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Past trends and future prediction of mesothelioma incidence in an industrialized area of Italy, the Veneto Region

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ABSTRACT

Background Malignant Mesothelioma (MM) is so associated with (professional, familial or environmental) asbestos exposure that trends in incidence and mortality parallel, after 30–40 years, the trend in asbestos consumption. In recent decades, the industrialized countries have witnessed a steady growth of pleural MM (MPM), following a stabilization or decline in rates in the countries that first adopted restrictive policies. The aim of this study was to evaluate the temporal variations of pleural MM incidence in the Veneto Region of Italy in the period 1987–2010. *Methods* We included only MPM with histological or cytological diagnosis. Age-Period-Cohort (APC) models were used to assess the trend in the incidence of MPM in both genders. Future predictions were evaluated by using a Bayesian APC model. *Results* In the period 1987–2010, 1600 MPMs have occurred. We observe a positive trend in the incidence in the whole period considered. The APC model showed that in both genders the cohort at higher risk is the one born between the years 1940–1945. Future projections indicate that the trend will decrease after the incidence peak of 2010; yet 1234 men are expected to develop a mesothelioma between 2011 and 2026. Among women, the future MPM rates will be stable or slightly decreasing. *Conclusions* The asbestos ban introduced in Italy in the year 1992 as a prospective result will certainly determine a decreasing incidence. However, the extremely long latency of MPM means that its influence is not yet observable.

1. Introduction

Malignant Mesothelioma (MM) is so associated with asbestos exposure, be it professional, familial or environmental, that the trends in incidence and mortality parallel the trend in asbestos consumption, with a latency of 30–40 years [1–3]. Since the end of the World War II, the process of industrialization in western countries lead to the production and use of asbestos products with a peak in the 1970s [3]. The association of mesothelioma with past asbestos exposure is very strong, with an aetiological fraction well over 80% [4–6] that reached 94.9% among occupationally exposed subjects [7]. Because of this strong correlation, many Western countries are currently suffering from a MM epidemic, which reflects the industrial applications of asbestos occurred between the 1940s and 1980s [8–10]. Forecasts of the incidence or mortality from MPM in various countries have proven to be strongly influenced by the asbestos consumption patterns of the past [11–17]. In the last decades we have witnessed a steady growth of MM cases among industrialized countries, following a stabilization or decline in the rates among the countries that first adopted restrictive policies and regulations against asbestos [18,19]. In Italy, from the end of the World War II to 1992 (the year of the asbestos' ban), 5,649,435 tonnes of raw asbestos were consumed, with a peak of about 160,000 tonnes/year between 1976 and 1980 [2]. While in countries such as the United States, Australia, United Kingdom and the Nordic European countries asbestos consumption levelled off during the 1960s and 1970s and then decreased, in Italy, Spain and France, asbestos imports gradually decreased since the 1980s only, the decline thus starting some 10–20 years afterwards [1,20,21]. Accounting for the long latency period for mesothelioma, and depending on times when an asbestos ban or regulations have been introduced, some authors subsequently questioned the appropriateness of previous predictions on mesotheliomas burden and upgraded previous estimates as a consequence of the extreme sensitivity of the models based on APC analyses [1,16,22–24].

The goal of this study is to evaluate the temporal variations in the incidence of MM in the population of an industrialized region of the Italy, the Veneto Region. In the period 1993–2008, the Veneto Region represented 8.3% of all MM cases in Italy, with a

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pleural MM incidence rate of 2.60 per 100,000 person-years (PYs) among males and 0.89 among females in 2008 [2]. The study analyzed the period 1987–2010, and predicted future cases of pleural MM in the short-medium period by using a Bayesian APC model.

2. Materials and methods

2.1. Background

In the last decades, the Veneto Region (Northeast of Italy, 4.5 million of inhabitants, reference year: 2001), had experienced a robust industrial development, gradually accelerating its growth economic rate: in the 1970s, the Gross Domestic Production (GDP) increased more than 30% per year, doubling in two decades; the Veneto Region became the second Italian region for GDP following the Lombardy Region. In the late 90s, the Region reached a full employment. The workers employed in the manufacturing industry almost tripled: from 267,000 workers in 1951 to 378,000 workers in 1961, to 480,000 in 1971 and 617,000 in 1981 [25]. The industrial network was formed by a synergistic combination of large industries (mechanical manufacturing, chemical industry, precision engineering, and shipbuilding) and small-medium factories (jewellery, footwear, eyewear and leather).

2.2. Population

The Regional Mesothelioma Registry is an Operating Centre of the National Mesothelioma Registry (ReNaM) and acts by applying standardized methods [2,26]. MM cases are identified by active search strategies. Enquiries are made at all the hospital departments involved, such as chest surgeries and oncological referral centres, on the files of all pathology units in public and private hospitals, and on the records of hospital discharges. A Cancer Registry is active in the Region since 1987, and covers half of the population. Relevant clinical information is retrieved and evaluated for every possible MM case; eventually, diagnoses are classified in categories of diagnostic certainty. In this study, only MPM defined as "definite" or "probable" were included, that is, when a morphological (cytological or histological) and, if available, immune-phenotypic feature typical of MM was available, or, if not typical, compatible with MM. Data concerning occupational and residential history together with lifestyle habits were obtained by using a standardized questionnaire administered by a trained interviewer. The information was reported directly from the subject (direct interview) or the next of kin (indirect interview) and, only occasionally, through documents. Questionnaire data were gathered trough interviews in 84.6% (1354) of the MPM cases. The Registry may consult public health and safety agencies to gain supplementary information on occupational and residential history of exposure. An industrial hygienist classifies and codifies the asbestos exposure, after examining the collected information [2]. Cases were categorized by exposure circumstance and probability: occupational, non-occupational, not exposed, unknown, not classified and no information; occupational exposure was classified, as definite, probable or possible, considering the probability, intensity and duration of exposure at work during lifetime. Domestic, environmental and hobby exposure to asbestos was defined as non-occupational exposure [26].

2.3. Descriptive analysis

MM cases are described by year of diagnosis, age, gender, and site (pleural, peritoneal) for numerical and categorical variable, respectively (mean and standard deviation (SD) or percentage). A comparison between groups was performed by parametric and non-parametric tests when appropriate.

2.4. Age-Period-Cohort analysis

APC models were used to estimate temporal trends [27,28]. APC models provide an evaluation of the effects of age, cohort of birth, and period of diagnosis on time trend, and on the joint estimation of the Relative Risk of each effect. The data were organized in 18 five-year age groups (from 0–4 to 90+ years old), 6 four-year incidence periods (from 1987–1990 to 2007–2010) and 18 five-year birth cohorts (years 1890–1970). For descriptive purposes, data were analyzed by a log-linear Poisson regression. We fitted the complete APC model to calculate the age-specific incidence rates by birth cohort and period, selecting the best fitting model on the basis of the decrement in residual deviance [29].

We applied a Bayesian procedure to estimate marginal APC effects. The approach combines prior knowledge with observed data to derive a posterior distribution (posterior distribution prior distribution*likelihood), from which we can draw inferences about parameters, or functions of the parameters, to identify the relative contribution of age, period, and cohort to the risk of MPM [30–33]. The algorithm is implemented in the BAMP free software package [32]. A Bayesian APC model provides a more robust methodology compared to a log-linear model, particularly for the prediction of future occurrence [34]. The model has some a priori assumptions: (i) the Risk Ratios (RR) for each effect sum to zero over the observed interval; (ii) the effects have to be constant, so that small deviations from a constant rate are favoured over large ones. The analysis requires parameters ("hyperpriors") to be estimated for the gamma distribution used to model the probabilities, and the model will then attempt to converge to the "true" values. We intentionally started with highly non informative parameters for the Gamma prior distribution (α and β parameters equal to 1 and 0.0005, respectively) in order to avoid the imposition of assumptions for which no a priory knowledge was available. Parameter estimates, their 25–75% and 5–95% Credible Intervals (CI) were obtained by Markov chain Monte Carlo simulations in state-space models using a first order Randow Walk process. The statistical program R 3.0 [35] performed the statistical analyses.

3. Results

In the period 1987–2010, out of 1749 new MM cases arose among the residents of the Veneto Region, 1600 were MPMs (139 from peritoneum, 6 from tunica vaginalis or the testis, 4 from pericardium) and met the inclusion criteria. MPM predominated among males (72.7%), and the average age at diagnosis was 68.2 years (SD = 10.2). MPMs showed a growing trend over time (169 cases in 1987–1990, 404 cases in 2007–2010). Peritoneal MMs decreased from 12.8% in 1987–1991, to 5.6% in 2007–2010 (χ^2 $p = 0.007$; Table 1).

Exposure to asbestos was mostly occupational among male MPM subjects, while females had either occupational or not occupational exposure (χ^2 test $p < 0.001$; Table 2). As expected, very few MPMs occurred before the age of 40 years, and, in both genders, MPM steadily increased at each subsequent age, up to age 79. The last age group accounted for a small number of new cases, whereas about 12.1% of cases occurred in the age 85+ among male gender, 17.6% among female gender. Incidence of MPM among subjects aged less than 50 years showed a decreasing number (from 9.5% in 1987–1991 to 3.2% in 2007–2010; χ^2 $p = 0.009$).

The number of new MPMs steadily increased in all periods (Table 2).

Among male MPMs, an occupational exposure were assessed in more than 70% of subjects with a initial increasing trend and a peak

Table 1
MM cases by site and period of incidence.

Site	Period 1987–1990	1991–1994	1995–1998	1999–2002	2003–2006	2007–2010	Total
Pleural	169 (86.2)	140 (92.7)	238 (88.5)	318 (92.2)	325 (91.8)	410 (94.5)	1600 (91.5)
Peritoneal	25 (12.8)	10 (6.6)	26 (9.6)	27 (7.8)	27 (7.6)	24 (5.6)	139 (8.0)
Testicle	–	–	5 (1.9)	–	1 (0.3)	–	6 (0.3)
Pericardium	2 (1.0)	1 (0.7)	–	–	1 (0.3)	–	4 (0.2)
Total	196	151	269	345	355	428	1749

Table 2
Main characteristics of the pleural MM cases and gender.

Characteristics	Male (n = 1178)	Female (n = 422)	p-Value*
Histology (%(n))			
Desmoplastic	2.9 (34)	0.5 (2)	**0.003**
Epithelial	64.3 (757)	71.1 (300)	
Mixed	14.5 (171)	11.9 (50)	
Sarcomatoid	9.5 (112)	10.2 (43)	
Unknown	8.8 (104)	6.4 (27)	
Age at diagnosis (%(n))			
≤39	0.6 (7)	2.4 (10)	**0.001**
40–49	3.1 (37)	4.5 (19)	
55–59	14.8 (174)	12.1 (51)	
65–69	36.5 (430)	30.3 (128)	
75–79	32.9 (387)	33.2 (140)	
≥85	12.1 (143)	17.6 (40)	
Year at diagnosis (%(n))			
1987–1990	10.2 (120)	11.6 (49)	0.066
1991–1994	9.4 (111)	6.9 (26)	
1995–1998	13.4 (158)	19.0 (80)	
1999–2002	20.4 (240)	18.5 (78)	
2003–2006	20.5 (242)	19.7 (83)	
2007–2010	26.1 (307)	24.4 (103)	
Exposure classification (%(n))			
Occupational	80 (946)	29 (125)	**<0.001**
Non-occupational	4.4 (51)	33.7 (142)	
No exposure	0.6 (7)	2.6 (11)	
Unknown	8.1 (96)	19 (82)	
Not classified, no information	6.6 (78)	14.7 (62)	

* Statistically significant difference by gender in bold.

in the period 1995–1998, followed by a stabilization/decrease. Only in 4.3% of male MPM cases a non-occupational exposure was assessed with a slightly increase in the last periods (Table 3).

In both genders, the full APC model was the best model in terms of minimising the residual deviance (Table 4).

Older age groups expressed the highest incidence rates by birth cohort and by period, with rates up to 6.0 and 2.0 (per 100,000 PYs) among males and females, respectively (Fig. 1). Younger cohorts reported lower incidence rates for all ages both in males and in females. The two genders expressed a clear difference in incidence among youngest age groups: only among men the age groups up to 55 years showed a clear declining trend since 2000. For females the rates appeared to increase steadily in each age-classes considered in all periods.

Considering the age effect estimated by using a Bayesian APC model (Fig. 2), in both genders the age-class with the highest risk was 74–79 (median RR: 25.3 among males, 7.9 for females; reference age-class: 44–49). In both genders the period effect expressed a slight increase. The cohort effect related to men showed an increase for the cohorts born between the 1930s and 1955, with a peak for the one born in 1940–1944 (median RR = 1.79, reference cohort 1920–1925). Among women the cohort effect was similar, even if more sloped (median RR = 1.13). An age-class prediction up to 2011–2026 showed that the MPM incidence among males aged 75–79 and 80–84 is expected to increase with more than 15 cases per 100,000 PYs in 4-year period, while the age-classes before 75 years showed an incidence rate in constant decrease (Fig. 3).

Table 3
Asbestos exposure classification among male pleural MM cases and period of incidence.

	Period 1987–1990	1991–1994	1995–1998	1999–2002	2003–2006	2007–2010	Total
Occupational	75.0 (90)	75.7 (84)	88.0 (139)	82.5 (198)	79 (191)	79.5 (244)	80.3 (946)
Non-occupational	2.5 (3)	4.5 (5)	2.5 (4)	5.8 (14)	5.9 (12)	4.3 (13)	4.3 (51)
No exposure	1.7 (2)	–	0.6 (1)	0.4 (1)	1.2 (3)	–	0.6 (7)
Unknown	10.8 (13)	12.6 (14)	6.4 (10)	6.7 (16)	9.1 (22)	6.8 (21)	8.2 (96)
Not classified, no information	10.0 (12)	7.2 (8)	2.5 (4)	4.6 (11)	5.8 (14)	9.4 (29)	6.6 (78)
Total	120	111	158	240	242	307	1178

Table 4
Comparison of APC sub-models for the MPM incidence by gender in order to separate contributions from each of the time variables.*

Term	Males			Females		
	D (df)	Δ*D* (Δdf)	*p*-Value	*D* (df)	Δ*D* (Δdf)	*p*-Value
Age	248.5			120.2		
Age + Drift	101.4	147.1 (1)	**<0.001**	77.5	42.7 (1)	**<0.001**
Age + Period	48.5	52.9(4)	**<0.001**	71.6	5.9 (4)	0.208
Age + Period + Cohort	36.1	12.4 (4)	**0.014**	58.8	12.8 (4)	**0.012**
Age + Cohort	88.9	−52.8 (−4)	**<0.001**	64.2	−5.5 (−4)	0.243
Age + Drift	101.4	−12.5 (−4)	**0.014**	77.5	−13.2 (−4)	**0.010**

* The sub-models are compared between adjacent lines (using the Δ in deviance and the *F* test); statistically significant difference among models in bold.

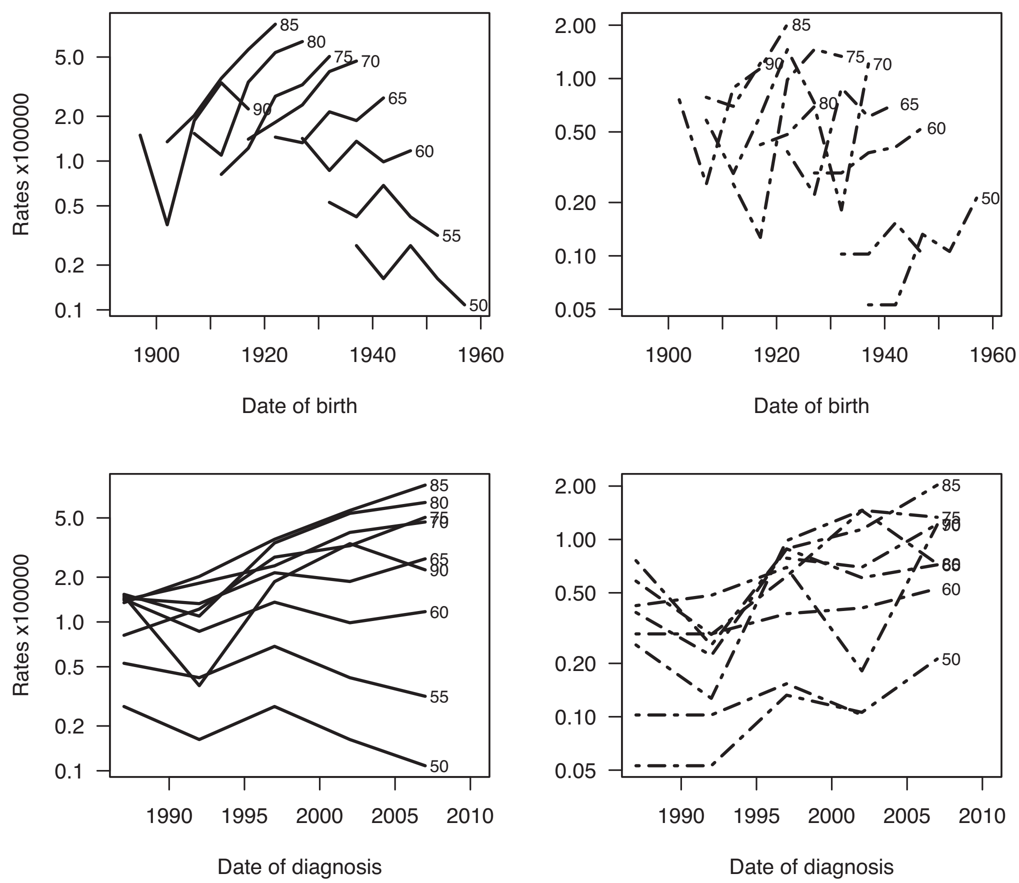

Fig. 1. Age-specific incidence (per 100,000 PYs) by birth cohort (first row) and period cohort (second row) among males (continuous lines) and females (dotted lines).

As for the male gender the peak of incidence was estimated to have been reached in 2010, with a slight decline thereafter. 300 new MPM cases are predicted for 4-year period with a total of 1236 pleural MM cases (95% CI: 890–1626) in the period 2011–2026. Among females, the rate is predicted as stable or in slight increase after a maximum reached in the year 2010: overall 378 MPM cases (5–95% CI: 235–607) are expected in the period 2011–2026 (Fig. 4).

4. Discussion

We assessed the effect on MPM incidence due to the components of age at diagnosis, birth cohort and time period for both genders in the population of a Northern region of Italy. Previous studies based on World Health Statistics Annual on mortality [2,21] reported that, in Italy, the overall the trend in MPM mortality would have been similar to what observed in other European countries [17,36]: the incidence rates were always more pronounced among males, the temporal trends correlated with historical asbestos consumptions, and the increment in incidence was explained in most part by an age-cohort effect with a high risk among oldest age-classes and for cohorts born around the years 1940. Our results suggest that the risk of MPM incidence gradually increased among subjects aged 50 or older, among males being three times higher than among females, and reached a peak at the age 74–79. Only for males we observed a robust cohort effect: the cohort at higher risk was born between 1940–1944, a results fitting with the peak of asbestos consumption occurred in Italy, in the period 1970–1975 [1], and the high proportion of MPM due to occupational exposures [7].

In the Veneto Region, the industrial context is characterized by a large spectrum of industrial productions run by small, medium, and large enterprises. An occupational exposure was detected on a very large proportion of MPM cases (80.1% for males, 29.2% for females), while non-occupational asbestos exposure accounted for 4.4% and 34.1% for males and females, respectively [37]. Raw asbestos or asbestos-based products have been used in the past in

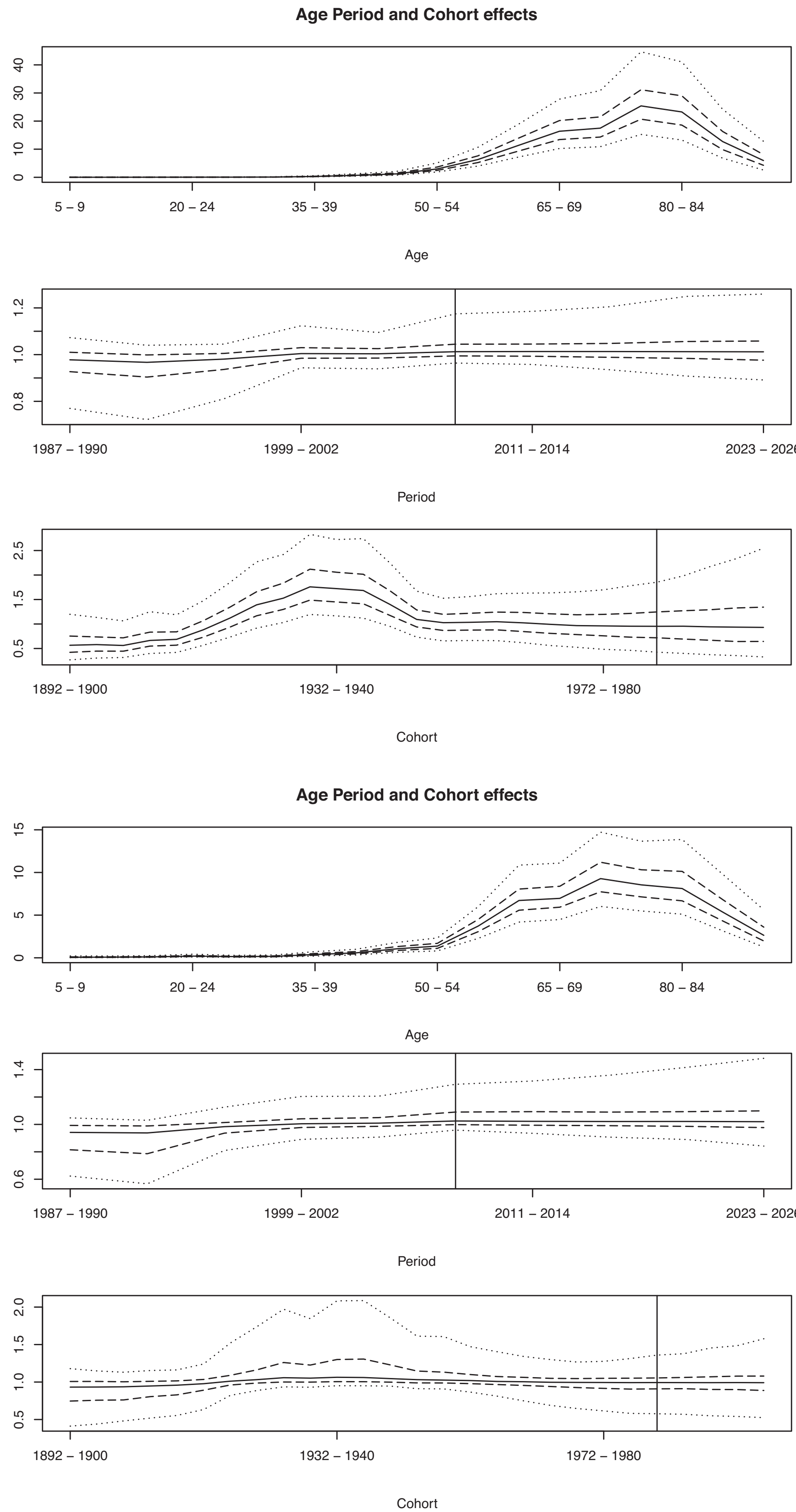

Fig. 2. Age, period and cohort effects from the Bayesian APC model in males (a) and females (b) over the period 1987–2010. Quantiles 5–95 (dashed), 25–75 (light lines) and 50 (bold) of the posterior distribution were added.

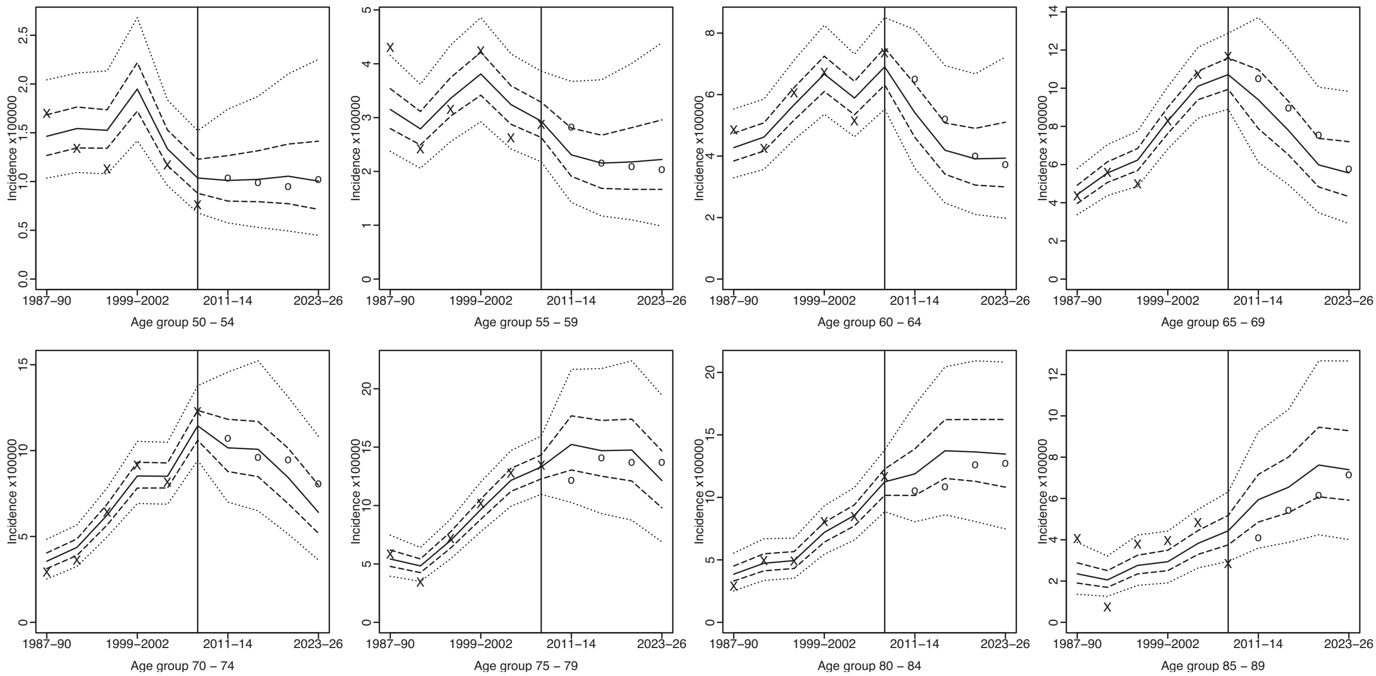

Fig. 3. Age-specific MPM incidence (per 100,000 PYs) in males in 5-year age groups from 50 to 89 years with forecast incidence up to the year 2026. Incidence rates marked with x symbol (predicted rates with o). Quantiles 5–95, 25–75 (dashed) and 50 (continuous) of the posterior distribution were added.

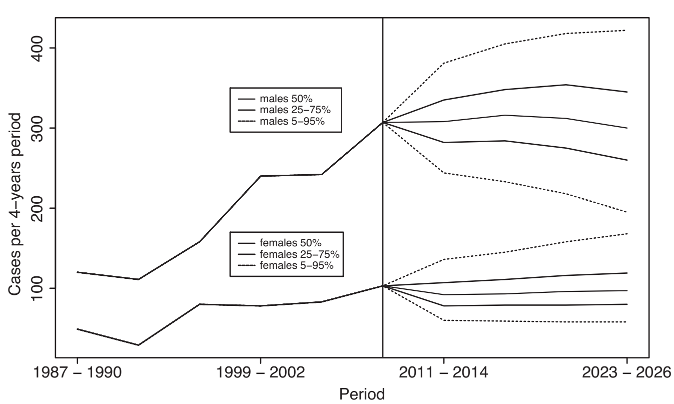

Fig. 4. Observed (up to the year 2010) and predicted (years 2011–2026) MPM cases by gender. Quantiles 5–95 (dashed), 25–75 (light lines) and 50 (bold) of the posterior distribution of the number of cases were added.

several working activities in our Region, such as chemical industry, construction and renovation of rail-road carriages and cars, asbestos-cement industry, shipbuilding, and construction. The textile industry or asbestos-cement production employed a substantial number of women.

For males, the incidence rate and the future burden of MPM showed a marked decrease in some age classes: the decrease has already started in 1999–2002 in the age-classes 50–54 and 55–59, while at older classes the decrease will only begin after the year 2010. Generally, the incidence rate will be more than halved in the next 16 years in the population aged less than 75, a trend similar to that of other European countries [15,16]. For both genders, the incidence peak was expected to occur approximately in the year 2010 that is 5–10 years beforehand projections based on mortality [1].

Our results are in line with estimates in Great Britain [15] and in The Netherlands [16]. Other studies have anticipated the peak in MPM incidence: in 2005 for Spain [14,17], in 2003 for France [20]. An anticipation of the peak in some countries was already evidenced by Montanaro in 2003 [18]. Also outside Europe, the peak has already passed or will soon pass: in the years 2000–2004 in United States [6], in the year 2010 in Australia [38] and between 2010 and 2016 in Japan [39] (the latter study was based on a probabilistic risk model rather than on APC models).

The occurrence of MM among females is seldom presented and predictions are few [15,40]. Following the peak reached in the period 2007–2010, we do not observe a rapid decrease, as previously showed in United States [41] and Norway [42]. In the Veneto Region, a consistent number of cases among women reflected environmental or domestic asbestos exposures.

In the light of several uncertainties, because we restricted our predictions to the year 2026, we cannot state when the decrease in incidence will reach its maximum. Other researchers have suggested that it may occur around the year 2040–2050 in Britain [15], in the USA [6] and in Denmark [43].

The burden of MPM incidence is expected to remain high among both genders for the next 15 years, totalling more than 400 pleural MPM cases at each 4-year period. It is worth noting that the Italian National Mesothelioma Registry suggests that, during the period 2004–2008 a lower occurrence of MPM is evident among the employees of industrial activities heavily exposing to asbestos in the past [2]. This may add evidence that the incidence will decrease in the coming years. However, due to the ageing of the population, in the next 10–15 years the burden of MPM among older ages will remain high.

Our analysis did not consider population dynamics and concomitant risks of other diseases, which are more pronounced in the older age-classes. The decreasing trend among the youngest male age groups will results in a declining trend in future years: the most recent birth cohorts should represent those less heavily exposed to asbestos in comparison with the oldest cohorts, especially if working conditions are considered [22]. Our study is indeed based on incidence, not on mortality due to MPM, thus avoiding the bias inherent in the disease definition and due to changes in ICD codes adopted over time. Instead of the classical log-linear APC model, predictions made with Bayesian APC methods permitted a robust estimation both of the temporal components and of the future predictions [33].

In addition to the delayed effects of asbestos, an increasing trend in MM may be explained by factors that influenced the identification of the disease. In the period under study, there has been an exponential availability of immuno-histochemical tests supporting the microscopic observation of pleural biopsies, leading to improved sensitivity and specificity of the MPM diagnoses.

Our study is limited to a single region of Italy, representative of other Italian industrialized areas. Our evaluation was limited to pleural mesotheliomas: MMs affecting other sites (up to 8.5% of total MM) are also related to asbestos exposure, but they are not considered in this study.

Data about exposure intensity or asbestos consumption patterns are lacking at the regional or national level, impairing the possibility to add these covariates into the models [15,24,43,44]. Positively, the analyses are based on for the first time in Italy on incidence for both genders.

5. Conclusions

Our study showed that the past use of and exposure to asbestos has caused over the last thirty years an incessant increasing trend in the incidence of MPM in an industrialized area of Northern Italy, definitively stronger among the male gender: the peak in incidence may have been reached around year 2010, and the rates are now expected to recede, even if later than in other countries.

Additional 1614 pleural MM cases (1236 males and 378 females) are projected to occur among the residents of the Veneto Region between the years 2011 and 2026.

This information may be helpful in planning surveillance, cure, remediation, and compensation.

Finally, the asbestos ban introduced in Italy in 1992 will certainly contribute to the decreasing incidence as a result of the period effect in future years, but its influence is not yet fully observable.

Author contribution statement

Conception and design: Merler Enzo, Girardi Paolo, Bressan Vittoria.

Analysis and interpretation: Girardi Paolo, Merler Enzo.

Data collection: Merler Enzo, Bressan Vittoria, Girardi Paolo.

Writing the article: Girardi Paolo, Merler Enzo.

Critical revision of the article: Merler Enzo, Bressan Vittoria.

Final approval of the article: Girardi Paolo, Bressan Vittoria, Merler Enzo.

Statistical analysis: Girardi Paolo, Merler Enzo, Bressan Vittoria.

Overall responsibility: Merler Enzo, Girardi Paolo, Bressan Vittoria.

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