compared by means of the observed proportion of agreement and the weighted kappa [Fleiss, 1981].

RESULTS

Interviews were obtained for 132 of the 134 cases eligible for the study (participation 98.5%); of them 117 (88.6%) were identified from 24 hospitals in Barcelona and 15 from 6 hospitals in Cádiz. A total of 297 patients were identified as potential controls of which 257 were interviewed (participation rate 87%). Only eight subjects refused to answer, while the remaining 32 did not participate for other reasons.

The main characteristics of cases and controls are shown in Table I. Seventy-seven percent of cases were men, with a mean age of 65.7 years, ranging from 35 to 92 years. In 59 cases (44.7%) the information was obtained from relatives, mainly from the spouse or a son or daughter. Controls had sex and age distribution similar to cases, given the stratified design. Cases and controls were very similar regarding the education level and average number of jobs reported; these characteristics were also similar according to the type of respondent among cases (results not shown).

Results on the univariate analysis of risk of mesothelioma associated with selected groups of occupation and industrial activities are presented in Table II. Three occupational groups had a significantly high risk of mesothelioma: printers and related workers, material-handling, and production and related workers not elsewhere classified (n.e.c.): the latter includes the subgroup of manufacture of asbestos cement. Four groups of industrial activities presented a significant increased risk: manufacture of rubber and plastic products, manufacture of transport equipment

TABLE I. Main Characteristics of Cases of Pleural Malignant Mesothelioma and Controls in Spain

	Cases		Controls	
	n	%	n	%
Center				
Barcelona	117	88.6	227	88.3
Cádiz	15	11.4	30	11.7
Gender				
Males	102	77.3	202	78.6
Females	30	22.7	55	21.4
Age group				
35–44 years	6	4.5	10	3.9
45–54 years	16	12.1	29	11.3
55–64 years	31	23.5	58	22.6
65–74 years	56	42.4	115	44.7
75–84 years	19	14.4	34	13.2
85–94 years	4	3.0	11	4.3
Education level[a]				
Primary school not completed	44	36.4	76	31.7
Primary school completed	34	28.1	83	34.6
Secondary school or higher	43	35.5	81	33.7
Type of respondent				
Subject	73	55.3	256	99.6
Spouse	29	22.0	–	
Son/daughter	25	18.9	1	0.4
Other	5	3.8	–	
Occupational history				
Number of jobs reported mean, standard deviation	4.86	2.78	4.45	2.31

[a]For 11 cases and 17 control information on education was missing; percents for this variable are given over 121 cases and 240 controls.

(including shipbuilding), manufacturing n.e.c., and manufacture of non-metallic products, which includes manufacturing of asbestos cement.

The risk of occupational exposure to asbestos according to the probability and intensity assigned by the panel of hygienists is shown in Table III. The categories of possible exposure and high probability were combined in order to have enough individuals to allow for estimations of the OR. Compared to those who never worked or who were considered as never exposed, all levels of probability and intensity had an increased significant risk, except subjects with low probability of exposure. For exposure classified as sure the OR was 13.2, and for the highest intensity it was 27.1. A dose–response trend was evident for both characteristics; there was also an increase in risk with increase in probability within each level of intensity, as well as an increase in risk with increase in intensity within each level of probability. The OR for those with sure exposure at the highest level of intensity was 41.6. Subjects with unknown probability or intensity of exposure tended to have an increased risk.

Subjects with exposure classified as sure were further examined. There was a remarkable predominance of men: 49 out of 53 cases and all the 29 controls were males. Cases

TABLE II. Risk of Pleural Malignant Mesothelioma According to Selected[a] Major Groups of Occupations and Industrial Activities

ISCO code	Job title	Cases/controls	OR	CI-95%
011-999	Professional, technical, and related workers	13/30	0.82	0.41–1.64
311-399	Clerical and related workers	24/51	0.90	0.52–1.55
400-490	Sales workers	27/46	1.19	0.70–2.02
500-599	Service workers	30/62	0.91	0.55–1.50
601-649	Agriculture, animal husbandry, forestry workers, fishermen and hunters	41/95	0.78	0.49–1.24
751-759	Spinners, weavers, knitters, dyers and related workers	17/34	0.96	0.50–1.84
831-839	Blacksmiths, toolmakers, and machine-tool operators	12/16	1.49	0.67–3.28
841-849	Machinery fitters, machine assemblers, and precision instrument makers (excluding electrical)	17/28	1.22	0.63–2.36
851-859	Electrical fitters and related electrical and electronic workers	12/15	1.64	0.74–3.65
871-874	Plumbers, welders, sheet metal and structural metal preparers and erectors	15/17	1.80	0.86–3.78
891-899	Glass formers, potters and related workers	13/19	1.37	0.65–2.88
921-929	Printers and related workers	6/1	11.9	1.41–101
941-949	Production and related workers n.e.c.	13/7	3.89	1.50–10.0
951-959	Bricklayers, carpenters and other construction workers	26/42	1.30	0.74–2.28
971-979	Material-handling and related equipment operators, dockers and freight handlers	30/28	2.42	1.36–4.28
981-989	Transport equipment operators	16/32	0.98	0.51–1.89
999	Labourers not elsewhere classified	21/32	1.34	0.74–2.44
NACE section	**Group of activity**			
A	Agriculture, hunting, and related service activities	42/94	0.82	0.52–1.30
DA	Manufacture of food products, beverages and tobacco	19/26	1.53	0.80–2.92
DB	Manufacture of textiles and textile products	27/58	0.85	0.49–1.46
DG	Manufacture of chemicals, chemical products, and man-made fibers	12/20	1.18	0.56–2.50
DH	Manufacture of rubber and plastic products	13/10	2.66	1.11–6.39
DI	Manufacture of other non-metallic mineral products	26/26	2.23	1.22–4.09
DJ	Manufacture of basic metals and fabricated metal products	18/25	1.44	0.74–2.82
DK	Manufacture of machinery and equipment n.e.c.	14/22	1.27	0.62–2.60
DM	Manufacture of transport equipment	21/22	2.08	1.08–4.00
DN	Manufacturing n.e.c.	16/14	2.47	1.16–5.24
F	Construction	34/65	1.04	0.63–1.73
G	Wholesale and retail trade; repair of motor vehicle, motorcycles and personal and household goods	28/68	0.75	0.45–1.24
I	Transport, storage, and communication	16/38	0.81	0.43–1.53
L	Public administration, defence; social security	34/81	0.74	0.44–1.23

[a]Only groups with significant OR or at least 10% of cases or controls exposed are presented. The reference category for each occupational or industrial activity group consisted of the subjects who had never been employed in occupations (or activities) of this particular group.

had longer duration than controls in occupations with sure exposure (median of 21.5 vs. 13.5 years) and they started to work at a younger age, although the difference was small. On an average these subjects started to work in jobs with high exposure to asbestos during the 1950s but some of them started during the last decade. The median latency was 40 years. The analysis on probability of asbestos exposure was restricted to some subgroups: subjects younger than 55 years (11 cases and 4 controls) showed an OR of 10.0 (CI 1.86–53.9) for the category of sure exposure. Among women, five cases and one control had high or sure levels of exposure, the combined OR being 11.3 with CI 1.23–103.

A total of 39 occupations (defined by 3-digits ISCO codes) were considered as occupations at risk of asbestos exposure according to their probability score (Table IV). Manufacture of non-metallic products showed the highest score and also the highest risk; this job title includes the specific occupation of manufacture of asbestos cement. Launderers, cleaners and pressers, electrical fitters, plumbers, and workers using material handling and related equipment also had a high risk. Other known or suspected occupations involving potential asbestos exposure are also included in this list, but some of them were held by few subjects thus precluding estimations of risk. Overall, 61% of cases and 42% of controls had ever worked in an occupation

TABLE III. Risk of Pleural Malignant Mesothelioma by Probability and Intensity of Occupational Exposure to Asbestos

	Probability of exposure					
Intensity of exposure	**Never worked/ not exposed**	**Low probability**	**Possible/high probability**	**Exposure, sure**	**Exposure, unknown**	**Overall**
Not exposed (background)	**1** *30/127*	–	–	–	–	**1** *30/127*
Low	–	**1.54** (0.54–4.36) *6/27*	**3.72** (1.65–8.37) *16/28*	**6.40** (2.52–16.3) *13/15*	–	**3.35** (1.72–6.52) *35/70*
Medium	–	–	**6.87** (2.12–22.3) *7/8*	**12.9** (5.0–33.6) *18/10*	–	**9.96** (4.38–22.7) *25/18*
High	–	–	– *0/2*	**41.6** (12.3–140) *22/4*	–	**27.1** (9.28–79.3) *22/6*
Unknown	–	**2.26** (0.90–5.68) *9/26*	**3.92** (1.01–15.2) *4/7*	–	**17.8** (4.09–77.8) *7/3*	**3.68** (1.72–7.87) *20/36*
Overall	**1** *30/127*	**1.89** (0.87–4.13) *15/53*	**4.05** (1.97–8.30) *27/45*	**13.2** (6.44–27.3) *53/29*	**17.9** (4.10–77.9) *7/3*	

ORs adjusted by center, sex, and age in bold with 95% CI in parentheses; cases/controls in italic type.

TABLE IV. Risk of Pleural Malignant Mesothelioma for Occupations with Risk of Exposure to Asbestos, According to the Expert's Evaluation[a]

ISCO code	Job title	Cases/controls	OR	CI-95%
560	Launderers, dry-cleaners, and pressers	6/1	17.91	(2.08–155)
841	Machinery fitters	6/6	3.59	(1.08–12.0)
849	Machinery fitters and assemblers n.e.c.	9/8	4.07	(1.44–11.5)
851	Electrical fitters	5/2	9.10	(1.68–49.4)
855	Electricians	7/9	2.87	(0.97–8.45)
871	Plumbers	4/2	7.49	(1.30–43.3)
872	Welders	6/8	2.45	(0.78–7.63)
873	Sheet metal workers	5/7	2.53	(0.74–8.64)
943	Manufacture of non-metallic products	12/2	21.17	(4.45–101)
951	Bricklayers	20/36	1.99	(1.01–3.95)
974	Driver of material-handling and related equipment	3/1	10.76	(1.08–107)
	Any occupation with high risk of exposure to asbestos[a]	81/109	2.59	(1.60–4.22)

[a]See text for definition of occupations with risk of asbestos exposure. Only occupations with at least 5 cases or a significant OR are presented in the table. In addition to those in the table, other occupations with risk of asbestos exposure are listed below with the corresponding ISCO code and job title (in parentheses, cases/controls):

039 Draughtsman (1/2), 043 Ships officers (1/-); 079 Nurses, medical assistants (-/3), 322 Card- and type-punching machine operators (-/1), 399 Other clerical and related workers n.e.c. (-/1), 410 Working proprietors (wholesale and retail trade) (1/2), 500 Managers, catering and lodging services (1/-), 589 Protective services workers n.e.c. (2/6), 722 Metal processors, rolling mill (-/1), 723 Metal processors, smelters (3/7), 724 Metal processors, casting (3/-), 726 Metal processors, treating and coating (1/-), 741 Chemical processors, crushing and mixing (2/3), 744 Chemical processors, still operator (1/-), 771 Food processors, miller (1/-), 833 Machine-tool fitters (1/-), 834 Machine-tool operators (3/4), 839 Blacksmiths, machine-tool operators n.e.c. (4/10), 843 Mechanics, motor vehicles (3/14), 874 Structural metal workers (2/-), 891 Glass formers (3/5), 893 Glass workers, furnace operator (2/2), 932 Painters, vehicles (-/1), 959 Construction workers n.e.c. (3/-), 969 Stationary engine and related equipment operators (3/4), 973 Driver of material-handling and elevator equipment (2/4), 981 Sailor, dockhand and foreman (1/1).

The reference category is always formed by the 51 cases and 148 controls who had never worked in any of the listed occupations.

with risk of asbestos exposure; compared to those who had never been employed in any of these occupations they had a significant OR of 2.59.

We estimated the PARP of mesothelioma for several levels of probability of occupational exposure to asbestos. In our population 62% (CI 48.4–75.6) of all cases may be attributed to occupational exposure to asbestos, including all probability categories. The proportion of cases due to sure exposure is 37.1% (CI 28.1–46.1). On the other hand, 37.7% (CI 2.1–53.3) of cases are due to exposure to any of the occupations considered at risk of asbestos exposure.

In our study the prevalence of smokers was similar in cases and controls; the proportion of subjects with past exposures to radiation was very low and again did not show any difference between cases and controls. Relative risk for both factors were close to unity and are not presented.

DISCUSSION

We used several approaches to assess occupational risk of mesothelioma. Our main results are based on the classification of occupational exposure to asbestos provided by experts, on the basis of an occupational history and a structured questionnaire with detailed descriptions for a list of jobs. We found a relative risk of 13.2 for subjects exposed to asbestos at the maximum level of probability and 27.1 for those with the maximum level of intensity according to the evaluation by experts. There was a dose–response relationship both with probability and intensity.

Comparisons with other case–control studies providing similar indicators of occupational exposure to asbestos are complicated because of differences in the method of collecting information, coding schemes, and criteria of assessing exposure. Among those recently published, a hospital-based case–control study in France [Iwatsubo et al., 1998] also used a classification of exposure by experts based on occupational histories. They created a cumulative index of exposure according the probability, intensity and frequency; for the highest level the OR was 8.7, and a clear dose–response relation was observed. One study in UK [Howel et al., 1997] classified subjects as likely, possible and unlikely exposed according to a list of occupations defined *a priori*; the risk for likely vs. possible or unlikely was 9.1. In Canada [Teschke et al., 1997], an OR of 9.3 for exposure to asbestos, queried in an exposure history, was observed. In the USA [Spirtas et al., 1994] an estimation based on a list of defined occupations had an OR of 13.9, while another based on a job–exposure matrix had an OR of 21.5. A hospital-based study in USA [Muscat and Wynder, 1991] by using a predefined list of occupations found an overall OR in men of 8.1. In Finland [Tuomi et al., 1991] the exposure was assessed by a panel of experts on the basis of occupational history; the OR of having definite exposure was 17.7, and 3.0 for those with exposure probable. In a study based on a cancer registry from Los Angeles County (USA) [Cicioni et al., 1991] using a list of job titles defined *a priori*, the ORs for low and high probability of exposure were 1.6 and 6.3, respectively. In Australia [Rogers et al., 1991], the index of exposure was based on fiber content in lung tissue, the OR for a ten-fold increase in fiber concentration was 29.4 for crocidolite, 15.7 for chrysotile, and 2.3 for amosite. Finally, a hospital-based study in Massachusetts [Huncharek et al., 1996] where criteria to define exposure to asbestos are not clearly stated, observed an OR of 25.8.

In addition to manufacture of asbestos cement, our analysis based on occupational groups and industrial activities showed a positive association for printers, material-handling workers, laborers n.e.c., those in manufacture of non-metallic products, those in manufacture of transport equipment, and those manufacturing n.e.c. The risk observed for printers is rather surprising, as no significant exposure to asbestos has been described. However, this is a broad group, including many specific occupations and the estimation is based on only six cases and one control. The possibility that other occupations held by these subjects involved exposure to asbestos can not be ruled out. Among the previously cited studies, only one [Teschke et al., 1997] provided detailed results on the analysis by occupational groups; they found a significantly increased risk for sheet metal workers, plumbers and pipefitters, shipbuilding workers, painters, and machinists. A small study in Canada [Finkelstein, 1996], found a high risk (OR 24.5) for maintenance workers of a petroleum refinery in Ontario.

The combination of both approaches gives additional help in identifying occupations possibly responsible for the risk observed. In our study, most occupations identified in the areas of study as involving a risk of asbestos exposure had been previously identified; however, no estimations of risk regarding mesothelioma were available in Spain. It must be taken into account that risk estimates for these occupations are probably better than those derived only from the occupational history, since they are compared to a reference category including subjects who never worked in occupations considered at risk of asbestos exposure. There was special interest in the potential risk associated with some occupational or industrial activity groups. We identified 14 subjects which had sometime been employed in manufacture of non metallic products (Table IV), among which 12 had worked sometime in manufacture of asbestos cement (ISCO 943.30). All of them were male cases and had worked in a big plant of asbestos cement located in the province of Barcelona. These 12 subjects lived in the same municipality where the plant was located or in two neighboring towns. The majority started to work in such employment during the 1960s. On the other hand, 14 subjects (10 cases and 4 controls) had sometime been employed in companies whose activity was building and repairing ships and boats (NACE 35.1); all of them were males, 9 were from Cádiz (7 cases and 2 controls), and 5 (3 cases and 2 controls) were from Barcelona. Compared to the same reference category used in Table IV they had an OR of 11.9 (CI 3.15–44.8).

The main results of our study rely on the expert's assessment of exposure. The assessment of risk based on occupational history alone has the major drawback of lacking a clean reference category: those never exposed to a specific group may have worked in other occupations of risk. Another alternative is the utilization of job–exposure matrices; they are simpler but they are suspected of producing greater non-differential misclassification [Bouyer and Hémon, 1993]. The overall quality of the experts assessment procedure depends as much on the experts as on the information collected in the questionnaire. It also depends on precise rules and criteria of classification, as well as on the standardization of the procedure [Bouyer and Hémon, 1993]. The main advantage is that it exploits all the available information. Furthermore, experts used the information on the occupational history without taking into account the opinion of the subjects, and blinded to the case–control status of the subject being evaluated. In this way we probably minimized both information bias and exposure assessment, two major sources of bias in studies on asbestos exposure and mesothelioma [Siemiatycki and Boffetta, 1998].

Some degree of misclassification cannot be ruled out. Nevertheless, it seems likely that the experts only assigned a determined degree of probability or intensity of exposure when they were strongly convinced, as may be suggested by the fact that individuals classified with unknown degree of exposure showed a high relative risk both for probability and intensity of exposure. Furthermore, the risk in the highest categories of probability and/or intensity of exposure are remarkably higher than for intermediate categories. This is important because in polychotomous exposure variables, misclassification, although nondifferential, does not always produce estimates biased away from the null [Dosemeci et al., 1990].

As the exposure depends upon information provided by subjects, its validity must be considered. Information for 44% of cases was provided by a relative; this is a common practice in studies on diseases with short survival after diagnosis. In a study in the UK [Teschke et al., 1997] information for the majority of cases was provided by relatives, as it was in a study in the USA [Finkelstein, 1996]. In another study in USA [Spirtas et al., 1994], information was provided by relatives for 33% of cases and 13.6% of controls. In other studies information on occupation was extracted from death certificates and coroner's records. A validation study showed that information on number of areas and usual work area assignment provided by the spouse performed quite well when compared with the subject itself [Bond et al., 1988].

We had answers from relatives only among cases but not controls, this would produce, if any, a bias toward the null hypothesis. It seems reasonable that a relative might forget to mention some occupation the subject had actually had, but is less likely to assign him a job he had never had. The validity of information provided by relatives was assessed in a sample of 18 cases. Comparison of classification of probability of exposure by experts based on the information provided by the subject against information provided by a relative showed an agreement of 0.59 measured by the weighted kappa; it was higher when the relative was the spouse (0.79) than for son or daughter (0.46). More importantly, comparison of prevalence of probability of exposure from two sources produced a small decrease of the highest level of exposure when based on a relative's answers (from 55.5% to 50%), while the proportion for the remaining three levels of exposure remained unchanged. This suggests that if some bias may affect the estimates it would be in the direction of underestimation. An additional assessment on comparability of information is indirectly provided by the fact that the average number of jobs reported did not differ between cases and controls, and did not differ either by type of respondent among cases.

Overall, 37% of cases of mesothelioma in our population are attributed to a sure (or almost sure) occupational exposure to asbestos and this proportion comes up to 62% when occupations with any probability of exposure are included. Both are in agreement with estimates from other European countries [Albin et al., 1999]. These estimates rely on the validity of estimates of relative risk as well as on the proportion of exposed cases in the population. In our study, cases may be considered as representative since we included almost all cases diagnosed in the study base. According to mortality rates and the incidence/mortality ratio [GEMEBA, 1993; López-Abente et al., 1996] for both areas (Barcelona and Cádiz) the number of expected cases were 119 and 13, respectively, while in our study 117 and 15 were included. Additionally, all these cases were histologically confirmed by a referent pathologist, thus the main findings of our study could hardly be distorted by some substantial degree of misdiagnosis (over or underdiagnosis) bias [Siemiatycki and Boffetta, 1998].

Around 40% of cases of mesothelioma in our population could be due to causes other than occupational exposure to asbestos, although possibility of other occupational exposures in non-traditionally hazardous scenarios cannot be ruled out [Pinto et al., 1995]. One study [Muscat and Wynder, 1991] examined the effect of cigarette smoking but no higher risk was found; the same result was found in our study. History of cancer in parents or first degree relatives has also been considered [Huncharek et al., 1996; Heineman et al., 1996] but no clear pattern was shown. A recent study

[Muscat and Huncharek, 1996] suggested that some vegetables may exert a protective effect on the risk of mesothelioma. Other factors such as radiation or virus SV40 have been proposed [Hubbard, 1997]. However, most cases not related to occupational exposure to asbestos could in fact be caused by other sources of asbestos exposure, mainly domestic (including family contacts) or environmental. Proper research on such relationships must be conducted on subjects where the direct occupational exposure has been previously evaluated and discarded.

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