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ORIGINAL CONTRIBUTIONS

Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study

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A hospital-based case-control study of the association between past occupational exposure to asbestos and pleural mesothelioma was carried out in five regions of France. Between 1987 and 1993, 405 cases and 387 controls were interviewed. The job histories of these subjects were evaluated by a group of experts for exposure to asbestos fibers according to probability, intensity, and frequency. A cumulative exposure index was calculated as the product of these three parameters and the duration of the exposed job, summed over the entire working life. Among men, the odds ratio increased with the probability of exposure and was 1.2 (95% confidence interval (CI) 0.8–1.9) for possible exposure and 3.6 (95% CI 2.4–5.3) for definite exposure. A dose-response relation was observed with the cumulative exposure index: The odds ratio increased from 1.2 (95% CI 0.8–1.8) for the lowest exposure category to 8.7 (95% CI 4.1–18.5) for the highest. Among women, the odds ratio for possible or definite exposure was 18.8 (95% CI 4.1–86.2). We found a clear dose-response relation between cumulative asbestos exposure and pleural mesothelioma in a population-based case-control study with retrospective assessment of exposure. A significant excess of mesothelioma was observed for levels of cumulative exposure that were probably far below the limits adopted in most industrial countries during the 1980s. *Am J Epidemiol* 1998;148:133–42.

asbestos; case-control studies; mesothelioma; occupational exposure

Mesothelioma is a rare cancer that is mainly due to occupational or nonoccupational asbestos exposure. The background level is assumed to be as low as 1–2 per million inhabitants (1). During recent decades, however, its prevalence has been increasing in the general populations of most industrialized countries (2, 3).

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Abbreviations: CEI, cumulative exposure index; CI, confidence interval; ISCO, International Standard Classification of Occupations (1968 edition); ISIC, International Standard Industrial Classification of All Economic Activities; OR, odds ratio.

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In the cohorts of workers occupationally exposed to asbestos that have been followed since the 1960s, the risk of mesothelioma has increased with the level or duration of exposure or both (4–14). The absence of accurate measurements for low exposure levels limits the reliability of any current quantitative assessments of the risk they carry. Furthermore, since only a few subjects in these cohorts were exposed to low levels of asbestos, there is not enough statistical power to show any significant association with mesothelioma.

Case-control studies among the general population and its variety of occupational categories exposed to different asbestos levels are more likely to include subjects whose exposure was low. Despite recent developments in retrospective assessment of exposure (15, 16), the quantitative assessment of low levels remains difficult, since measurements of dust concentration during the relevant periods are not often available.

Previous studies of mesothelioma (4–14) have examined exposure parameters, including cumulative exposure and such time-related variables as time since or age at first exposure. Other exposure parameters, in particular, the time-related pattern of exposure, might be useful. Although the current asbestos exposure pro-

file involves mostly intermittent exposure, the data now available do not allow any conclusion about whether asbestos inhalation at intermittent peaks contributes to the risk of mesothelioma.

The aims of this study were to examine the dose-response relation by using several types of exposure parameters and to study the role of time-related exposure patterns (intermittent compared with continuous) in a large case-control study conducted in France since 1987.

MATERIALS AND METHODS

This report is based on data collected in a hospital-based case-control study of pleural malignant mesothelioma (hereafter referred to as mesothelioma). This study is ongoing, and the present analysis is limited to data collected between January 1, 1987, and December 31, 1993. Five administrative regions of France are currently participating: The study began in the Paris metropolitan area in 1987 and was extended in 1989 to the region of Provence-Alpes-Côte-d'Azur and to Corsica and, in 1992, to Lorraine and Auvergne. The respiratory disease, chest surgery, and oncology departments of all public hospitals and the main private clinics were informed of the study and invited to participate.

Mesothelioma patients in this study met the following criteria: 1) consultation, at any stage of the disease, in a participating hospital; 2) histologically confirmed diagnosis; 3) resident in a participating region at diagnosis; and 4) alive at the time of interview.

The diagnosis of mesothelioma was confirmed by the French Mesothelioma Panel (17, 18). The panel excluded 46 (10 percent) of the subjects initially considered eligible (for whom, after pathology review, the principal diagnosis was adenocarcinoma). In 125 subjects (31 percent of the remaining 405 cases), however, the panel could not reach a conclusion because the histologic sample was insufficient or because the slides had not been sent to the panel. The likelihood of diagnosis was then determined by reviewing clinical data (clinical history, radiologic data), laboratory test reports, and the histologic conclusions of the local pathologists. Hospital controls were individually matched for sex, age (±5 years), place of residence (administrative department), and racial or ethnic origin (black, white, North African, Asian, or other) and were selected in the departments of internal medicine, ophthalmology, and surgery. Patients with a medical history of malignant tumors or asbestos-related diseases (i.e., asbestosis and lung cancer) were excluded as controls. To the extent possible, controls were chosen in the same hospital as their matching cases.

Data collection

An experienced interviewer questioned patients during their hospitalization. In a few cases, the subject was interviewed at home. A standardized questionnaire was used to collect information on work history: work periods, including the starting and ending dates of each job that lasted at least 6 months; the company's economic branch of activity; and a description of the tasks performed by the subject. This information allowed us to classify the subject's job according to the International Standard Classification of Occupations (ISCO) code for occupations (19) and the International Standard Industrial Classification of All Economic Activities (ISIC) code (20) for industrial activities. For each job period, the subjects were asked five specific questions about direct (handled) and indirect (working in the immediate vicinity of colleagues who handled) asbestos exposure.

Exposure assessment

A panel of five experts in industrial hygiene evaluated occupational exposure to asbestos, as follows: 1) all job periods of all subjects (cases and controls) were sorted by economic branch of activity (ISIC codes) and occupation (ISCO codes); 2) the job periods were selected for review according to the likelihood of exposure of the job titles, classified by ISIC and ISCO codes; 3) the job periods for which subjects reported exposure were selected; and 4) occupational exposure to asbestos was evaluated for all job periods selected in either step 2 or step 3, in sequential order of both the ISIC and ISCO codes. Each job period for each subject was thus evaluated independently. This procedure was chosen to minimize errors in the exposure assessment due to knowledge of the subjects' lifetime exposure.

The experts were blinded to the case-control status of each job period, and decisions were made by consensus. The experts had access to all information from the questionnaire, such as job history, tasks performed, and self-report of direct or indirect exposure to asbestos.

This evaluation of each job allowed each job period to be classified according to the probability, intensity, and frequency of exposure. Categories of intensity and frequency were established by the experts before the evaluation began by using the following semiquantitative scale: probability of exposure: not exposed, possible, definite; frequency: sporadic (less than 5 percent of work time); irregular (5–50 percent of work time); continuous (more than 50 percent of work time); intensity: low (less than 1 fiber/ml); medium (1–2 fibers/ml); high (2–10 fibers/ml); very high (>10 fibers/ml).

We attributed weighting factors to each exposure category to calculate an exposure index: probability:

null = 0, possible = 0.5, definite = 1; frequency: sporadic = 0.025, irregular = 0.25, continuous = 0.75; intensity: low = 0.1 fiber/ml, medium = 1 fiber/ml, high = 10 fibers/ml, very high = 100 fibers/ml.

Because the latency period of the disease is so long, we did not analyze asbestos exposure during the 20 years before the mesothelioma diagnosis (1, 21, 22).

We used the following exposure parameters for each subject.

Highest probability, intensity, and frequency. Each subject's highest probability of exposure was determined by the highest probability of any job period during lifetime work history. Highest intensity and frequency were determined in the same way.

Duration of exposed jobs. Duration of exposed jobs (years) is defined as the total duration of job periods involving possible or definite exposure.

Cumulative exposure index (CEI). CEI is the lifetime sum of the products of probability, frequency, intensity, and duration for each job period. Because no measurements of airborne asbestos levels were available, all estimations of exposure parameters were based on the experts' subjectivity, that is, semiquantification, to which we subsequently assigned weighting factors. This index of cumulative exposure was expressed in terms of fibers/ml-years inside quotation marks ("f/ml-years").

Pattern of exposure in time. We examined the relative risks associated with the pattern of exposure by distinguishing subjects who had undergone only intermittent exposure from those whose exposure was considered continuous. Subjects' exposure was classified as intermittent if it was sporadic or irregular and if they had never worked at a job with continuous exposure. The continuous category was reserved for subjects who had been employed in at least one job with continuous exposure.

In addition to these composite variables, age at first exposure and time since first exposure were also examined.

Statistical analysis

We calculated the odds ratio by using logistic regression and the unconditional maximum likelihood method, with the aid of BMDP software (23). This technique allowed us to include the cases who had no controls. The analysis took the matching variables into account. The relation between asbestos exposure and mesothelioma was examined separately for men and women.

Quantitative parameters were categorized by percentile points. To allow us to consider the effect of some previously used cutoff points, we used additional categories for studying cumulative exposure (5 and 10 "f/ml-years").

The effect of the time-related exposure pattern (that is, intermittent vs. continuous) was analyzed after taking into account cumulative exposure.

RESULTS

The study included 405 cases and 387 controls (table 1). The largest group of cases (69.9 percent) came from the Paris metropolitan area. Cases and controls did not differ significantly by sex (82 percent and 81 percent men, respectively) or age at interview (63.5 and 63.9 years, respectively). Since almost the entire sample was white (96.8 percent of cases and 97.7 percent of controls), we did not adjust for race or ethnic origin. The socioeconomic category of the subject was determined by the last occupation held before the interview and coded using the major groups of the ISCO (table 2). Cases and controls differed significantly, with more blue-collar workers among the cases. Thus, for all comparisons, the odds ratios were adjusted for socioeconomic category.

Table 3 presents the main occupations and industries that entailed asbestos exposure among the 3,498 job periods for men. We consider in this table only activities and professions that contained at least 50 job periods and for which at least 25 percent of the job

TABLE 1. Main characteristics of cases and controls by study area, French Mesothelioma Case-Control Study, 1987–1993

Study area and years of study	Cases					Controls				
	No.	% of males	Age (years)			No.	% of males	Age (years)		
			Mean	(SD)*	Range			Mean	(SD)	Range
Paris metropolitan area (1987–1993)	283	78	62.9	(10.8)	25–88	279	78	63.4	(11.2)	29–93
Provence-Alpes-Côte-d'Azur (1989–1993)	82	92	64.5	(8.9)	44–85	73	89	65.2	(9.4)	43–84
Corsica (1989–1993)	8	75	67.5	(7.0)	60–81	7	86	64.7	(4.9)	56–71
Lorraine (1992–1993)	28	89	64.8	(12.2)	32–85	25	89	65.8	(10.7)	47–87
Auvergne (1992–1993)	4	88	68.0	(4.1)	63–73	3	75	66.0	(4.0)	62–70
Total	405	82	63.5	(10.5)	25–88	387	81	63.9	(10.7)	29–93

* SD, standard deviation.

TABLE 2. Distribution of mesothelioma cases and controls according to socioeconomic category,* French Mesothelioma Case-Control Study, 1987–1993

	ISCO code (major groups)	Men				Women			
		Cases		Controls		Cases		Controls	
		No.	%	No.	%	No.	%	No.	%
Professional, technical, and related workers	0/1	47	14.3	45	14.5	7	9.6	15	20.3
Administrative and managerial workers	2	22	6.7	17	5.5	1	1.4	0	0
Clerical and related workers	3	35	10.6	40	12.9	28	38.4	25	33.7
Sales workers	4	30	9.1	24	7.7	5	6.9	3	4.1
Service workers	5	14	4.3	32	10.3	13	17.8	20	27.0
Agricultural, animal husbandry, and forestry workers; fishermen; and hunters	6	2	0.6	8	2.6	0		3	4.1
Production and related workers, transport equipment operators, and laborers	7/8/9	179	54.4	145	46.6	19	26.0	8	10.8
No occupational activity		1		1		2		1	

* Socioeconomic category corresponding to the International Standard Classification of Occupations (ISCO) code of the last job held by the subject before interview.

periods were evaluated as possibly or definitely exposed. In the industries and occupations in which we had anticipated asbestos exposure, the proportions of exposure were high. For example, exposure was likely to have occurred in 264 of the 487 (54 percent) men's job periods in the construction industry and in 55 of the 70 (79 percent) men's job periods in the shipbuilding industry. In some occupations, exposure was frequent, e.g., 82 percent among motor vehicle mechanics and 85 percent among plumbers and pipe fitters. The proportion of exposed job periods in the categories of other industrial activities and occupations was low (16 and 19 percent, respectively).

Table 4 indicates the distribution of job periods of male cases and controls according to starting date and exposure intensity for possibly and definitely exposed job periods. Very few job periods were considered as very highly exposed, and those were found mainly among cases (18 job periods in cases vs. four among controls). These were observed after 1950 when the industrial use of asbestos had developed.

Table 5 reports the distribution of male cases and controls according to various exposure parameters. The exposure measures in this table have not been adjusted for the other exposure parameters. Mesothelioma risk increased with exposure probability, intensity, and frequency. The odds ratio for possible exposure was 1.2 (not significant), and for definite exposure, it was 3.6. Risk increased with frequency of exposure, but subjects with sporadic exposure were not at greater risk of mesothelioma than were controls. Risk also increased with the total duration of exposed jobs: The odds ratio for subjects exposed for at least 20 years was 5.4.

The odds ratio for the relation between pleural mesothelioma and asbestos exposure parameters did not increase with time since first exposure, nor was any consistent trend observed with age at first exposure.

As determined by the experts' evaluations and the weighting factors, the cumulative exposure of our population was rather low. Twenty-three percent of the cases and 35 percent of the controls had been exposed to less than 0.5 "f/ml-years." A gradient was observed with the CEI; the odds ratio rose from 1.2 for the subjects with less than 0.5 "f/ml-years" to 8.7 for the category with more than 10 "f/ml-years."

Among women, a significant risk of mesothelioma was observed among those possibly and definitely exposed to asbestos, considered together (odds ratio (OR) = 18.8, 95 percent confidence interval (CI) 4.1–86.2). Because of the small number of women exposed to asbestos, especially among controls (25 cases and two controls, for 33 and 3 percent of their respective categories), we did not analyze the dose-response relation among women any further.

The results about the time-related pattern of exposure reveal a significantly elevated odds ratio among workers whose exposure to asbestos was intermittent (OR = 1.8, 95 percent CI 1.3–2.6). The odds ratio was much greater, however, for continuous exposure (OR = 5.7, 95 percent CI 3.4–9.7). The median CEI within each category considered, i.e., <0.5, 0.5–0.99, 1–9.99, and ≥10 "f/ml-years," was similar among intermittent and continuous exposure cases, except in the highest class of CEI (≥10 "f/ml-years") (0.1, 0.65, 3.5, and 38.7 "f/ml-years" for the intermittent exposure groups and 0.075, 0.65, 3.1, and 71.3 "f/ml-years" for the continuous groups, respectively). We attempted

TABLE 3. *Selected principal industrial activities and occupations entailing asbestos exposure among men, French Mesothelioma Case-Control Study, 1987–1993**

Title	No. of job periods	Proportion of exposed job periods† (%)
Industrial activities (4-digit ISIC‡ code)		
5000 Construction	487	54
3843 Manufacture of motor vehicles	113	27
7111 Railway transport	76	30
3841 Shipbuilding and repairing	70	79
3813 Manufacture of structural metal products	65	49
3511 Manufacture of basic industrial chemicals, except fertilizers	52	54
9513 Repair of motor vehicles and motorcycles	62	71
3823 Manufacture of metal and wood working machinery	58	26
3829 Manufacture of machinery and equipment, except electrical not elsewhere classified	54	30
3845 Manufacture of aircraft	51	31
3710 Iron and steel basic industries	51	61
Other industries and industries not specified ($n = 7$)	2,359	16
Occupations (3-digit ISCO‡ code)		
9–99 Laborers not elsewhere classified	152	26
8–41 Machinery fitters and machine assemblers	110	38
8–55 Electrical wiremen	107	54
8–49 Machinery fitters, machine assemblers, and precision instrument makers (except electrical) not elsewhere classified	99	57
8–73 Sheet-metal workers	85	49
9–54 Carpenters, joiners, and parquetry workers	75	37
8–71 Plumbers and pipe fitters	73	85
9–51 Bricklayers, stonemasons, and tile setters	69	58
8–43 Motor vehicle mechanics	67	82
3–91 Stock clerks	58	28
Other professions	2,603	19
Total job periods	3,498	27

* In these tables, only activities and professions that contained at least 50 job periods and for which at least 25 percent of the job periods were evaluated as possibly or definitely exposed were considered.
† Possible or definite exposure to asbestos without taking into account the 20-year latency period.
‡ ISIC, International Standard Industrial Classification of all Economic Activities; ISCO, International Standard Classification of Occupations.

to separate the possible effect of the exposure delivery pattern from that of cumulative exposure by a stratified analysis. The odds ratios increased with the CEI among subjects with intermittent and with continuous exposures (table 5). The amplitude of the odds ratio differed, however, between these categories. When we examined the odds ratios for subjects within each of our CEI categories, they were almost twice as high for subjects with continuous exposure as for those intermittently exposed, except for the CEI category of 0.5–1 "f/ml-years."

DISCUSSION

This study, one of the larger population-based case-control studies published (24–37) sheds light on several important aspects of mesothelioma and asbestos.

As far as we know, our study is the first conducted in a general population that uses a semiquantitative assessment of exposure to examine the dose-response relation between asbestos exposure and mesothelioma.

The mesothelioma cases of this study were identified in hospitals that had agreed to participate in the case-control survey. Cases seen in other hospitals and those who were not followed within a hospital structure were not included. There is no reason to suppose, however, that the type of health care facility depended on the level of asbestos exposure. We ought to point out another source of selection bias. Mesothelioma diagnosis remains difficult. The patient who has a known history of asbestos exposure is more likely to be diagnosed with mesothelioma than a patient with similar symptoms but no known history of asbestos exposure. This bias could have heightened the dose-response relation between asbestos exposure and mesothelioma. There are probably few cases erroneously diagnosed as mesothelioma, since the French Me-

TABLE 4. Distribution of job periods among men, according to the intensity of exposure* and decade of beginning, French Mesothelioma Case-Control Study, 1987–1993

Probability of exposure	Distribution job periods													
	Before 1930		1930–1939		1940–1949		1950–1959		1960–1969		1970 and after		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cases														
Not exposed	83	77.6	172	75.1	332	66.9	280	62.8	202	61.2	215	69.8	1,284	67.0
Low	10	9.4	25	10.9	65	13.1	55	12.3	54	16.4	38	12.3	247	12.9
Medium	12	11.2	26	11.4	74	14.9	64	14.4	50	15.2	29	9.4	255	13.3
High	2	1.9	6	2.6	23	4.6	40	9.0	20	6.1	21	6.8	112	5.9
Very high	0		0		2	0.4	7	1.6	4	1.2	5	1.6	18	0.9
Total	107	100	229	100	496	100	446	100	330	100	308	100	1,916†	100
Controls														
Not exposed	65	82.3	192	84.2	341	80.6	282	80.8	218	79.3	183	83.9	1,281	81.5
Low	2	2.5	21	9.2	46	10.9	33	9.5	29	10.6	17	7.8	148	9.4
Medium	7	8.9	13	5.7	31	7.3	27	7.7	26	9.5	15	6.9	119	7.6
High	4	5.1	2	0.9	4	1.0	6	1.7	1	0.4	3	1.4	20	1.3
Very high	1	1.2	0		1	0.2	1	0.3	1	0.4	0		4	0.3
Total	79	100	228	100	423	100	349	100	275	100	218	100	1,572‡	100

* Intensity for possible or definite exposure to asbestos without taking into account the 20-year latency period.
† Job periods for which the year of beginning is missing = 6.
‡ Job periods for which the year of beginning is missing = 4.

sothelioma Panel excluded, after pathology review, 10 percent of subjects initially considered eligible and confirmed the diagnosis for 62 percent of the cases on the basis of pathology reports. We accepted the remaining 28 percent after reviewing available histologic data and hospital records.

The use of hospital controls could have entailed some bias. In particular, cases and controls differed in socioeconomic status, with the latter group containing fewer blue-collar workers. This difference could have arisen from a selection bias and might reflect the controls' failure to represent adequately the population from which the cases were drawn, or it might be due to a particularly high rate of pleural mesothelioma among blue-collar workers because of their high prevalence of asbestos exposure. In the latter case, taking socioeconomic status into account could have led to overadjustment of the relation between asbestos exposure and pleural mesothelioma. The crude odds ratios, however, were of same order of magnitude as the adjusted values.

The validity of the information about asbestos exposure depends on how well we have avoided three types of errors: difference in the quality of interview data according to disease status (recall bias or interviewer bias), errors by the experts in classifying the subjects into defined categories, and errors related to the accuracy of the weighting factors subsequently assigned to each category. As recently stated in an International Agency for Research on Cancer meeting on retrospective assessment of occupational exposure in epidemiology (38), the validity of expert judgment, which relies on both the knowledge and the experience of industrial hygienists, has rarely been evaluated. Indeed, when no objective method of measuring exposure is available, their judgment is most often considered the gold standard.

Our study assessed frequency and intensity of exposure by using ordinal categories with specific boundaries. This procedure should have minimized the misclassification of subjects between extreme exposure categories. The experts themselves, however, reported sometimes encountering difficulties in distinguishing between sporadic and irregular exposure and between low and moderate exposure.

Moreover, they suggested that the quality of their assessment for the periods under consideration (20 or more years ago) might not be as good as for more recent years because of the lack of published data for these periods. These errors could have led to the nondifferential misclassification of subjects into exposure categories and the possible underestimation of the odds ratios (39).

To avoid the exposure suspicion bias, the experts were blinded to case-control status when they evaluated exposure. Recall bias could have influenced the quality of the answer to the questionnaire and, subsequently, the expert judgment. To test this potential bias, we compared the experts' assessment with results from an asbestos job exposure matrix (40). We found no difference between cases and controls (data not shown), suggesting that it was unlikely that a substantial recall bias had affected the experts' judgment. The interviewers, however, were aware of case-control status and thus might have conducted the interviews of the case subjects more thoroughly than those of controls. Since the experts considered all of the information available, they might have been able to evaluate

TABLE 5. Odds ratios for relations between pleural mesothelioma and asbestos exposure parameters among men, French Mesothelioma Case-Control Study, 1987–1993, with a latency period of 20 years

Asbestos exposure parameters	No. of cases	No. of controls	OR*	95% CI†
Highest probability of exposure				
Not exposed	95	154	1.0	
Possible	51	71	1.2	0.8–1.9
Definite	184	87	3.6	2.4–5.3
Highest intensity of exposure				
Low	55	74	1.2	0.8–1.9
Medium	106	66	2.8	1.8–4.3
High	74	18	7.1	3.9–12.9
Highest frequency of exposure				
Sporadic	56	86	1.0	0.7–1.6
Irregular	94	46	3.3	2.1–5.1
Continuous	85	26	5.7	3.4–9.7
Duration of exposed job (years)				
1–7	63	64	1.7	1.1–2.6
8–19	74	60	2.0	1.3–3.1
≥20	98	34	5.4	3.2–8.9
Time since first exposure (years)				
20–37	77	53	2.3	1.4–3.6
38–48	83	47	2.8	1.8–4.5
≥49	75	58	2.2	1.4–3.6
Age at first exposure (years)				
<16	66	55	1.9	1.2–3.1
16–22	96	52	3.0	1.9–4.6
≥23	73	51	2.3	1.5–3.7
Cumulative exposure ("f/ml-year"‡)				
0.001–0.49	77	109	1.2	0.8–1.8
0.5–0.99	29	12	4.2	2.0–8.8
1–9.9	80	27	5.2	3.1–8.8
≥10	49	10	8.7	4.1–18.5
	Cumulative exposure ("f/ml-year")			
Temporal exposure pattern§				
Intermittent				
<0.5	66	98	1.1	0.8–1.7
0.5–0.99	19	8	4.0	1.7–9.7
1–9.99	48	21	4.0	2.2–7.2
≥10	17	5	5.9	2.1–16.7
Continuous				
<0.5	11	11	1.9	0.8–4.8
0.5–0.99	10	4	4.6	1.4–15.4
1–9.99	32	6	9.2	3.7–23.1
≥10	32	5	11.3	4.1–30.7

* Odds ratios (ORs) adjusted for age and socioeconomic category.

† CI, confidence interval.

‡ Cumulative exposure index was based on subjective assessment, that is, semiquantification of exposure by the experts and selected weighting factors assigned to each category of exposure, with no objective measurement of airborne asbestos levels. Thus, the exposure unit, f/ml-years, is expressed in quotation marks.

§ Subjects' exposure was classified as intermittent if it was sporadic or irregular and if they had never worked at a job with continuous exposure. The continuous category was reserved for subjects who had been employed in at least one job with continuous exposure.

exposure more precisely for the cases than for the controls. The frequency of the exposure category "possible," used when the experts could not reach a definite conclusion, was higher among controls than among cases, so that this type of error cannot be excluded. We thus undertook a supplementary analysis to examine, at least in part, the effect of this bias. First, we considered all of the jobs in the possible category as nonexposed. The pattern of dose-response relation was very similar to that observed: no significant risk for subjects in the category of less than 0.5 "f/ml-years" and an odds ratio of 7.8 (95 percent CI 3.8–16.2) for those in the category of more than 10 "f/ml-years." Classifying all of the possibly exposed subjects as definitely exposed did not change the dose-response relation pattern very much either (OR = 1.0, 95 percent CI 0.7–1.6 for the lowest category and OR = 7.7, 95 percent CI 3.8–15.7 for the highest).

The validity of the dose-specific risks in our study also depends greatly on the values of the weighting factors selected for each exposure category. For this purpose, we attempted to retain the intervals used by the experts. Although this procedure is assumed to provide more precise exposure evaluation than would a relative ranking of subjects by an ordinal scale without specified boundaries, some misclassification of subjects according to dose-specific exposure probably occurred. Indeed, all jobs classified in the same exposure category were assigned the same weighting value without consideration of the variability of exposure within the category. Such nondifferential misclassification of the subjects usually attenuates the relation between exposure and disease and flattens the dose-response curve (39). We should note that the intervals used by the experts for the categories of intensity were rather dissymetric—narrow for medium exposure and large for very high exposure. There were few job periods with very high exposure, however, so that errors due to the variability in this category should have had little effect on the dose-response relation observed.

We observed a dose-response relation with cumulative exposure. Because, as stated, the exposure assessment for the earliest periods might have been underestimated and because of the imprecision of intensity weighting factors, we tested two models using two other series of coefficients for weighting intensity of exposure: 1) second model: 0.5, 1.5, 6, and 550 fibers/ml, for low, medium, high, and very high exposures, respectively (midpoints of boundaries), and 2) third model: 0.5, 5, 50, and 500 fibers/ml for low, medium, high, and very high exposures, respectively. These models showed a dose-response relation with the CEI similar to that in the first model, but they did not show as clear a dose-response trend as the first model. In the second model, the odds ratio was 1.0 (95 percent CI 0.7–1.6) for the lowest dose and 6.4 (95 percent CI 3.4–12.2) for the highest. The corresponding odds ratios for the third model are 0.9 (95 percent CI 0.5–1.4) for the lowest and 7.1 (95 percent CI 4.2–11.9) for the highest.

The pattern of the dose-response curve could have depended on the length of latency period selected. We have used a 20-year latency period, as suggested by McDonald and McDonald (1, 21), who concluded that latency is seldom less than 20 years and usually 30–40 years. We also examined the effects of 10- and 30-year latency periods. The results obtained with the former were very similar to those we found with the 20-year latency period. A 30-year latency period resulted in a lower odds ratio and a less clear dose-response relation, suggesting that exposure misclassification occurred using such a long latency period.

Because no objective measurement was available to test the validity of the experts' evaluation, we express the cumulative exposure using units of f/ml-years in quotation marks. Even in cohort studies, however, precise measurement of exposure is difficult (2, 41).

In this study, we used several surrogate parameters for dose to examine dose-response relation, as suggested by Blair and Stewart (42) and Suarez-Almazor et al. (43). We considered separately the intensity, frequency, and duration of exposure, and each was significantly related to mesothelioma. The relative risk increased along with each parameter. In addition, when each of these parameters was adjusted for the others, the relative risk of each, although lower, remained significant. These results suggest that each exposure parameter contributed to some extent to the occurrence of mesothelioma, although the dose-response relation seemed to be described best by the CEI.

The existence of a causal association between asbestos exposure and mesothelioma was first demonstrated in 1960 (44). Both cohort (6–9, 11–14, 45) and case-control (32, 34–37, 46, 47) studies focusing on mesothelioma and examining surrogate parameters for dose have reported a dose-response relation.

However, because of the rarity of mesothelioma, even among asbestos workers, little quantitative information is available from which the dose-response relation can be precisely estimated (1, 41, 48).

Peto et al. (49), using mathematical models, observed that the risk of mesothelioma in one occupationally exposed cohort (North American insulators) was best described by a model in which the risk increases with the third or fourth power of time since first exposure. They also concluded that their data were compatible with a linear dose-response relation

between the level of asbestos exposure and the risk of mesothelioma. Our data for the higher categories of CEI also support this conclusion. The pattern of a dose-response relation is more doubtful at low doses because the uncertainties of exposure evaluation are highest for low doses.

Some indication of the effect of exposure that is low level by the brevity of its duration comes from industrial cohort studies. Very few cases of mesothelioma have been observed among those whose exposure was very brief: There were no cases of mesothelioma among members of the cohort of Australian Blue Asbestos workers who were exposed for less than 3 months (47), none among the North American insulators whose exposure lasted less than 15 months (4), and only one, rather than the 25 expected, among Rochdale textile workers exposed for less than 10 years (8). These cohorts do not, however, provide data that allow us to examine the effect of low-intensity exposure.

Illgren and Browne (50) considered whether a threshold exposure might exist and concluded that mesothelioma was unlikely in persons exposed for less than 5 f/ml-years. Our results indicate, however, that mesothelioma cases occurred below a cumulative exposure of 5 f/ml-years and perhaps below 0.5 f/ml-years.

Very few studies have focused on the time-related pattern of exposure as a factor in mesothelioma. Schenker et al. (51) examined the risk of mesothelioma among railroad workers, distinguishing between "intermittent" and "regular" asbestos exposure on the basis of job categories. No significant risk was observed for those whose exposure was intermittent, but those in the regular exposure category were at high risk.

Our study examined the temporal exposure pattern according to the frequency of exposure and the CEI. We observed a dose-response relation with cumulative exposure for both intermittent and continuous patterns of exposure. Much more attention to the role of these temporal patterns is needed, adjusting for cumulative exposure. Our results suggested that intermittent exposure does not entail as high a risk of mesothelioma as does continuous exposure. Assessment of this apparent excess risk of continuous compared with intermittent exposure, however, should bear in mind the likelihood that more subjects with intermittent exposure are misclassified.

We could not examine mesothelioma risk according to fiber types because our study design (i.e., case-control study in a general population) did not allow us to identify those subjects whose exposure was only to chrysotile fibers.

The odds ratio between exposure to asbestos and mesothelioma was much higher for the women in our study than for the men. No evidence of individual, sex-related susceptibility to mesothelioma has been found (52). One explanation for this might be the different distributions of asbestos-related occupations between men and women. Since asbestos-related occupations were rarely held by women, any exposure that did occur may have been very well characterized, leading, in turn, to fewer misclassification errors than for males, particularly among controls.

We found a clear dose-response relation between cumulative exposure to asbestos and pleural mesothelioma in a population-based case-control study with retrospective assessment of exposure. A significant excess of mesothelioma was observed for levels of cumulative exposure that were probably far below the limits adopted in many industrial countries during the 1980s.

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