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

Paolo Girardi *, Vittoria Bressan, Enzo Merler

Venetian Mesothelioma Registry, Occupational Health Unit, Local Health Authority of Padua, Via Ospedale 22, 35128 Padua, Italy

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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

* Corresponding author. Tel.: +39 049 8214330; fax: +39 049 8214100.
E-mail address: paolo.girardi@sanita.padova.it (P. Girardi).

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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