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RESEARCH ARTICLE

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Malignant asbestos-related disease in a population exposed to asbestos

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Abstract

Objectives: The first asbestos fiber cement plant in Spain operated in Cerdanyola, in the Barcelona metropolitan area, between 1907 and 1997. We describe clinical and epidemiological characteristics of patients diagnosed with the malignant asbestos-related disease (ARD) in the area of the plant between 2007 and 2016.

Methods: A prospective, descriptive study was undertaken in the 12 municipalities of the county of Barcelona most proximate to the plant. We describe malignant ARD cases by time of diagnosis, source of exposure, periods of exposure and latency, and distribution by sex. Cumulative incidence and age-standardized incidence rates (ASIR) are calculated.

Results: Of 477 patients diagnosed with ARD between 2007 and 2016, 128 (26%) presented with asbestos-associated malignancy. Pleural mesothelioma was noted in 105 patients (82.0%) with a linear trend Z-score of −0.2 (NS) in men and 2.7 ($P < .01$) in women. The highest ASIRs for malignant ARD (6.1/100 000 residents/year; 95% confidence interval [CI], 2.2-13.3) and pleural mesothelioma (4.8/100 000 residents/year; 95% CI, 1.5-11.6) occurred in municipalities closest to the focal point of contamination. The origin of malignant ARD was nonoccupational in 32.2% of men and 81.6% of women ($P < .001$).

Conclusions: More than 20 years after the closure of the fiber cement plant, the grave consequences of exposure to asbestos remain. The detection of cases of pleural mesothelioma in men seems to have plateaued whereas in women an ascending trend continues, which principally has its origin in nonoccupational exposures.

KEYWORDS
asbestos, epidemiology, mesothelioma

1 | INTRODUCTION

In 1907, the first and largest fiber cement plant in Spain opened in the town of Cerdanyola in the Barcelona metropolitan area, which acted as a focal point for contamination until its closure in 1997. In the 90 years during which it was active, the plant processed 227 365 tonnes of asbestos from several different countries.[1] This figure represents 9% of the total imported by Spain during the 20th century. The mineral arrived by sea and was transported by rail from the port of Barcelona to the plant. It was received in hessian sacks and stored in the open air in the urban area of the town. Unpacking, dry milling and manufacture were performed in the plant without the necessary measures of protection until its closure.[2] This industrial activity not only exposed the plant workers but also family members

who lived with the workers and the local population.[3,4] Until the end of the 1980s, residues from the plant's production were used in the repair of streets and paths of the neighboring towns of Cerdanyola and Ripollet in substitution for asphalt. It should also be mentioned that other work activities in the area, such as building, smelting, brake and clutch industries, and plumbing, also made use of asbestos.

Given the long persistence of asbestos and the prolonged period of latency of asbestos-related related diseases (ARD), these diseases will continue to appear in Europe until the mid-21st century.[5]

Our group performed a retrospective study in Cerdanyola and its surrounding municipalities[3] that enumerated ARD cases diagnosed between 1976 and 2006 in the primary healthcare area of the population close to the fiber cement plant. Following on from this, a prospective protocol was designed.[6] The objective of the present study was to describe the incidence of malignant ARD in the subsequent10 years.

2 | METHODS

We undertook a prospective, descriptive study based on an analysis of all the cases of malignant ARD from all centers of primary healthcare and the only hospital of reference in the zone (Parc Taulí Hospital, Sabadell), diagnosed between 2007 and 2016. The study included the 12 closest municipalities to the principal point of contamination, the fiber cement plant located between Cerdanyola and Ripollet. We considered two areas: the first covered the area within 2000 m of the factory belonging to Cerdanyola and Ripollet municipalities, with the second and larger area, between 2000 and 10 000 m from the factory, within other surrounding municipalities. The patients were all evaluated and followed by their family practitioner and/or a pulmonologist. The diagnosis of ARD was validated by our team, who completed a data-gathering sheet following our protocol.[6] When additional information was required to complete the sheet, the patient or a family member was contacted. Cases were considered positive for ARD if the disease met two conditions: (a) the diagnosis was made by clinical and epidemiological criteria, imaging, and/or morphological techniques (cytology or histology), and (b) other diagnostic possibilities had been excluded.[3,4] When a single patient had both benign findings (pleural plaques, pachypleuritis/pleural thickening, rounded atelectasis, benign pleural effusion, or asbestosis) and malignant disease at the time of diagnosis, for the purposes of this study the subject was recorded as having malignant ARD. In the case of malignancy (pleural mesothelioma, peritoneal mesothelioma, bronchopulmonary cancer, and laryngeal cancer), cases were only considered positive with histological confirmation. The presence of other findings compatible with ARD was also required to record a case of bronchopulmonary or laryngeal cancer in patients with exposure due to shared accommodation or environmental exposure.

Patients were classified by their source of exposure as: (a) occupational (the presentation of reliable documentation demonstrating occupational activity of the worker with exposure to asbestos); (b) shared accommodation (having habitually shared one's residence with a worker who was occupationally exposed to asbestos); (c) environmental. If a patient was subject to more than one type of exposure, he or she was assigned to the exposure group that presumably had the most intense exposure: occupational, shared accommodation, and environmental in that order. For occupational source cases, the duration of exposure was recorded as the time working in an occupational activity whereas for cases with a shared accommodation source as the time spent in shared living quarters with a worker exposed to asbestos. For environmental cases, the duration of exposure was established as the time living in the area of the asbestos cement plant between 1907 and 1997. The latency period was the time from the start of the exposure until diagnosis. For environmental cases, exposure was defined as starting in the year that the patient established residence in the asbestos cement plant area. This 10 000-m area is situated in Catalonia, a region in the northeast of Spain. This is a mostly industrial area of 449 767 inhabitants, 49.4% of whom are men, with an average age of 40.1 years.

The study was conducted in accordance with the rules established by the Declaration of Helsinki and the Code of Good Scientific Practice of the Carlos III Institute of Health. The protocol was approved by the Clinical Research Ethical Committee of the Institut d'Investigació en Atenció Primària (IDIAP) Jordi Gol of Catalonia. The participants received written information and were informed of the implications of the study before giving their consent to participate. Confidentiality and anonymization of data were in accordance with Spanish personal data protection regulations.

2.1 | Statistical analysis

Data analysis was performed using the SPSS statistical package.[7] Population data from the municipalities included during the period of study were obtained from the Statistical Institute of Catalonia.[8] Cumulative incidence rates (CI) were calculated using annual case counts by year of diagnosis between 2007 and 2016. The population according to the 2011 census was used for the denominator: 449 767 inhabitants for the whole area, of which 95 595 lived in the towns of Cerdanyola and Ripollet. CI rates were applied to the standardized world population to calculate the age-standardized incidence rate (ASIR). Exact confidence intervals were calculated using the inverse of Fisher's F test and χ^2 functions.[9,10] Results are provided for the overall zone of the study and by proximity to the principal focus of contamination. A Z-score test of the number of cases of pleural mesothelioma diagnosed during the period of the study was performed to determine the time trend of incident cases.[11]

3 | RESULTS

Of a total of 477 patients with ARD, 128 (26.8%) presented with a malignant ARD, with an overall mean age at diagnosis of 70.9 ± 10.8 years. 90 (70.3%) were men and 38 (29.7%) were women (Table 1).

TABLE 1 New patients, cumulative incidence (CI), and age-standardized incidence rates (ASIR) of ARD/100 000 inhabitants/year, 2007 to 2016

	The whole area			Cerdanyola-Ripollet area			Remaining 10 municipalities		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Malign ARD									
N	90	38	128	46	24	70	44	14	58
CI (CI 95%)	4.1 (1.9-7.7)	1.7 (0.4-4.5)	2.8 (1.5-4.9)	9.7 (2.9-23.5)	5.0 (0.6-17.0)	7.3 (2.9-15.1)	2.5 (0.7-6.3)	0.8 (0.0-3.7)	1.6 (0.6-3.7)
ASIR (CI 95%)	3.6 (0.9-9.8)	1.2 (0.0-6.2)	2.3 (0.3-8.0)	8.9 (4.0-17.1)	3.9 (0.9-10.3)	6.1 (2.2-13.3)	2.3 (0.3-7.9)	0.5 (0.4-4.8)	1.3 (0.6-6.5)
Pleural mesothelioma									
N	70	35	105	33	22	55	37	13	50
CI (CI 95%)	3.2 (1.3-6.5)	1.5 (0.4-4.2)	2.3 (1.1-4.2)	7.0 (1.4-19.9)	4.6 (0.6-16.0)	5.8 (2.0-12.9)	2.1 (0.5-5.7)	0.7 (0.0-3.6)	1.4 (0.5-3.3)
ASIR (CI 95%)	2.8 (0.5-8.7)	1.1 (0.0-6.0)	1.9 (0.1-7.4)	6.4 (2.3-13.7)	3.6 (0.9-9.7)	4.8 (1.5-11.6)	1.9 (0.1-7.5)	0.5 (0.0-4.7)	1.1 (0.0-5.9)
Peritoneal mesothelioma									
N	3	2	5	2	1	3	1	1	2
CI (CI 95%)	0.1 (0.0-2.2)	0.1 (0.0-1.9)	0.1 (0.0-1.0)	0.4 (0.0-9.3)	0.2 (0.0-8.4)	0.3 (0.0-5.0)	0.1 (0.0-2.3)	0.1 (0.0-2.3)	0.1 (0.0-1.2)
ASIR (CI 95%)	0.1 (0.0-4.2)	0.03 (0.0-3.8)	0.1 (0.0-4.0)	0.4 (0.0-5.2)	0.1 (0.4-4.0)	0.3 (0.0-4.6)	0.1 (0.0-3.9)	0.02 (0.0-3.8)	0.04 (0.0-3.8)
Lung cancer									
N	17	1	18	11	1	12	6	0	6
CI (CI 95%)	0.8 (0.1-3.1)	0.04 (0.0-1.8)	0.4 (0.0-1.6)	2.3 (0.1-12.3)	0.2 (0.0-8.4)	1.3 (0.0-6.4)	0.3 (0.0-2.9)	0.0 (0.0-2.1)	0.2 (0.0-1.4)
ASIR (CI 95%)	0.7 (0.0-5.2)	0.04 (0.0-3.8)	0.3 (0.0-4.9)	2.1 (0.3-7.5)	0.2 (0.0-4.4)	1.0 (0.0-5.7)	0.3 (0.0-4.9)	0.0 (0.0-3.7)	0.2 (0.0-4.2)
Benign ARD									
N	238	111	349	173	93	266	65	18	83
CI (CI 95%)	10.7 (6.8-16.0)	4.9 (2.4-8.7)	7.8 (5.4-10.8)	36.5(21.2-58.3)	19.3 (8.8-36.5)	27.8 (18.3-40.6)	3.7 (1.4-7.9)	1 (0.1-4.0)	2.3 (1.0-4.6)
ASIR (CI 95%)	9.3 (4.3-17.7)	3.7 (0.9-9.9)	6.2 (2.3-13.4)	33.0 (22.7-46.4)	14.9 (8.2-24.7)	23.1 (14.6-34.6)	3.2 (0.7-9.2)	0.8 (0.0-5.5)	1.8 (0.1-7.2)
Total ARD									
N	328	149	477	219	117	336	109	32	141
CI (CI 95%)	14.8 (10.1-20.8)	6.5 (3.6-10.9)	10.6 (7.8-14.1)	46.2(28.8-70.2)	24.3(12.3-42.9)	35.1 (24.3-49.2)	6.2 (3.1-11.3)	1.8 (0.4-5.1)	4.0 (2.2-6.7)
ASIR (CI 95%)	13.0 (6.8-22.4)	4.9 (1.5-11.7)	8.5 (3.7-16.6)	41.9 (30.1-56.7)	18.8 (11.2-29.5)	29.2 (9.6-41.9)	5.5 (1.8-12.6)	1.3 (0.0-6.4)	3.1 (0.6-9.0)

Abbreviations: ARD, asbestos-related disease; CI 95%, confidence interval of 95%; N, number of new patients diagnosed between 2007 and 2016.

The age at diagnosis of malignant ARD varied significantly depending on the source of exposure and was lower in exposure through shared accommodation (62.8 ± 10.3) and higher in occupational cases (72.9 ± 9.4) ($P < .001$). The number of patients with pleural mesothelioma was 105 (70 men, 35 women). Although the time trend of this disease was not significant during the period studied in men (Z for linear trend = −0.21; pNS), it showed a significant progressive increase for women ($Z = 2.68$; $P < .01$) (Figure 1). It should be noted that 12 (3.4%) of the patients initially diagnosed with a benign pathology later presented a malignant disorder during the period of the study. The time after the initial benign diagnosis until the presentation of malignancy was 3.2 ± 2.0 years. In the case of pleural mesothelioma, the 10-year birth cohort with the most cases was the decade 1940 to 1949 in men and the decade 1930 to 1939 in women, for both those who were exposed occupationally and nonoccupationally. For cohorts born after 1960, the number of cases dropped notably for both sexes and for all types of exposure.

The ASIR for pleural mesothelioma in the Cerdanyola-Ripollet area, which is the closest to the main focus, was 4.8 per 100 000 residents per year (1.5-11.6) and 1.1 (0.0-5.9) in the remaining municipalities (Table 1). The female/male ratio of cases of pleural mesothelioma in the Cerdanyola-Ripollet area was 0.66, whereas in the other municipalities, it was 0.35.

Of the 128 patients with malignant ARD, 68 (53.1%) (61 men, 7 women) had been exposed occupationally. Of these, 31 were workers in the fiber cement plant, and 37 worked for other companies or engaged in activities related to the handling of asbestos. Of the 105 cases of pleural mesothelioma, 51 (48.6%) (46 men, 5 women) had occupational exposure, whereas 54 (51.4%) (24 men, 30 women) had nonoccupational exposure. Nonoccupational exposure in cases of malignant ARD was more common in women than in men (85.7% and 34.3%, respectively). Therefore, the type of exposure in cases of pleural mesothelioma varied by sex (χ^2: 24.71; $P < 0.001$). In patients with bronchopulmonary cancer or peritoneal mesotheliomas, occupational exposure was 72.2% and 80.0%, respectively. In patients with occupational exposure, bronchopulmonary cancer/pleural mesothelioma ratio was 0.42 in the Cerdanyola-Ripollet area and 0.16 in the remainder of the municipalities.

The types of ARD and the times of exposure and latency by the source of exposure are shown in Table 2. Of the 38 malignant ARD cases with environmental exposure, 28 (74%) had lived mainly in the proximate area of the plant (within 2000 m) and 10 in the area from 2000 to 10 000 m.

In patients with pleural mesothelioma, the meantime of exposure was 16.8 ± 9.1 years in the case of patients who had been exposed through shared accommodation, 20.1 ± 15.0 for the occupational cases and 32.6 ± 19.3 for persons who had environmental exposure ($P < .001$). In patients with pulmonary cancer, the exposure time was greater (47.3 ± 13.3 years) in those who were exposed environmentally. The latency time for malignant ARD and pleural mesothelioma was 50.2 ± 13.8 and 50.8 ± 13.9 years, and there were no significant differences in latency between the different types of exposure.

4 | DISCUSSION

This study describes the significant impact of a focal point of asbestos production and exposure that was active until 1997 on the population that lived in the surrounding area during a period between 10 and 20 years after closure. The cumulative incidence of pleural mesothelioma was 2.3 patients per 100 000 inhabitants per year, although the incidence was 5.8/100 000/year in the Cerdanyola-Ripollet area. These figures exceed the incidence figures of 1.5 and 4.7, respectively, that were estimated in the area in the 2000 to 2006 period.[3] Furthermore, these results represent a much higher CI than is estimated for the whole of Spain, which was 0.41 between 1994 and 2010[12] and 0.7 between 2000 and 2015.[13]

Our study also shows that 20 years after the closure of the fiber cement plant, 51.4% of the cases of pleural mesothelioma were of nonoccupational origin. Similar situations of environmental contamination from a fiber cement plant in Casale Monferrato in Italy have resulted in epidemics of environmental pleural mesothelioma.[14] A recent review also confirms the high risk of pleural mesothelioma of environmental origin in different countries and periods in similar

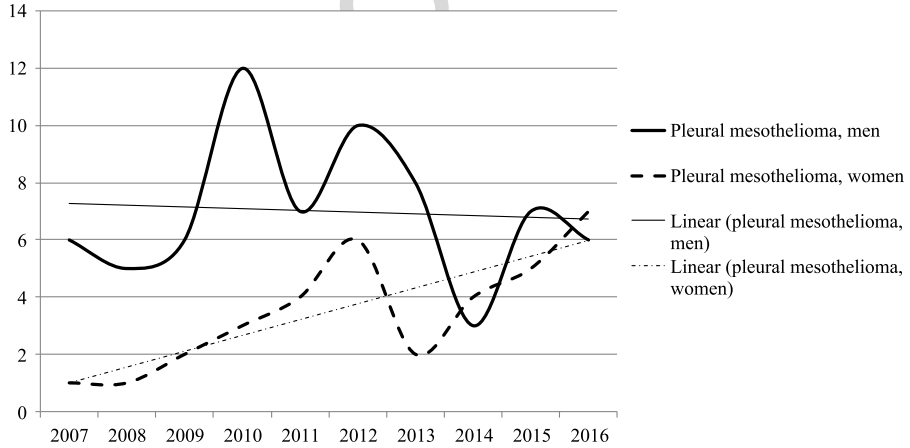

FIGURE 1 Patients with pleural mesothelioma, by the year of diagnosis. Linear trend* in the 2007 to 2016 time period. *Trend Z-score not significant for men ($Z = -0.2081$; $P = .8352$); positive and significant for women ($Z = 2.6776$; $P = .0074$)

TABLE 2 Malignant asbestos-related disease cases, time of exposure, and period of latency by type of exposure, 2007 to 2016

	Total	Occupational	Cohabiting	Environmental	*P*
Malignant ARD					
Patients	128 (26.8%)	68	22	38	
Exposure time	23.8 ± 16.6	20.5 ± 14.7	16.7 ± 8.9	33.7 ± 19.1	<.001
Latency period	50.2 ± 13.8	47.7 ± 11.0	53.8 ± 8.5	52.8 ± 19.1	.1
Pleural mesothelioma					
Patients	105 (22.0%)	51	21	33	
Exposure time	23.4 ± 16.7	20.1 ± 15.0	16.8 ± 9.1	32.6 ± 19.3	<.001
Latency period	50.8 ± 13.9	48.7 ± 10.4	53.9 ± 8.7	52.1 ± 20.0	.3
Peritoneal mesothelioma					
Patients	5 (1.0%)	4		1	
Exposure time	14.8 ± 12.1	14.8 ± 14.0		15.0	1
Latency period	41.7 ± 10.1	41.7 ± 11.6		42.0	1
Lung cancer					
Patients	18 (3.8%)	13	1	4	
Exposure time	28.6 ± 16.7	23.9 ± 14.0	15.0	47.3 ± 13.3	<.05
Latency period	49.1 ± 13.3	45.2 ± 12.6	52.0	60.8 ± 10.7	.1
Benign ARD					
Patients	349 (73.2%)	177	86	86	
Exposure time	22.5 ± 14.9	18.3 ± 12.7	19.6 ± 8.9	34.2 ± 17.6	<.0001
Latency period	53.2 ± 11.6	47.3 ± 8.8	59.5 ± 8.0	59.0 ± 13.4	<.0001
All forms of ARD					
Patients	477 (100%)	245 (51.4%)	108 (22.6%)	124 (26.0%)	
Exposure time	22.9 ± 15.4	18.9 ± 13.3	19.0 ± 9.0	34.0 ± 18.0	<.0001
Latency period	52.4 ± 12.3	47.4 ± 9.4	58.4 ± 8.4	57.1 ± 15.6	<.0001

Note: Values expressed as the number of patients and % of total. Time of exposure and latency period expressed in mean years ± standard deviation.
Abbreviation: ARD, asbestos-related disease.

circumstances.[15] The long latency period from first exposure to diagnosis for pleural mesothelioma was 50.8 years, which may be relevant to predictions about the mesothelioma epidemic.

The number of new cases of pleural mesothelioma in men does not show a significant time trend within the period from 2007 to 2016, whereas it is significantly positive in women. This possibly suggests that after a prior period of increase, a plateau was reached in the case of men, as other authors had anticipated.[1,5,16,17] Therefore, the trend in men is still not decreasing. On the other hand, a significant upward trend is still observed in women. However, due to the relatively small number of cases, other studies are needed to confirm these results. The delay in reaching a plateau in the case of women could be due to the fact that most mesotheliomas in a woman (85.7%) were due to nonoccupational exposure, with a longer mean time of exposure and intensity of exposure that was lower than in those who were exposed occupationally, who were mainly men. In other countries, a continuing increase in pleural mesotheliomas of nonoccupational origin was also observed in women years after the closure of the principal focal point of contamination.[18,19] The female/male ratio of pleural mesothelioma that was observed is higher in proximity to the factory than in the municipalities that were more distant. This would indicate that the environmental risk diminishes as the distance from the focal point increases, while it is logical that the occupational risk, which is more frequent in men, persists in the more distant areas. This finding corresponds with the results obtained in other studies,[13,20] which observe that the proportion of women is higher when there is intense environmental exposure.

The bronchopulmonary cancer/pleural mesothelioma ratio varies considerably depending on the study.[21,22] In a study by Visona et al,[21] as in our own, the ratio is low. This could be due to underdiagnosis or underreporting in the case of patients whose bronchopulmonary cancer could have been attributed to smoking, given that exposure to asbestos was determined by interview or through existing documentation, despite long knowledge that lung cancer in

asbestos workers can be of occupational origin.[23] In contrast, in a cohort study[22] in which occupational exposure had been previously evaluated, the bronchopulmonary cancer/pleural mesothelioma ratio was higher. Other authors[24,25] note that this ratio could also be affected by different pathogenic mechanisms depending on the type of asbestos.

Our investigation confirms the rarity of peritoneal mesothelioma when exposure is not occupational, given that this location is habitually associated to a very high level of exposure to asbestos. The CI of peritoneal mesothelioma was 0.4 cases per 100 000 men for those in close proximity to the plant, which is similar to that found in other areas with intense exposure to asbestos.[26]

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CONFLICTS OF INTEREST

The authors declare that are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Dr John D Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

~~JT, CA-C, and RO~~ contributed to the conception or design of the work. ~~JT, CA-C, MR-M, JC-S, RA-H, and RO~~ contributed to the acquisition, analysis, or interpretation of data for the work. ~~JT, CA-C, MR-M, JC-S, RA-H, and RO~~ drafted the work or revised it critically for important intellectual content. All the authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

ETHICS APPROVAL AND INFORMED CONSENT

The study was conducted in accordance with the rules established by the Declaration of Helsinki and the Code of Good Scientific Practice of the Carlos III Institute of Health. The protocol was approved by the Clinical Research Ethical Committee of the Institut d'Investigació en Atenció Primària (IDIAP) Jordi Gol (P06/18) of Catalonia. The participants received written information and were informed of the implications of the study before giving their consent to participate. Confidentiality and anonymization of data were in accordance with Spanish personal data protection regulations.

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