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Malignant Mesothelioma Patterns in Emilia-Romagna: A Retrospective Asbestos Exposure Assessment (1996-2023)

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ABSTRACT

Background: *Malignant mesothelioma (MM) is a rare but lethal cancer strongly associated with asbestos exposure. This retrospective study examines mesothelioma trends and past asbestos exposure assessment in Emilia-Romagna, Northern Italy.* **Methods:** *Between 1996 and 2023, 3,513 cases of MM were recorded by the Regional Operating Center, predominantly in males (72%) and older than 65 years (79%). MM diagnosis was defined as certain, probable, and possible. Information concerning asbestos exposure was collected through an analytical questionnaire administered to patients or proxies and classified as occupational and non-occupational.* **Results:** *Occupational exposure accounted for 82% of cases, significantly increasing from 71% to 88% in the most recent period. A more accurate definition of occupational exposure indicates that specific exposure has gone from 49% in the first period to 62% and 58% in the last two periods; probable exposure decreased from 21% to 16%, while possible exposure decreased from 16% to 13%. Familiar exposure remained relatively constant at around 8%, environmental exposure slightly decreased from 4% to 2%, while non-occupational exposure remained stable at 2%. Among patients with exclusively occupational exposure (1,826 cases), 87% were male and aged between 65 and 75 years (36%) and 75+ (41%). Exposure rates for the province of residence see the province of Reggio Emilia with the highest occupational exposure rate (2.5 x 100,000 residents), followed by Ravenna (2.3 x 100,000 residents) and Parma and Piacenza, which have similar exposure rates with 2.2 x 100,000 residents. Occupational sectors such as construction, railway maintenance, and metalworking are identified as high-risk industries. Despite efforts to mitigate exposure, non-occupational and environmental exposures persist. The study highlights the importance of continuous surveillance and exposure monitoring to guide effective interventions and legal recognition of MM.*

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1. Introduction

Malignant mesothelioma (MM) represents a rare tumor, nevertheless significant in terms of public health, primarily due to its well-documented association with asbestos exposure in both occupational and environmental settings [1, 2]. This association has led to a concerning escalation in MM incidence rates across Italy and numerous other industrialized countries [3-8]. In our country, asbestos was definitively banned in April 1994 (Law 257/92); nevertheless, the long latency between exposure and onset of the disease, the extension of life, and the improvement of diagnostic techniques have recorded an increase in the incidence of MM in recent years, currently still ongoing, even if the incidence trends of population, according to the latest reports, do not seem to grow further [9-12].MM is a disease that mainly affects the pleura (80-90%) and peritoneum (10-15%) [13-15], although, in recent years, there has been growing interest in the forms that affect the pericardium and testicle [16, 17]. The main histological subtype of mesothelioma is represented by the epithelioid form, which has a better prognosis than biphasic and sarcomatoid tumors. The surgical approach involves a complete macroscopic resection in combination with chemotherapy or radiotherapy. In cases deemed unresectable, the therapeutic approach involves chemotherapy with the regimen of cisplatin plus pemetrexed [18]. The prognosis is poor, with a median survival between 10 and 13 months [19, 20].

Most cases of mesothelioma are attributed to occupational or environmental exposure to asbestos. The association of mesothelioma and exposure to asbestos fibers had been well documented by Wagner for the first time in 1960 [21]. The risk of mesothelioma onset after exposure to asbestos increases continuously with the time elapsed since exposure. It appears to peak approximately 45 years after exposure for pleural mesothelioma, while for peritoneal mesothelioma, it continues to increase even after exposure period [22]. In general, the incidence of mesothelioma has decreased over the years in the United States in conjunction with the decrease in occupational exposure to asbestos and has remained stable since 2003 [23]. There is approximately 20% of mesothelioma cases in which significant asbestos exposure is not documented, including radiations [24], mineral fibers other than asbestos [25], viruses [26], and genetic factors are other putative causes [27].

The onset of mesothelioma typically occurs in older patients: the average age at presentation is 74 years for pleural mesothelioma and 68 years for peritoneal mesothelioma [28]. For cases that arise at a younger age, considering the long latency period [29], one could hypothesize a genetic predisposition or environmental exposure to carcinogenic mineral fibers rather than asbestos exposure alone. MM shows a dose-responsive asbestos exposure in reaction to cumulative asbestos exposure [30, 31]; however, MM can also arise following modest and time-limited exposures [32], as well as among family members responsible for washing work clothes contaminated by asbestos [2, 33]. Furthermore, cases of MM resulting from environmental asbestos exposure have been well documented among residents living near industrial sites [34–36], underscoring the presence and pervasive use of asbestos. In the Emilia-Romagna Region, an MM registration activity started in 1996 to monitor the incidence of mesothelioma and evaluate exposure to asbestos with the possibility of creating a network of professionals sensitized on the topic. The National Mesothelioma Registry (ReNaM) was established by Prime Ministerial Decree 308/02; the regional registry was identified as leveraging a network of Regional Operations Centers (CORs).

The Emilia-Romagna COR collects all cases of mesothelioma of the pleura, pericardium, peritoneum, and tunica vaginalis testis from patients residing in the Emilia-Romagna Region at the time of diagnosis. Data collection was initiated in 1996, following the guidelines of the National Registry [36]. This study aims to describe, based on the malignant mesotheliomas registered in Emilia-Romagna, northern Italy (January 1996-June 2023), the mesothelioma trend and asbestos exposure concerning the type of exposure and residence of the exposed individuals.

2. Methods

The study includes all malignant mesotheliomas of the pleura, peritoneum, pericardium, and

tunica vaginalis of the testicle occurring in the resident population of Emilia-Romagna from 1 January 1996 to 30 June 2023. For each registered case, detailed anatomical-pathological reports and the medical records from relevant hospitalizations conducted at public and private healthcare facilities, within or outside the region, are acquired and reviewed by COR staff. The diagnostic classification of each case is determined according to the guidelines established by the National Registry [36] (Table S1-A) and includes only MM defined as certain, probable, and possible. Information concerning asbestos exposure, both occupational and non-occupational, is collected through an analytical questionnaire administered to patients or their closest family members by the sanitary personnel of the Public Health Departments, constituting the regional survey network. A panel of experts subsequently evaluates the questionnaire responses, and exposure classification is conducted again according to the national guidelines [36] (Table S1-B). This study includes exposures classified as categories 1-7 only.

Descriptive analyses of patient characteristics by sex, age of diagnosis, tumor site, and the province of residence were reported. The standardized incidence rate for the provinces was calculated. Population estimates, used to derive rates, are represented by the general population of the Emilia Romagna region registered on 1 January of each year. Incidence rates were adjusted to the 2013 European standard population and calculated per 100,000 person-years. Exposure levels were categorized by distinct periods (1996-2000, 2001-2005, 2006-2020, 2011-2015 and 2016-2019). 2020-2023 was excluded from the analysis due to ongoing data collection activities. Analyses were performed using STATA 16.1 software.

3. Results

Between 1 January 1996 and 30 June 2023, 3,513 cases of MM were registered (Table 1).

Predominantly, 72% of cases were diagnosed in males, with 79% occurring in individuals aged 65 and older, representing a median age of 72.5 years, and 22% are residents in Bologna.

Table 1. Emilia-Romagna Mesothelioma Registry 1996-2023. Cases by sex, age, province, and site.

	n	%
Overall	**3,513**	
Sex		
Female	977	27.8
Male	2,536	72.2
Age group		
0-44	50	1.4
45-54	159	4.5
55-64	526	15.0
65-74	1,111	31.6
75+	1,667	47.5
Province		
Bologna	774	22.0
Forlì-Cesena	250	7.1
Ferrara	342	9.7
Modena	391	11.1
Piacenza	298	8.5
Parma	408	11.6
Ravenna	364	10.4
Reggio Emilia	528	15.0
Rimini	158	4.5
Site		
Pleura	3,225	91.8
Peritoneum	256	7.3
Pericardium	10	0.3
Testicular	22	0.6
	mean	**sd**
Age at diagnosis	72.5	10.7

Concerning site distribution, 3,225 cases (91.8%) involved the pleura, while 256 cases (7.3%) affected the peritoneum. Smaller proportions were registered for pericardial (10 cases, 0.3%) and testicular (22 cases, 0.6%) mesotheliomas.

A detailed investigation through 2,226 questionnaires administered from 1996 to 2019 revealed evolving trends in asbestos exposure (Table 2). Occupational exposure was predominant across all periods, increasing from 70.7% in the initial period (1996-2000) to 87.9% in the most recent

Table 2. Emilia-Romagna Mesothelioma Registry. Years 1996-2019. Definition of the 2,226 questionnaires by year and type of exposure.

	Occupational exposure		Non-occupational exposure		Unexposed		
	N	%	N	%	N	%	Total
1996-2000	210	70.7	34	11.4	53	17.8	297
2001-2005	329	79.5	44	10.6	41	9.9	414
2006-2010	367	78.4	56	12.0	45	9.6	468
2011-2015	505	87.8	62	10.8	8	1.4	575
2016-2019	415	87.9	55	11.7	2	0.4	472

Table 3. Emilia-Romagna Mesothelioma Registry. Years 1996-2019. Definition of the 2,077 questionnaires (only exposed to asbestos) by year and subtypes of exposure.

	1		2		3		4		5		6		Total
	n	%	n	%	n	%	n	%	n	%	n	%	
1996-2000	120	49.2	52	21.3	38	15.6	21	8.6	9	3.7	4	1.6	**244**
2001-2005	224	60.1	52	13.9	53	14.2	27	7.2	12	3.2	5	1.3	**373**
2006-2010	267	63.1	58	13.7	42	9.9	36	8.5	9	2.1	11	2.6	**423**
2011-2015	353	62.3	89	15.7	63	11.1	41	7.2	16	2.8	5	0.9	**567**
2016-2019	275	58.5	77	16.4	63	13.4	36	7.7	9	1.9	10	2.1	**470**

1 occupational certain; 2 occupational probable; 3 occupational possible; 4 familial; 5 environmental; 6 non-occupational.

period (2016-2019). This upward trajectory persisted despite the progressive increase in questionnaires administered over time (Table 2). Conversely, non-occupational exposure exhibited a consistent pattern of stability throughout the study period, around 11%. Finally, cases with sufficient documentation but without a defined exposure to asbestos decreased substantially from 17.8% during the initial period to only 0.4% in the final period.

Excluding the 149 not exposed, Table 3 shows the trend over time based on an analysis focusing solely on exposed individuals divided by exposure levels. *Specific occupational exposure* has demonstrated an upward trend, increasing from 49.2% in the first period to 62.3% and 58.5% in the last two periods. Conversely, *probable occupational exposure* decreased from 21.3% to 16.4%, while possible *exposure* decreased from 15.6% to 13.4%. *Family exposure* remained relatively constant at around 8%. *Environmental exposure* decreased slightly from 3.7% to 1.9%, whereas *non-occupational exposure* remained stable at approximately 2%.

Among patients with only occupational exposure (1,826 cases) (Table 4), a substantial majority were male (87.4%) and belonged to older age groups, specifically 35.6% aged 65-74 years and 41.1% aged 75 or older.

When examining the province of residence among patients with occupational exposure, we observed that 21.9% resided in Bologna, 16.7% in Reggio Emilia, and 11.7% in both provinces of Parma and Ravenna. However, when assessing exposure rates for the province of residence, Reggio Emilia emerged with the highest rate of occupational exposure (2.5 x 100,000 residents), followed closely by Ravenna (2.3 x 100,000 residents) and Parma and Piacenza, which exhibit similar exposure rates at 2.2 x 100,000 residents. Considering the differences between sexes, the provinces with the greatest male exposure are confirmed as Reggio Emilia, Ravenna,

Table 4. Emilia-Romagna Mesothelioma Registry. Years 1996-2019. Definition of the 1826 questionnaires (only occupational exposures to asbestos) by sex, age, province of residence, and tumor site.

	Total			Males			Females		
	n	%	TSD	n	%	TSD	n	%	TSD
Overall	1,826								
Sex									
Females	230	12.6							
Males	1,596	87.4							
Age group									
0-44	24	1.3		23	1.4		1	0.4	
45-54	93	5.1		72	4.5		21	9.1	
55-64	309	16.9		276	17.3		33	14.4	
65-74	650	35.6		563	35.3		87	37.8	
75+	750	41.1		662	41.5		88	38.3	
Province									
Bologna	400	21.9	1.7	353	22.1	2.5	47	20.5	0.3
Forlì-Cesena	124	6.8	1.4	115	7.2	2.2	9	3.9	0.1
Ferrara	177	9.7	2.0	162	10.1	2.8	15	6.5	0.2
Modena	165	9.0	1.0	145	9.1	1.6	20	8.7	0.2
Piacenza	148	8.1	2.2	127	8.0	3.0	21	9.1	0.3
Parma	214	11.7	2.2	174	10.9	2.9	40	17.4	0.6
Ravenna	213	11.7	2.3	201	12.6	3.3	12	5.2	0.2
Reggio Emilia	307	16.8	2.5	247	15.5	3.7	60	26.1	0.7
Rimini	78	4.3	1.1	72	4.5	1.8	6	2.6	0.1
Site									
Pleura	1711	93.7		1,504	94.2		207	90.0	
Peritoneum	101	5.5		78	4.9		23	10.0	
Pericardium	4	0.2		4	0.3		0	0.0	
Testicular	10	0.6		10	0.6		0	0.0	

and Piacenza. The provinces with the highest exposure for females are Reggio Emilia and Parma, followed by Piacenza and Bologna.

4. Discussion

This study aimed to describe the trends of malignant mesothelioma and asbestos exposure in northern Italy. The work included 3,513 cases of malignant mesothelioma occurring in Emilia-Romagna from January 1996 to 30 June, 2023. The analysis of 2,226 questionnaires from 1996-2019 documented occupational exposure in 82% of cases, non-occupational exposure in 11%, and 7% of cases were declared unexposed.

These findings highlight the persistent public health challenges associated with asbestos exposure, prompting a series of considerations.

First, the increase in occupational exposure, particularly within specific sectors like construction and metalworking, underscores the persistent risk despite regulatory measures. Our analysis revealed an increasing trend in occupational exposure over time, rising from 71% in the first period to 88% in the

last period. Conversely, non-occupational exposure remained stable, with a decline in the proportion of unexposed subjects, dropping from 18% to 0.4% in the most recent period. However, it is crucial to note that this escalation in exposed cases may be attributed more to improved exposure definition than an actual increase in occupationally exposed incidents. This interpretation is supported by the diminishing number of unexposed subjects over time, from 53 cases in the first period to merely 2 cases in the last period. Additionally, the most significant increase was observed in the category of *specific occupational exposure*, reflecting a rate of 10% over time. This category requires robust documentation to validate exposure, including morphological certainty, immunohistochemical confirmation, and a compatible clinical picture.

The second consideration delves into gender disparities observed in asbestos-related MM, where a clear predominance of cases in males emerged, consistent with global trends [37]. Nonetheless, the lower proportion of female cases in occupations historically linked to asbestos exposure quite clearly explains the difference in the exposure rates. When focusing solely on occupational exposure, our findings confirmed a predominance of male individuals, typically older, and predominantly manifesting pleural mesothelioma.

The geographic distribution of exposed individuals is noteworthy, with the majority residing in the province of Reggio Emilia. This province harbored the highest concentration of asbestos-cement-producing industries across the region, a significant factor in explaining the elevated exposure rates. Furthermore, a substantial portion of these industries' labor force comprises females.

An additional concern deals with the specific asbestos-related industries and occupations associated with an increased risk of malignant mesothelioma, already described in the literature [11,38]. In Emilia-Romagna, specific industries, such as building construction (uniformly distributed throughout the Region), railway rolling stock construction/repair (predominantly in Bologna and Reggio Emilia provinces), metalworking, sugar factories/other food industries, and asbestos-cement product manufacturing (with nearly 80% based in Reggio Emilia province), as well as in the petrochemical hubs located in the provinces of Ravenna and Ferrara were prominently associated with mesothelioma onset.

According to WHO, about 125 million individuals worldwide are highly exposed to asbestos at work, resulting in over 255,000 deaths annually from asbestos-related diseases [39]. Considering E.U. statistics on occupational diseases collected by Eurostat, 78% of recognized cases of occupational cancer in the E.U. are linked to asbestos [40], and 85% affect males [41].

In Italy, asbestos was extensively used from 1945 to 1992. For instance, in Lombardy during the period from 2000 to 2012, 4,442 cases of MM were recorded with occupational asbestos exposure more prevalent in men (73.6%) than in women (38.2%) [42], figures comparable to those reported in our study (76% and 14%, respectively). Despite the ban on asbestos in 1992, its exposure among construction workers in Italy remains a significant concern. Among over 31,000 cases of MM reported between 1993 and 2018, asbestos exposure was documented in 78.2% of cases, with occupational exposure noted in 69.1% of subjects. In the construction sector, there has been a concerning trend of increasing exposure from 15.8% in 1993-1998 to 23.9% in 2014-2018 [43].

Our study indicates 11% non-occupational exposure, with literature reporting an excess risk for familial (HR 5.4; 95% CI 2.6-11.2) and environmental (HR 6.9; 95% CI 4.2-11.4) exposures, with no significant variation concerning the type of fiber (chrysotile, mixed and amphibolic) [44]. Although environmental exposure appears to be slightly decreasing, it remains a risk for the general population through contact with commercial products containing asbestos (e.g., housing materials) [34]. Notably, data on environmental exposures typically exhibit a male-female ratio of 1, albeit less robust compared to occupational exposures [45]. Presently, approximately 8,200 asbestos-related cancer deaths occur annually, with projections suggesting a rise to approximately 9,700 cancer deaths per year by 2000. [46]. Globally, the burden of mesothelioma continues to increase, with an estimated 34,511 incident cases and 29,251 deaths recorded in 2019. Also, while the burden rate decreased among individuals

under 70, it increased within the population over 80, especially in regions with a high socio-demographic index [47]. Projections based on SEER data for 2008 estimate approximately 2,400 mesothelioma cases, with asbestos identified as the probable cause in 58% of instances. Encouragingly, these data predict that asbestos will no longer be a significant factor in mesothelioma cases after 2042. However, for the period spanning from 2008 to 2042, estimates suggest over 68,000 cases of mesothelioma, with asbestos implicated as the probable cause in 34% of cases [48]. These projections emphasize the enduring impact of past asbestos exposure and the imperative for sustained efforts in prevention, early detection, and comprehensive management strategies to mitigate the future burden of asbestos-related diseases.

Among the strong points of this work, it is highlighted that these are cases with a high percentage of microscopic confirmations (95%), which reflects the attitude of the registry to build a real detection network at the regional level which includes pathologists, pulmonologists, thoracic surgeons, gynecologists and internal medicine doctors, as well as occupational doctors. Such collaboration contributes to the high percentage of extra-pleural tumors observed, surpassing the Italian average, and facilitates the thorough collection of detailed questionnaires. Furthermore, our effort to directly gather patient information, rather than relying on family members, ensures the accuracy and reliability of documentation regarding previous exposures. Given the high mortality rate associated with MM, this approach requires considerable organizational efforts to conduct patient interviews, often managed at home or in hospital settings. This meticulous process underscores the importance of comprehensive data collection in informing effective prevention and management strategies for MM.

The study faces several significant limitations. Its retrospective design introduces biases that may skew findings. Accurately assessing asbestos exposure proves challenging; relying on occupational histories or geographic data may overlook environmental or distant exposures. Mesothelioma's long latency requires prolonged follow-up to detect cases reliably. Small sample sizes outside specific occupational groups limit generalizability. Addressing these challenges demands meticulous study design, rigorous data collection, and interdisciplinary collaboration to provide accurate evidence for informing public health policies and preventive measures.

5. Conclusion

Our study highlights ongoing concerns regarding asbestos exposure in northern Italy, revealing persistent occupational risks, gender disparities, and a global rise in asbestos-related diseases. Moving forward, continued research and comprehensive data collection are crucial for informing effective prevention strategies and improving outcomes for individuals affected by MM and other asbestos-related conditions. Furthermore, such efforts could facilitate improved diagnostic and therapeutic approaches for the patient, rationalize the eligibility for the public insurance entity's privileged protection against work-related injury, and reduce legal disputes over the identification of disease-related effects.

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Supplementary material

Table S1. Diagnostic definition of the level of certainty of malignant mesothelioma (A) and exposure to asbestos (B) according to the guidelines of the National Mesothelioma Registry (ReNaM).

A. Definition of the level of certainty of malignant mesothelioma	
MM certain	Histology presents with characteristic morphological picture, characteristic/suggestive/absent immunohistochemistry + diagnostic confirmation by imaging/clinical discharge diagnosis
MM probable	Histology presents with doubtful morphological picture or cytology with characteristic picture + diagnostic confirmation by imaging/clinical discharge diagnosis
MM possible	Absent histology/cytology, indicative clinical and radiological data + hospital discharge diagnosis of MM
MM to define	"Temporary container" for cases that do not fall into any of the previous levels
Non mesothelioma	Cases deceased for at least two months who do not meet the requirements to be included in the first three levels
B. Definition of the level of exposure to asbestos	
1	reliable professional
2	probable professional
3	professional as possible
4	familiar
5	environmental
6	extra-professional (no 4 and 5)
7	unlikely (not exposed)
8	unknown (no one knows)
9	to be defined (questionnaire to be completed)
10	not classifiable (no interview due to refusal or otherwise)