Trends and projections of pleural mesothelioma incidence and mortality in the national priority contaminated sites of Sicily (Southern Italy)

Trend e proiezioni di incidenza e mortalità dei mesoteliomi pleurici nei siti di interesse nazionale (SIN) della Sicilia

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ABSTRACT

OBJECTIVES: to evaluate short-medium term incidence and mortality projections of pleural malignant mesothelioma (PMM) in Sicily Region (Southern Italy) and in its four National Priority Contaminated Sites (NPCSs).
DESIGN: population-based prediction study.
SETTING AND PARTICIPANTS: PMM cases from 1998 to 2016 registered by the Regional Operations Centre of the Sicilian Region.
MAIN OUTCOME MEASURES: incidence and mortality trends of PMM were estimated for the period 1998-2016 from the relationships among mortality, incidence, and survival. Projections of incidence and mortality rates were obtained up to 2026.
RESULTS: age-standardized incidence rates of PMM in Sicily were estimated to increase in men from 1.4 (x100,000) in 1998 to 2.29 in 2021 and to slightly decrease down to 2.2 in 2026. Women age-standardized rates in the same period are estimated to decrease from 0.52 to 0.27. In Biancavilla, age-standardized incidence rates were estimated to remain stable between 8.1 and 8.0 in men, while crude rates increased from 8.3 in 1998 to 10.7 in 2026. For women, the estimated age-standardized incidence rates are increasing from 3.08 to 6.75. In the three pooled NPCSs of Augusta-Priolo, Gela, and Milazzo, the estimates of age-standardized incidence rates show an initial trend to growth followed by a decreasing trend, both in men and women, down to predicted values in 2016 of 3.0 in men and 0.77 in women. Estimated age-standardized and crude mortality rates show, for both sexes and all areas, similar patterns as those estimated for incidence.
CONCLUSIONS: in Sicily and in the three NPCSs of Gela, Milazzo, and Priolo, incidence and mortality projections are downward in both sexes. In Biancavilla, mesothelioma occurrence is estimated to increase up to 2026, slightly in males and more significantly in females.

Keywords: asbestos, contaminated site industry, mesothelioma, projection, Biancavilla

WHAT IS ALREADY KNOWN

- In Sicily, there were many industrial plants which used asbestos fibres.
- The heavy use of asbestos fibres in different industrial sectors caused, in the last decades, an increase in incidence and mortality for pleural malignant mesothelioma.
- In Sicily, there are 4 National priority contaminated sites (NPCSs), investigated in the Italian SENTIERI study.
- The estimated mortality trend in Italy may decrease starting from 2020-2026.
- Literature shows that a decreasing trend both for incidence and for mortality for pleural malignant mesothelioma will be present 30-35 years after the end of asbestos use.

WHAT THIS STUDY ADDS

- To the Author's knowledge, this is the first comparative analysis on incidence projection trends of pleural malignant mesothelioma (PMM) in Italy and its NPCSs.
- Observed and estimated mortality trends are provided.
- The method used to estimate expected future incidence and mortality trends of PMM appeared to be applicable to data of a rare cancer, such as PMM.
- The burden of PMM should decrease in Sicily in the years 2020-2024 in men; in females, this burden started to decrease in 2012-2014.
- Biancavilla is the only NPCS for which MMP incidence and mortality are expected to increase, especially in females.

RIASSUNTO

OBIETTIVI: valutare le proiezioni dell'incidenza e della mortalità del mesotelioma maligno pleurico (MMP) a breve e medio termine nella Regione Sicilia e nei suoi quattro siti di interesse nazionale (SIN).
DISEGNO: studio predittivo su base di popolazione.
SETTING E PARTECIPANTI: casi di MMP dal 1998 al 2016 registrati dal Centro operativo regionale della Regione Sicilia.
PRINCIPALI MISURE DI OUTCOME: sono stati stimati i trend di incidenza e mortalità del MMP per il periodo 1998-2016 attraverso le relazioni tra mortalità, incidenza e sopravviven-

za. Le proiezioni dei tassi di incidenza e mortalità sono state ottenute fino al 2026.

RISULTATI: si stima che i tassi di incidenza standardizzati per età del PMM in Sicilia aumenteranno negli uomini da 1,4 (x100.000) nel 1998 a 2,29 nel 2021 e diminuiranno leggermente fino a 2,2 nel 2026; nelle donne diminuiranno da 0,52 a 0,27. A Biancavilla, si stima che i tassi di incidenza standardizzati per età negli uomini rimarranno stabili tra l'8,1 e l'8,0, mentre i tassi grezzi aumenteranno dall'8,3 nel 1998 al 10,7 nel 2026. Per le donne, le stime dei tassi di incidenza standardizzati per età prospettano un aumento da 3,08 a 6,75. Nei tre SIN raggruppati di Augusta-Priolo, Gela e Milazzo, le stime dei tassi di incidenza standardizzati per età mostrano in entrambi i generi una tendenza iniziale alla crescita seguita da una tendenza a diminuire, fino ai valori previsti nel 2016 di 3,0 negli uomini e 0,77 nelle donne. I tassi stimati di mortalità standardizzati per età e grezzi mostrano, per entrambi i generi e tutte le aree, modelli simili a quelli stimati per l'incidenza.

CONCLUSIONI: nella regione Sicilia e nei tre SIN di Gela, Milazzo e Priolo, le proiezioni di incidenza e mortalità sono al ribasso in entrambi i generi. Per il sito di Biancavilla, invece, si stima che la presenza di mesotelioma aumenti fino al 2026, leggermente nei maschi e più significativamente nelle femmine.

Parole chiave: amianto, siti industriali contaminati, mesotelioma, proiezioni, Biancavilla

INTRODUCTION

Pleural malignant mesothelioma (PMM) was evaluated by the International Agency for Research on Cancer (IARC) as causally related to the asbestos carcinogenicity; this causal link was initially recognized on the basis of studies published in the Sixties of the last century; for a review, the reader is referred to the most recent evaluation by IARC, from 2012.[1] All asbestos fibres can cause mesothelioma. This relation has been widely confirmed in literature,[2,3] raising also differences in mesothelioma-inducing potency by types of asbestos fibres according to the hypothesis that different fibres may have different probabilities of reaching pleural surfaces when inhaled into the lungs; toxicologic studies[4] and epidemiological data support the hypothesis that fibres such chrysotile may have lower mesothelioma-inducing potential than the amphibolic forms of asbestos,[5] e.g., crocidolite, tremolite, and amosite, whereas chrysotile and amphibole fibres exposures yield risks of the same magnitude for lung cancer.[6]

Asbestos was used in Italy until the ban of 1992,[7] in shipyards, building, thermal insulation, railways, and in many other industrial sectors.[8-10] The industrial use of asbestos has caused in Sicily (Southern Italy), as in other Italian regions, an increase of incidence and mortality from PMM in the last decades.[11] Furthermore, a natural asbestos-like mineral with fluoro-edenitic composition, found in Biancavilla,[12] a town near Etna volcano (Eastern Sicily), has been classified as carcinogenic to humans (Group 1) according to IARC.[13,14] Because of the latter mentioned mineral, which was related to an unusual epidemiological cluster of mesothelioma mortality,[15,16] and of the petrochemical and oil refinery industries operating in this region, four National Priority Contaminated Sites (NPCSs) were identified in Sicily to be of national interest for reclamation activities according to the Italian laws: Biancavilla, Gela, and Milazzo and Priolo.[17] The estimated high proportion of mesotheliomas attributable to asbestos pollution[18] has produced great concern among the local population, medical, and research community and stakeholders[19] in the Italian industrially contaminated territories and, specifically, in the Sicilian NPCS areas. Population-based registration of PMM started in Sicily in 1998 to describe the burden, to monitor the dynamics, and to control the impact of this malignancy and became a regional section, so called regional operating centre (COR), of the Italian National Mesothelioma Registry (ReNaM) in 2003. The registry was established by the Italian Law[20] and a Sicilian Government Act.[21]

Some studies have estimated the effect of cessation of asbestos production on incidence of PMM, generally based on forward projection of trends observed in the previous periods in New South Wales,[22] the United States,[23] South East England,[24] Quebec and Canada,[25] South Korea,[26] and Sweden.[27] The results show a higher incidence rate in men compared to women, and occurrence rates estimated in both sexes are expected to increase until approximatively 30-35 years since the cessation of asbestos use, and then progressively to decrease.

This study aims to evaluate trends and projections of PMM incidence and mortality in Sicily and in its NPCSs after the year 1992, when the Italian law banning asbestos came into force.[7]

MATERIALS AND METHODS
SOURCE OF DATA

All the cases of PMM in the period 1998-2016 were selected from the Sicilian COR.[14,15] The NPCSs are those defined by the Minister of the Environment and Protection of the Territory Legislative Decrees No. 426/98 (Gela e Priolo), No. 468/2001 (Biancavilla) and No. 266/2005 (Milazzo). In the analysis here presented, the Priolo site includes the municipalities of Augusta, Melilli, and Siracusa for consistency with previous studies[28,29] and with the ministerial decree. Both Siracusa and San Filippo del Mela, the latter municipalities included in the NPCS of Milazzo, were characterized by the presence of plants manufacturing asbestos-cement products, a former asbestos-cement plant Eternit, and Sacelit factories, respectively.[30,31]

The Gela NPCS includes the municipality of Gela. The NPCS of Milazzo includes the municipalities of Milazzo, Pace del Mela, and San Filippo del Mela. Finally, the Biancavilla NPCS considers only the municipality of Biancavilla.

The residential history, lifestyles, and professional history of malignant mesothelioma cases registered by the COR were carried out by administering a standard questionnaire directly to the subject or to his/her family members by a trained interviewer;[7] in Sicily, interviews were administered by medical doctors specialised in occupational medicine. For all cases, the COR collects a copy of all the pertinent clinical documentation: medical record with clinical notes, copy of radiographic report and CT scans, copy of the surgical report if any, and a copy of the histological report with specific immunohistochemical determinations.

On the basis of the interviews, the cases are classified by a multilevel standard classification, which allows the presence or absence of asbestos exposure to be assessed with homogeneous criteria. Depending on the diagnostic level, the cases are defined as:

- certain malignant mesothelioma;
- probable malignant mesothelioma;
- possible malignant mesothelioma;
- cases to be defined;
- not malignant mesothelioma.

The morphology is defined and codified according to the International WHO classification and the third edition of the International Classification of Oncological Diseases (ICD-O-3). The case collection and classification methodology based on exposure has been reported elsewhere.[9,10] Specifically, in this study, only pleural mesotheliomas were considered, regardless the level of certainty of diagnosis with exclusion of death certificate only (DCO) cases; therefore, peritoneal mesotheliomas, pericardial mesotheliomas, and mesotheliomas of the vaginal tunic were excluded.

Mortality data in the period 1998-2016, coded according to the 9th revision of the International Classification of Diseases (ICD-9), were obtained from the Regional Causes of Deaths Registry. Survival data for the period of diagnosis 1995-2007 and collected by Regional Network of Cancer Registries were obtained using on-line data published by EUROCARE project.[32]

STATISTICAL ANALYSIS

Incidence and mortality estimates were computed for all ages, for the total of Sicily, for the NPCSs of Augusta-Priolo, Gela, and Milazzo pooled together (industrial petrochemical areas) and for the NPCS of Biancavilla. The estimates of incidence and mortality in the period 1998-2026 of malignant mesothelioma in Sicily and its

NPCSs were computed by the MIAMOD model.[33] The MIAMOD method is based on a retrospective (back calculation) approach that allows to estimate incidence and mortality trends based on mortality and relative survival data, for all causes and for PMM, and on an estimate of relative survival for PMM in the period of interest. These survival estimates were obtained from the EUROCARE project data and extrapolated for follow-up periods beyond 5 years since diagnosis. The relative survival was assumed to be stable throughout the considered period.[8] This method is based on the mathematical relationship between mortality, incidence, and survival holding for an irreversible disease. The incidence assumes a polynomial age-period-cohort model, whose parameters were back calculated using Poisson maximum likelihood regression based on observed mortality.[34,35] The incidence and mortality trends were projected for 10 years starting since the last year of observed mortality (2016) based on the age-period-cohort covariate. Incidence and mortality data for PMM from ReNaM source for Sicily were also considered for descriptive analysis limited to the observation period 1998-2016 and for independent checks of the estimated time trends.

The resident population by sex, age, and calendar year for the study period was obtained from the Italian National Institute of Statistics (Istat). The age-standardized rates were estimated based on the European reference population.

RESULTS

In Sicily, between 1998 and 2016, 1,498 cases of PMM were identified, 1,164 (77.6%) in men and 334 (22.4%) in women, with an M/F ratio of 3.5. The median age at diagnosis was 69 years in men and 70 years in women. Overall, 780 (52.1%) interviews were carried out, 53,9% among men and 45.5% among women, while for 7.3% the interview was non-executable and, in total, 47.9% of the interviews remains to be carried out. Occupational exposure was documented in 70.4% of interviewed men and in 8.1% women. While the extra-working, family, and environmental exposure was higher among women (28.5%) compared to men (3.3%). For 127 men (23.5%) and 62 women (50.4%) the exposure was undefined. Morphology was obtained in more than 89% of patients. The most represented type was the epithelioid (90,523) diagnosed in 63.7% of patients (table 1).

The number of men diagnosed with PMM has increased from 48 in 1998 to 92 in 2016. In women, an average number of 16 cases per year was diagnosed, with wide fluctuations going from a minimum of 6 cases in 1999 to a peak of 30 cases in 2009, making it difficult to identify a definite time trend (table 2).

	MALES		FEMALES	
	No.	%	No.	%
TOTAL	**1,164**	**100.00**	**334**	**100.00**
AGE AT DIAGNOSIS (YEARS)				
20-29	1	0.08	2	0.60
30-39	9	0.77	7	2.10
40-49	35	3.01	17	5.09
50-59	151	12.97	48	14.37
60-69	380	32.65	75	22.46
70-79	445	38.23	115	34.43
80-89	137	11.77	68	20.36
90-99	6	0.52	2	0.60
DIAGNOSIS				
PMM certain	961	82.56	263	78.74
PMM probable	57	4.89	21	6.29
PMM possible	146	12.54	50	14.97
MORFOLOGY (ICD-O)				
90503	167	16.09	46	16.00
90513	111	10.69	17	5.92
90523	661	63.68	202	70.38
90533	94	9.06	22	7.67
Other	5	0.48		0.00
Total	1,038		287	
Unknown	126	10.82	47	14.07
EXPOSURE MODALITY				
Occupational	380	70.37	10	8.13
Non occupational	2	0.37	3	2.44
Familiar	1	0.19	11	8.94
Environmental	15	2.78	21	17.07
Not probable	15	2.78	16	13.01
Unknown*	127	23.52	62	50.41
Total	540		123	
No available information / not classifiable^	624	53.60	211	63.18

* Persons with no identified exposure to asbestos. / *Individui senza alcuna esposizione ad amianto identificata.*

^ Not interviewed or with insufficient information for interview. / *Non intervistato o con informazioni insufficienti per l'intervista.*

Table 1. Pleural malignant mesothelioma cases (number and percentage), by gender, age, level of diagnostic certainty, morphology, and modalities of exposure. Sicily, 1998-2016.
Tabella 1. Casi di mesotelioma maligno pleurico (numero e percentuale) per sesso, età, livello di certezza diagnostica, morfologia e modalità di esposizione. Sicilia, 1998-2016.

YEAR	MALES		FEMALES	
	CASES (No.)	CRUDE RATE (x100,000)	CASES (No.)	CRUDE RATE (x100,000)
1998	48	1.91	12	0.45
1999	49	1.96	6	0.23
2000	53	2.12	11	0.42
2001	54	2.19	16	0.61
2002	47	1.96	21	0.82
2003	50	2.08	21	0.82
2004	62	2.56	29	1.12
2005	47	1.94	12	0.46
2006	50	2.06	11	0.42
2007	62	2.56	21	0.81
2008	61	2.51	12	0.46
2009	66	2.71	30	1.15
2010	68	2.79	20	0.77
2011	74	3.03	24	0.92
2012	60	2.48	21	0.81
2013	82	3.39	23	0.89
2014	73	2.95	14	0.53
2015	66	2.67	16	0.61
2016	92	3.73	14	0.54
Total	**1,164**	**2.65**	**334**	**0.71**

Table 2. Number of cases and crude rates (x100,000, age 0-100 years) of pleural malignant mesothelioma, by gender and year of diagnosis. Sicily Region Mesothelioma Registry, 1998-2016.
Tabella 2. Numero di casi e tassi grezzi (x100.000, età 0-100 anni) di mesotelioma maligno pleurico, per genere e anno di diagnosi. Registro del mesotelioma della Regione Sicilia, 1998-2016.

The crude rates ranged from 1.91 to 3.73 (x100,000) in men and from 0.23 to 1.15 (x100,000) in women. Rates increased by age during the entire period and in both genders, up to a peak in the 75-79 age group (13.29 in men and 3.09 in women), after which the incidence reduced (figure 1).
Figures 2 to 7 show the estimated time trends of incidence and mortality in Sicily, in Biancavilla, and in the

three pooled NPCSs Augusta-Priolo, Gela, and Milazzo, both for men and women. Each graph shows the observed and expected mortality, the expected incidence, and the age-standardized incidence and mortality rates.
Males standardized incidence rates are by far higher than those of women in all the different Sicilian areas under study. The incidence and mortality estimates of PMM up to 2026, based on the observation period 1998-2016, show in the Sicily region expected growing trends in men with a standardized incidence rate from 1.44 (crude rate – CR 1.80) to 2.23 (CR 4.6) cases x100,000 person-years and an age-standardized mortality rate from 1.24 (CR 1.56) to 1.95 (CR 4.1). The age-standardized rate is expected to reach its maximum value of 2.29 (CR 4.20) in 2021-2022 and then to decrease. Women show decreasing trends of age-standardized incidence and mortality rates, dropping, respectively, from 0.52 (CR 0.83) to 0.27 (CR 0.60) and from 0.44 (CR 0.72) to 0.26 (CR 0.50) (figures 2 and 3).
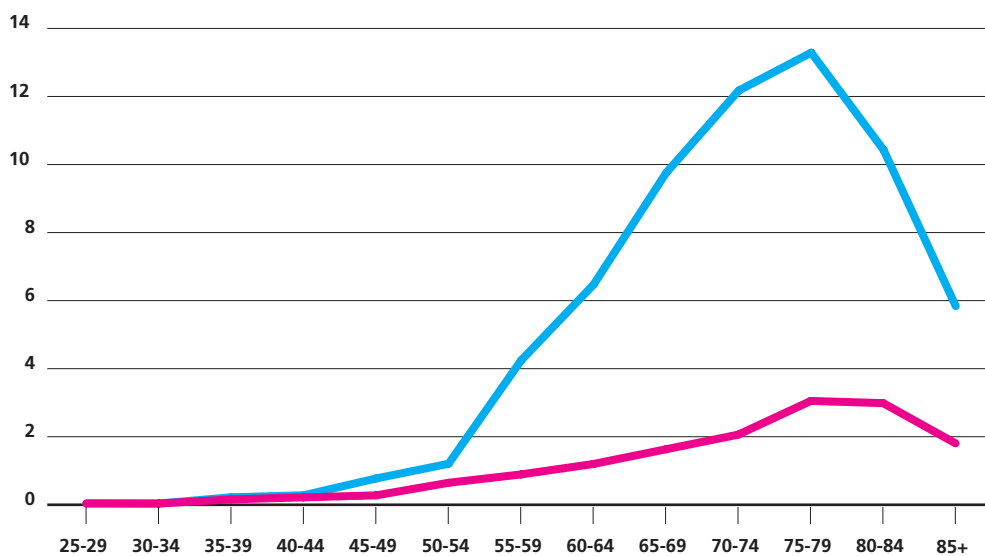
Figure 1. Age-specific incidence rates (x100,000) for pleural malignant mesothelioma. Sicily, 1998-2016.
Figura 1. Tasso d'incidenza (x100.000) specifico per età per mesotelioma maligno pleurico. Sicilia, 1998-2016.
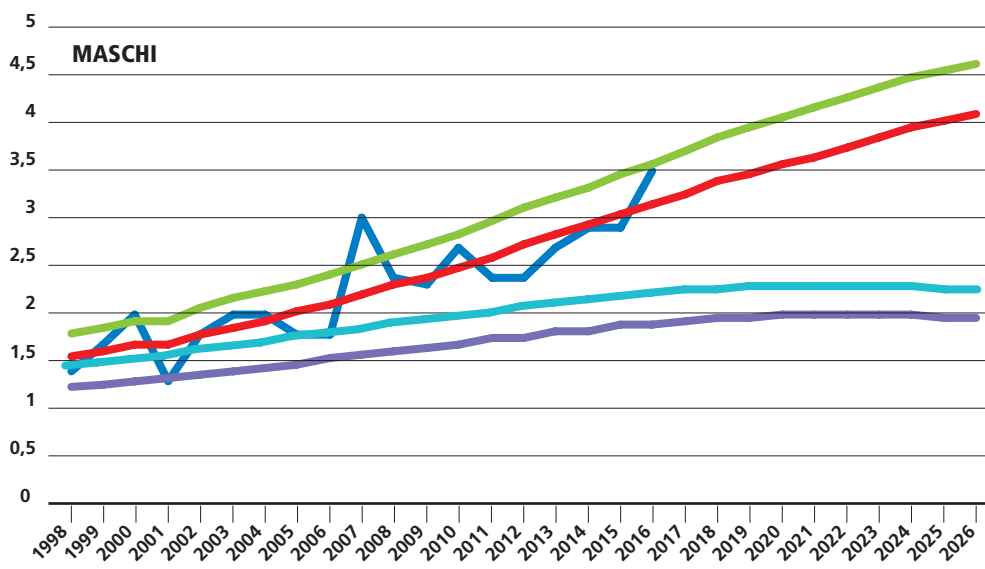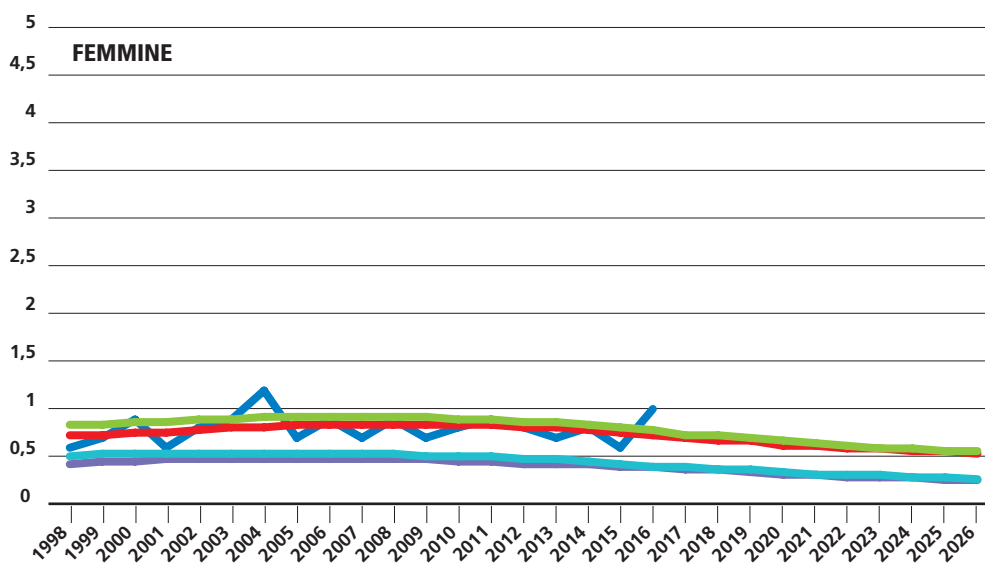
MASCHI
FEMMINE

Figure 2. Estimated mortality and incidence for mesotelioma maligno pleurico. Age-standardized rates (European population) x100,000. Males, age 0-100. Sicily, 2016-2026.
Figura 2. Mortalità e incidenza stimate per pleural malignant mesothelioma. Tassi standardizzati per età (popolazione europea) x100.000. Maschi 0-100 anni. Sicilia, 2016-2026.

MORTALITY
EXPECTED MORTALITY
EXPECTED INCIDENCE
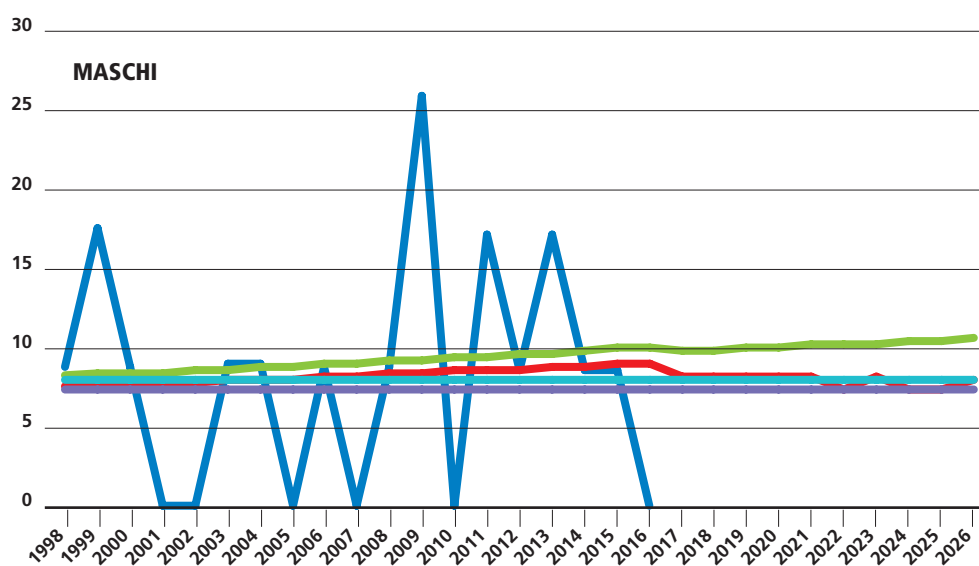STANDARDIZED EXPECTED MORTALITY
STANDARDIZED INCIDENCE

Figure 3. Estimated mortality and incidence for pleural malignant mesothelioma. Age standardized rates (European population) x100,000. Females, age 0-100. Sicily, 2016-2026.
Figura 3. Mortalità e incidenza stimate per mesotelioma maligno pleurico. Tassi standardizzati per età (popolazione europea) x100.000. Femmine, 0-100 anni. Sicilia, 2016-2026.

MORTALITY
EXPECTED MORTALITY
EXPECTED INCIDENCE
STANDARDIZED EXPECTED MORTALITY
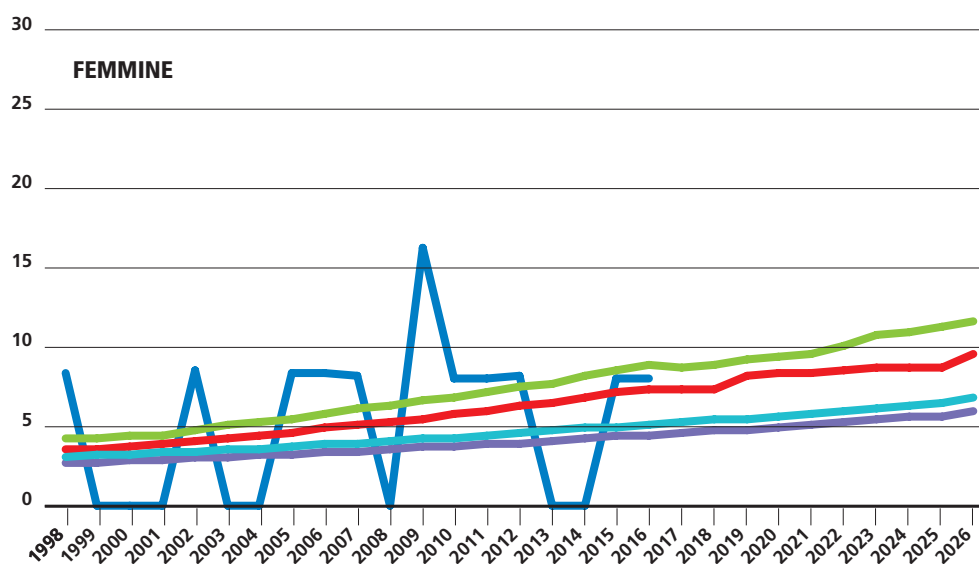STANDARDIZED INCIDENCE

Figure 4. Estimated mortality and incidence for pleural malignant mesothelioma. Age-standardized rates (European population) x100,000. Males, age 0-100. Biancavilla, 2016-2026.
Figura 4. Mortalità e incidenza stimate per mesotelioma maligno pleurico. Tassi standardizzati per età (popolazione europea) x100.000. Maschi, 0-100 anni. Biancavilla, 2016-2026.

Figure 5. Estimated mortality and incidence for pleural malignant mesothelioma. Age-standardized rates (European population) x100,000. Females, age 0-100. Biancavilla, 2016-2026.
Figura 5. Mortalità e incidenza stimate per mesotelioma maligno pleurico. Tassi standardizzati per età (popolazione europea) x100.000. Femmine, 0-100 anni. Biancavilla, 2016-2026.

For the Biancavilla NPCS, the incidence and mortality projections show stable values in men, in which the age-standardized incidence rate will slightly decrease from 8.10 (CR 8.33) to 8.03 (CR 10.7) cases x100,000 person-years. Also the age-standardized mortality rates are expected to very slightly decrease from 7.41 (CR 7.60) to 7.37 (CR 8.10). For women, instead, incidence and mortality for PMM are estimated increasing with age-standardized incidence and mortality rates growing, respectively, from 3.08 (CR 4.19) to 6.75 (CR 11.73) and from 2.68 (CR 3.54) to 5.89 (CR 9.61) (figures 4 and 5).
In the three pooled NPCSs of Augusta-Priolo, Gela,

and Milazzo, estimates of PMM rates show a decreasing trend, both in men and women. In men, with age-standardized rates expected to drop from 3.77 (CR 3.99) to 2.96 (CR 6.40) cases and from 3.32 (CR 3.51) to 2.64 (CR 5.70) deaths x100,000 person-years. In women, the incidence trend shows an initial increasing, in which the age-standardized rates reach the maximum value of 0.98 in 2015 (CR 1.98), before the decrease in 2026 to the value of 0.77 (CR 2:38). Mortality trend closely mirrors incidence trend, with an initial increase up to a maximum value of age-standardized rate equal to 0.85 (CR 1.64) in 2014, and a subsequent tendency to de-
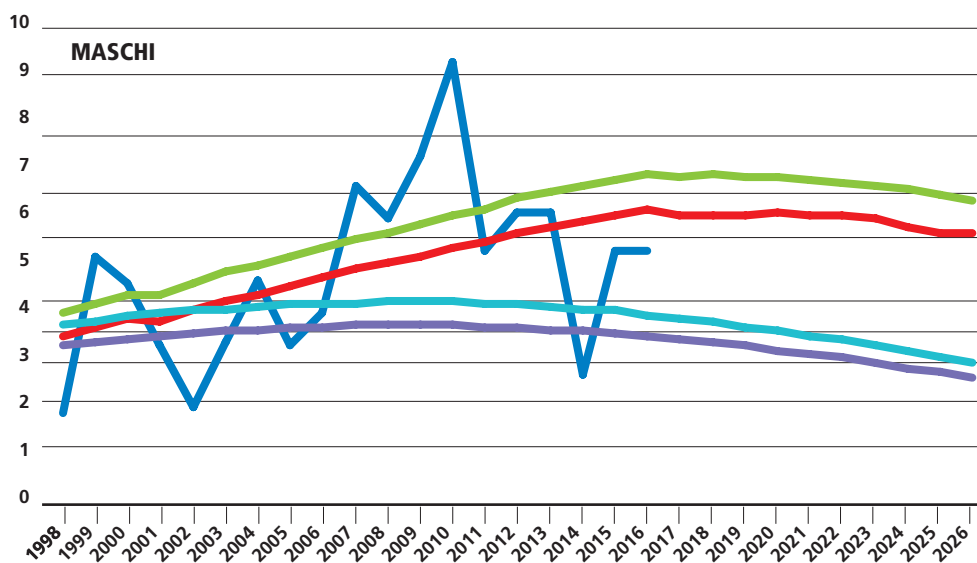
Figure 6. Estimated mortality and incidence for pleural malignant mesothelioma. Age-standardized rates (European population) x100,000. Males, age 0-100. Augusta-Priolo, Gela, and Milazzo, 2016-2026.
Figura 6. Mortalità e incidenza stimate per mesotelioma maligno pleurico. Tassi standardizzati per età (popolazione europea) x100.000. Maschi, 0-100 anni. Augusta-Priolo, Gela, e Milazzo, 2016-2026.

— MORTALITY
— EXPECTED MORTALITY
— EXPECTED INCIDENCE
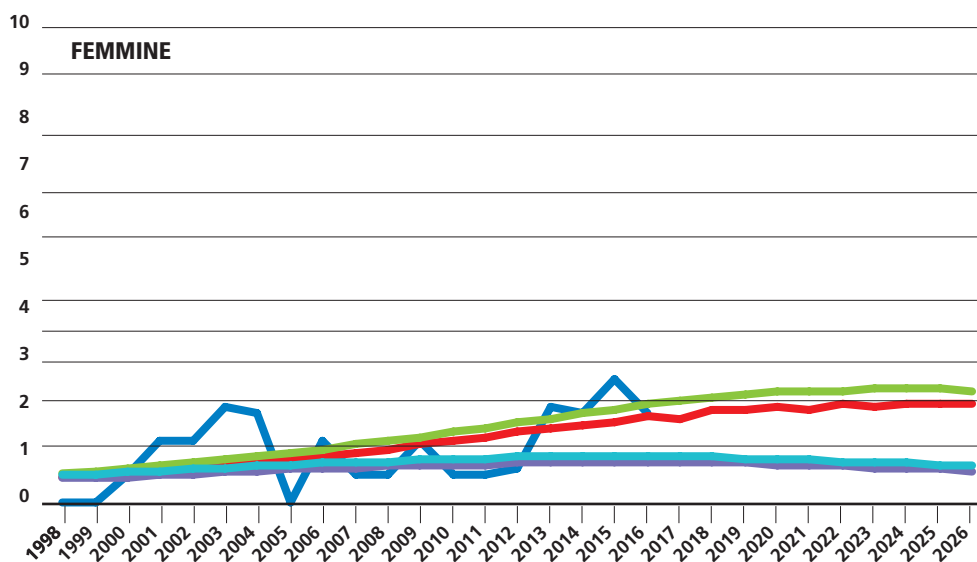— STANDARDIZED EXPECTED MORTALITY
— STANDARDIZED INCIDENCE

Figure 7. Estimated mortality and incidence for pleural malignant mesothelioma. Age-standardized rates (European population) x100,000. Females, age 0-100. Augusta-Priolo, Gela, and Milazzo, 2016-2026.
Figura 7. Mortalità e incidenza stimate per mesotelioma maligno pleurico. Tassi standardizzati per età (popolazione europea) x100.000. Femmine, 0-100 anni. Augusta-Priolo, Gela, e Milazzo, 2016-2026.

— MORTALITY
— EXPECTED MORTALITY
— EXPECTED INCIDENCE
— STANDARDIZED EXPECTED MORTALITY
— STANDARDIZED INCIDENCE

crease up to 0.68 (CR 2.06) in 2026 (figures 6 and 7). The incidence trends estimated through the mortality data were also compared with those directly observed by the ReNaM. The values of mortality observed were also reported in the comparison. Taking into account the 'smoothing' effect inherent in the estimation method, a good overall agreement is observed throughout the period in men (figure 8). The same agreement is highlighted (figure 9) for women in the 2000-2014 period, which however contrasts with a lower incidence observed by the ReNaM, compared to both the estimated incidence and mortality rates, for the first two years (1998-1999).

DISCUSSION

To the best of Authors' knowledge, this is the first comparative analysis on projection estimates of PMM incidence in an Italian region and in its identified NPCSs.[18,26,28,35,36] In addition, observed and estimated mortality trends are provided. The method used to forecast future trends of PM incidence and mortality turned out to be fully applicable to the data on a rare tumour as PM. The present analysis was based on mortality data, considered more stable and consolidated than incidence data provided by the Sicilian Registry, that was established only in the year 1998.
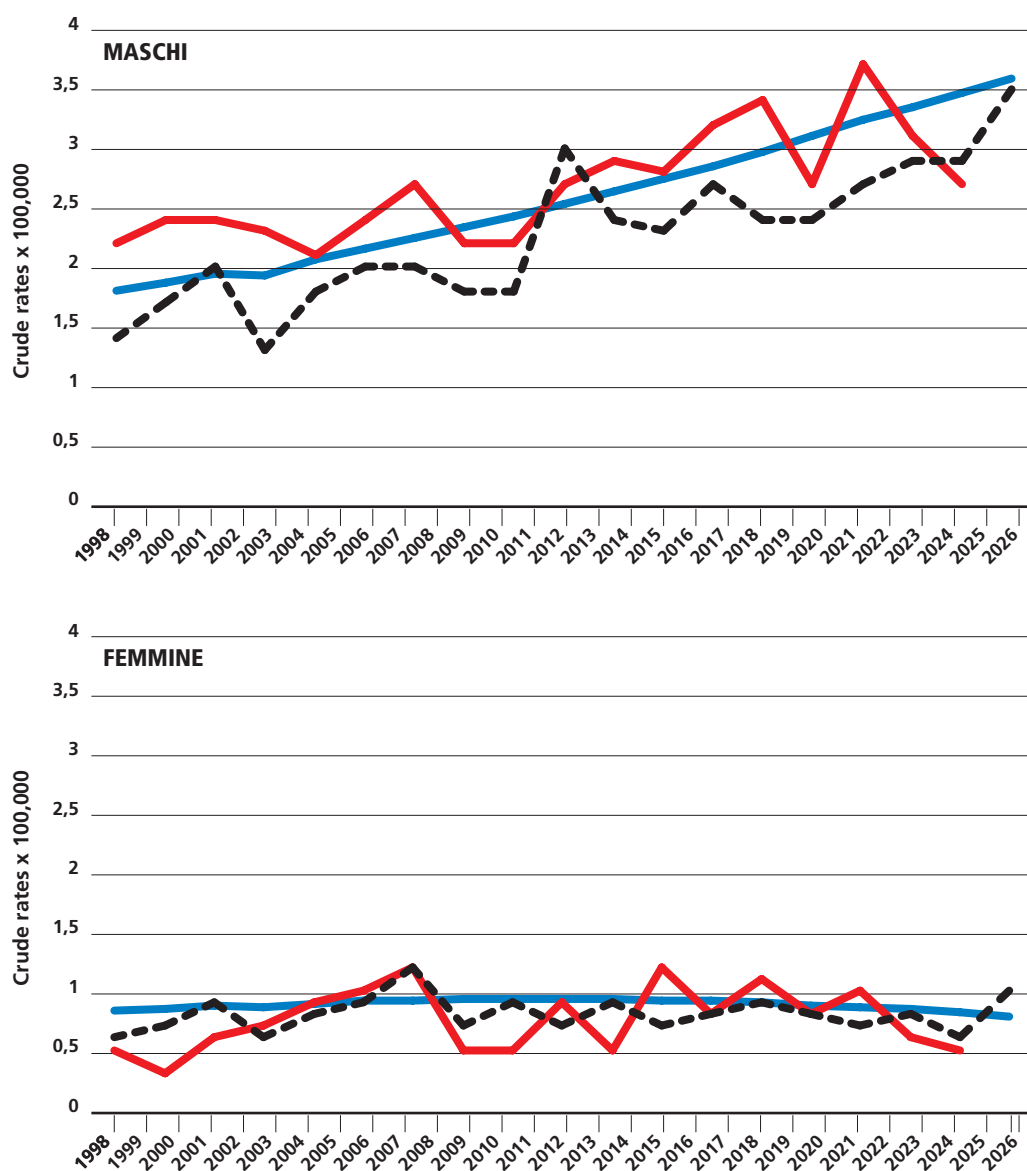
Figure 8. Time trends of mortality for pleural malignant mesothelioma (dotted line), time trends of incidence observed by ReNaM (red line), and estimated incidence by mortality data (blue line). Males. Sicilia, 1998-2016.
Figura 8. Trend temporali della mortalità mesotelioma maligno pleurico (linea tratteggiata), trend temporali dell'incidenza osservata da ReNaM (linea rossa) e stima dell'incidenza in base ai dati sulla mortalità (linea blu). Maschi. Sicilia, 1998-2016.

Figure 9. Time trends of mortality for pleural malignant mesothelioma (dotted line), time trends of incidence observed by ReNaM (red line), and estimated incidence by mortality data (blue line). Females. Sicilia, 1998-2016.
Figura 9. Trend temporali della mortalità mesotelioma maligno pleurico (linea tratteggiata), trend temporali dell'incidenza osservata da ReNaM (linea rossa) e stima dell'incidenza in base ai dati sulla mortalità (linea blu). Femmine. Sicilia, 1998-2016.

Standardised expected mortality and incidence projections are estimated to decrease in Sicily starting from the years 2020-2024 in males, whereas in females they started to decline from 2014 (figures 2 and 3). This earlier downward incidence projection may reflect differences in type of asbestos exposure by gender over time: in female, mainly related to non-occupational and unknown sources.[37] It appears that, in the whole Sicily, the 1992 asbestos ban has been positively affecting PMM occurrences in women more than in men population. Incidence estimates in males appear to be consistent with previous projections of PMM mortality in Italy,[35] showing a decline of mortal-ity after the years 2020-2024. The findings presented in this paper are consistent with the evidences reported in literature: a decrease starts after approximatively 30-35 years since the cessation of asbestos use.[22-27]

In males, the unadjusted expected mortality and incidence rates show that the burden of PMM is continuously increasing in Sicily, because of the eldering of the population across the thirty years of mesothelioma registration. This can be related to the very long latency of this tumour:[9] growing the proportion of old people also the more the probability of PMM onset for those people who had been exposed to asbestos in the decades before the 1992 ban in-

creases. In other words, these findings do not reflect an increased risk apart from that associated to the ageing.

Moving to the Sicilian NPCSs, findings from Biancavilla diverge from those of the other three areas of Priolo, Gela, and Milazzo. This result is not surprising, because the exposure in Biancavilla is related to fluoro-edenite, a natural fibrous amphibole identified in the Etna volcano area located close to this town.[12-15] In Biancavilla, the number of PMM is expected to increase slightly in males and much more in females; in the latter, a doubling standardised incidence rate was estimated: from 3.08 up to 6.75 x100,000, despite of the preventive measures already started in 2001-2003, as a response to the recognition of the NPCS by the Ministry of Environment, the Sicilian Region and the local administrators and public health officials.[19,39] Furthermore, in Biancavilla the proportion of females and that of cases aged less than 50 years are higher than in the rest of Sicily,[12,38] the latter determining a minor effect of statistical age-adjustment. In the other three Sicilian NPCSs of Priolo, Gela, and Milazzo, the asbestos exposures are related to industrial and refinery sources both occupational and environmental. In the years 2016-2026, the expected standardised incidence is estimated to decrease in these NPCSs in both sexes as in the rest of Sicily and in agreement with our literature search; in the present estimates, the decrease of PMM occurrence in males appears to start earlier (2016-2020) than in the rest of Sicily (2020-2024). This may suggest that the Italian asbestos ban in 1992 has influenced PMM occurrence in these industrial areas more than in the remaining Sicilian male population.

LIMITATIONS AND STRENGTHS OF THE STUDY

This analysis has some limitations. Firstly, it is a short-time projection estimate: more than10 years would be needed to encompass the very long time of latency for PMM onset. The latency of mesothelioma, the time elapsed between exposure to asbestos fibres and the diagnosis of the disease is very variable, with the median latency around 44.4 years.[9] A shorter latency period was documented among occupationally exposed subjects (43 years) in comparison to environmentally and household exposed ones (48 years).[9] Nevertheless, it is to be taken into account that the present projections cover 35 years of the hypothetical latency since the ban in 1992. Furthermore, in Biancavilla, where there is a relatively high percentage of patients aged <50 years,[12] our 35 years estimates cover a large lifespan of the local population under 50 assumed to be naturally exposed since birth. Secondly, in the Sicilian dataset (table 1), there is no information about the type of exposure at individual level for 55% of the registered cases,[10] affecting an exhaustive interpretation of the results. This is related to the low response rate to interviews according to

Italian law[20] among the patients and/or their relatives, because of their own unawareness and the low compliance (of the Sicilian Health Authorities) to the procedures to evaluate the type of exposure, which, in turn, are regulated by the Sicilian government laws.[21] Nevertheless, in Sicily, the procedure for exposure estimation, reported elsewhere,[10] and categorization of type of asbestos risk is performed by trained medical doctors specialised in occupational medicine: they follow a rigid protocol according to the above mentioned laws[20,21] which allows a definitive evaluation based, eventually, on asbestos and fluoro-edenite mutual consistency and integration in the case of Biancavilla mesotheliomas.

Despite these limitations, these results give some insights to evaluate the expected short-time incidence and mortality and can be the basis for further investigations. Finally, parametric models are well known[33] to be at risk to provide unreasonable estimates for the years after the observation time period due to the overfitting, i.e., to maximizing the fit of observed data, at the cost of leaving the behaviour of the model totally uncontrolled in the future. To avoid this risk, models with a high number of parameters, even when statistically significant, were not considered and, in any case, all models presenting a change of slope after the last two years of observation 2015-2016 were rejected.

CONCLUSIONS

The burden of pleural mesothelioma is expected to decrease in Sicily from the years 2020-2024 in males; in females, it started to decrease since the years 2012-14. With regards to the three NPCSs of Gela, Milazzo, and Priolo, the projections are downward in both sexes, suggesting some effect of the Italian asbestos ban of 1992 consistently with our Medline search. Only in the NPCS of Biancavilla, the expected mesothelioma occurrence is estimated to increase up to 2026, slightly in males and more substantially in females, making it compulsory to improve epidemiological and clinical surveillance in the population of this town where the underlying cause of PMM has not been eradicated yet. There is a need for further and continuous efforts to be added to the environmental clean-up so far realized in Biancavilla and funded by National Authorities; enforcing the cooperation of local administrators and public health officers appears to be mandatory.

RASSEGNE E ARTICOLI

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