



Mesothelioma in Italy: the Casale Monferrato model to a national epidemiological surveillance system

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Abstract

The purpose of the present paper is to review the origin and development of the epidemiology of mesothelioma in Italy, starting with the detection and investigation of the major outbreak of the disease observed in Casale Monferrato, Piedmont Region. Over the last four decades, mortality among the cohort of ex-Eternit workers has been measured at three points in time. More recently, population based case-control studies in the area of Casale Monferrato have provided new light on the dose-response curve of the relationship between asbestos exposure and mesotheliomas. The publication of the first Casale Monferrato study had a major impact in the country and contributed to the decision of the Italian Parliament to ban the use of asbestos. The experience of Casale Monferrato represents a lesson in several terms, from the epidemiological surveillance to the health care of the victims and the relationship between epidemiologists, victims, their relatives and residents in contaminated areas.

Key words

- asbestos
- mesothelioma
- prevention
- environmental cleanup
- community empowerment

FOREWORD

The purpose of the present paper is to review the origin and development of the epidemiology of mesothelioma in Italy, starting with the detection and investigation of the major outbreak of the disease observed in Casale Monferrato, Piedmont Region, and ending with an overview of the current national epidemiological surveillance system. The red thread of this analysis is the inextricable connection between epidemiology, prevention and the pursuit of equity in terms of support to affected individuals and communities.

HISTORICAL OVERVIEW

Asbestos mining, manufacture of asbestos-containing products (most important, asbestos-cement) and installation of asbestos containing materials in a wide range of industrial and residential settings have accompanied the industrialization of Italy for most of the twentieth century. In this frame, Piedmont was one of the most affected Italian regions, since it hosted the main Euro-

pean chrysotile quarry (Balangero, operating from 1917 through 1990) and the largest facility for the manufacture of asbestos-cement products (Casale Monferrato, operating from 1907 through 1985); for a historical overview see Vigliani 1991 [1], Carnevale and Chellini 1995 [2], Scansetti 1997 [3], Donelli *et al.*, 2012 [4].

Even if criteria for reducing occupational exposure to asbestos, focused on the prevention of asbestosis, had been provided since the 40s by Vigliani [5] a generalized process of decreasing airborne fiber concentrations took place only three or four decades later, because of the transpose of European legislation in Italy, while prohibition of asbestos use only took place in 1992 [6].

ORIGIN OF THE CASALE MONFERRATO STUDY

The advent of the 1978 health reform and the creation of the National Health Service in Italy prompted a number of local actions based on the principles of preventive medicine which was the core of the reform

itself. Many new activities were launched, particularly in the traditionally industrialized Italian regions. In 1981, the Health Secretariat of Piedmont created the Unit of Cancer Epidemiology in the University Hospital of Turin: one of us (BT) was appointed Head of the Unit (in the previous few years, he had run a non-compulsory course in epidemiology of cancer addressed to interested medical students). At the beginning, the staff included only the Head and one assistant, but the mission of the Unit was a sort of appeal for young medical graduates who had been assigned the responsibility for the safety of the workplaces in several towns in Piedmont. One of these (CM) who had graduated in Medicine with a thesis in cancer epidemiology, had, subsequently, postgraduated in Industrial Health and had started his activity. He was familiar with the occupational problems created by asbestos: in early 1983 he was invited to support a group of workers from the asbestos-cement Eternit factory of Casale Monferrato in a court case on compensation of asbestosis. During this duty, he was impressed by the rumor about a high number of pleural cancers being observed by the local physicians, including some in the non occupationally exposed population.

In order to evaluate this rumor, some (not much) help came from the consultation of the meagre cancer statistics which were available. Indeed, early in the 70s, Italian mortality statistics produced by the Italian Institute of Statistics (ISTAT) were rudimentary: total absolute number of deaths by cause were given by province, with no distinction between sexes and age classes. In a pioneering exercise, these crude figures were used by a handful of brilliant young (in those days) epidemiologists to apply indirect age- and sex-standardization in order to produce mortality rates for the years 1970-72 in Italian provinces. This was the seed of the first Italian Cancer Mortality Atlas, published by the Italian Ligue Against Cancer [7], chaired by Enrico Anglesio, who was also the Director of the Cancer Registry of Piedmont.

ISTAT was using the 7th revision of the International Classification of Diseases. Deaths from cancer of the pleura were included in the wider category of "Other malignant tumours of the respiratory system" (other than cancer of the lung and of the larynx). According to the Atlas, the 6 Italian provinces with the highest age- and sex-standardized mortality rate for such condition (exceeding 3 per 100 000 per year, vs a corresponding rate of 1.9 in the whole country) were Venice, Trieste, Gorizia, Alessandria, La Spezia and Genoa. All but one these provinces were characterized by the presence of shipyards. The exception was the province of Alessandria, which includes the town of Casale Monferrato.

The evidence on asbestos and cancer was summarized in 1972 by the International Agency for Research on Cancer (IARC) that published, in 1973, the first monograph evaluating the evidence of carcinogenicity of asbestos to man [8], which was updated in 1977.

Further, in 1981, the British epidemiologists Richard Doll and Richard Peto, in a report entitled "The causes of cancer" [9] had estimated the proportions of lethal cancers in the United States which could be attribut-

ed to tobacco, diet, occupational exposures and other broad categories of causes.

Worldwide, and particularly in Italy, the report was much (perhaps excessively) criticized, but no argument was raised on the estimate that in the US asbestos exposures in the workplace were responsible for 5% lung cancer. Although the extensive industrial use of asbestos in Italy had started a couple of decades later than in the US, the idea that a sizable number of lung cancers in Italy were asbestos-related was starting to be accepted.

In Piedmont, the news reported from Casale Monferrato, together with the mortality data and the knowledge about asbestos risks were enough to take action. In 1983, Enrico Anglesio and one of us (BT) expressed concern in a letter to the newly elected Mayor of Casale Riccardo Coppo. This coincided with the initiative of a number of physicians of the Santo Spirito Hospital in Casale Monferrato to count the number of hospitalized mesothelioma cases over the previous decade. They totaled more than 70, as reported in a specialization thesis in Pneumology, with crude rates of 35/100 000 person-years in men and 25 in women and over two thirds with no report of occupational exposure. The data were presented at a conference in Casale in 1983. Representatives of the worker unions also reported that they were aware of an epidemics of mesotheliomas and other cancers among workers at Eternit. This was reported to Mayor Coppo in June 1984.

Both Casale Mayor Riccardo Coppo and the Health Secretary of Piedmont Region Sante Baiardi immediately understood the need for more in depth epidemiological studies. They provided the Unit of Cancer Epidemiology in the University Hospital of Turin the financial support that was required to start a set of studies that was coordinated by a joint effort of a group of physicians of Casale Monferrato Hospital and of Turin team. Undoubtedly, without Coppo's and Baiardi's support and the activity of local doctors, the Unit would have never been able to produce the work in Casale Monferrato it was produced. The Unit also had the cultural support of professor of Pathology Giacomo Mottura. Mottura had spent most of his scientific life studying the pathology of pneumoconiosis. In 1943, he and Enrico Vigliani (first professor of Industrial Medicine in Italian universities) had been able to convince the fascist government to legislate about asbestosis as an occupational disease requiring *ad hoc* insurance for asbestos-exposed workers. Indeed, Mottura and Vigliani had taken part in the 1964 Asbestos International conference of the New York Academy of Sciences, where they had reported on the first occupational mesotheliomas observed in Northern Italy. In the scientific milieu, two more persons supported the Unit in its work in Casale Monferrato, one was Lorenzo Tomatis, who originally run the International Agency for Research on Cancer program for the identification of carcinogens for man and later became IARC director during 1984-1994. IARC was most helpful to make the Casale events known outside Italy and to establish international connections with other asbestos contaminated areas. In the late 80s, the Agency also provided the financial support needed to start a population-based registration of in-

cident mesotheliomas in Casale Monferrato. Finally, it should be recalled that in those days, most Italian medical schools were reluctant to recognize epidemiology as a scientific discipline on its own rights. However, in the University of Turin, the Unit of Cancer Epidemiology was repeatedly encouraged to proceed with the work (in Casale and elsewhere) by the Dean of the Medical School, Mario Umberto Dianzani.

The product of the Unit's work is well known. Over the last four decades, mortality among the cohort of Eternit workers has been measured at three points in time. Studies will last until exhaustion of the cohort. At the end of the 80s, the unusual occurrence of mesotheliomas in persons who had never worked at Eternit was so obvious to justify an *ad hoc* exhaustive population-based registration of newly diagnosed cases (which was the origin of the mesothelioma registry in Piedmont currently run by Dario Mirabelli). The collaboration of the Registrar Offices of Casale and surrounding towns was essential in order to create the cohort of Eternit's workers wives. This file is unique in the world. It contributes to assess the dimension of the tragic consequences of work at Eternit on the relatives of Eternit's workers. Finally, more recently, population based case-control studies in the area of Casale Monferrato have provided new light on the dose-response curve of the relationship between asbestos exposure and mesotheliomas.

However, the experience in Casale has been much more than the acquisition of databases to submit to sophisticated epidemiological models. A new perspective of the relationship between public health, local administration and victims of environmental pollution has brought about a solid connection between epidemiologists and asbestos victims, their relatives and residents in contaminated areas. Epidemiologists have learnt to share the purpose of their studies with the latter and with the public health authorities. They have realized that, although estimates of burden of asbestos-related disease are important, priorities include: i) remediation, ii) access of asbestos' victims to the best cancer care centres, iii) research leading to new therapeutic protocols for asbestos related diseases and iv) the request for justice. Through these lines, investigators and public health workers can contribute to the collective resilience. On the other hand, in Casale Monferrato (as well as in the course of other environmental disasters) asbestos victims – even if they did not graduate in Harvard – have shown to be aware of the frailty of science and scientists and to be able to keep it under control.

THE HEALTH IMPACT OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES IN CASALE MONFERRATO

Casale Monferrato is one of the Italian towns with the highest incidence and mortality of malignant mesothelioma [10, 11]. Observed incidence since 1990 has been constantly over 15 times the incidence in Piedmont. In 2010-2014, 121 cases of pleural mesothelioma (certain diagnoses only) were observed in residents in the town of Casale Monferrato, corresponding to incidence rates of 90.2/100 000 person years in men and 45.4 in women [Registry of Malignant Mesothelioma – ReNaM

– of Piedmont, www.cpo.it/it/articles/show/incidenza-e-sopravvivenza-dei-mesoteliomi-1990-2014/]. The outbreak has involved also the residents in several smaller towns close to Casale. Similar results were observed in the reports on spatial analyses of cancer mortality and on mesothelioma mortality in Italian municipalities, that always showed Casale as one of the highest mortality areas [12]. Time-trends suggest that, whereas at the regional level pleural mesothelioma incidence has just levelled-off, not yet showing hints of a decrease, in Casale Monferrato a slow decrease seems to have been going on for some time in both genders [Registry of Malignant Mesothelioma (ReNaM) of Piedmont 2018, www.cpo.it/it/articles/show/incidenza-e-sopravvivenza-dei-mesoteliomi-1990-2014/].

This paper summarizes the results of the epidemiological studies conducted to measure the effect of occupational and residential exposure to asbestos in the area of Casale Monferrato (Italy), where the major Italian asbestos-cement factory was active in 1907-1986 [13]. The previous paragraph has described the initial observations that prompted our research activity.

The asbestos cement factory, owned by Eternit, had an average workforce of over 1000 workers, and was located close to the town center of Casale Monferrato, causing also airborne asbestos contamination in the town. A cohort study of workers active in the plant in 1950 or hired in following years was the first epidemiological investigation, that was conducted in 1986 [14]. It included in its most recent update 3434 workers, of which 777 women, that were followed-up until 2003. A statistically significant increase was observed in both sexes for total mortality, cancers of pleura and peritoneum, lung cancer and asbestosis and for cancer of the ovary in women. Overall, the observed number of deaths exceeded the expected by 38%, corresponding to 497 deaths in excess over a period of 39 years, from 1965 to 2003 years. Incidence of mesothelioma was assessed with the record linkage to the Mesothelioma Registry of Piedmont, part of the ReNaM. In the period from 1990 to 2003, 49 cases of pleural and 23 of peritoneal mesothelioma were observed. Corresponding Standardized Incidence Ratios (SIRs), reference population of Piedmont, were: 34.47 and 178.05 for men and 59.52 and 185.92 for women [15, 16]. A report on the follow-up until 2013 is being prepared.

The plant produced plain and corrugated sheets, tubes, and high-pressure pipes. Raw material included chrysotile and crocidolite: in 1980 the latter represented 10% of the asbestos used and was used mainly in the production of high-pressure pipes. In the same year, total production was about 150 000 tons of final product, and 15 000 tons of asbestos were used. Figures on the amount of asbestos used in previous years are not available. The factory production was reduced and eventually stopped in 1986. Data on airborne asbestos concentration in the plant are limited but show very high exposure. In 1971, concentration of fibers (length greater than 10 microns) was above 12 f/ml in 11 samples out of 22. In 1973 asbestos fiber concentration was in the range 13-15 f/ml in the mixing area, 1.2-1.8 f/ml in the production, and 0.7-1.1 f/ml in

the finishing department. The company reported that working procedures had been improved in 1973 in order to reduce dust pollution, with regular monitoring starting in 1978, when average total concentrations of asbestos fibers were in the range 0.15-1.12 f/ml in the mixing, 0.18-1.05/ml in the production and 0.29-1.09/ml in the finishing departments. Measures repeated in the following years did not show major variations from these averages. However, methodology and sampling criteria used by the company for fiber measurement were criticized as may have led to underestimation of exposure [13]. No facility for cleaning working clothes was available.

Environmental asbestos exposure was documented with studies conducted from mid 1984, when the Eternit plant was already reducing its activity. Casale Monferrato is located in a district whose economy is largely based on agriculture, away from the hinterland of large industrial cities. Apart from Eternit, no other asbestos using industries were ever present in Casale Monferrato (40 000 total population) or in the Local Health Authority (LHA, 100 000 total population). At both the 1961 and 1971 censuses the textile industry employed less than 1% of the population, chemical industries less than 1% and metal works 10%. The Eternit factory was located at about 1000-1500 meters from the town center of Casale Monferrato and at about 500 meters from the nearest residential area. Because of the short distance and of the direction of winds, airborne asbestos contamination occurred within the town, but only limited data are available to quantify it. Marconi *et al.* in 1984 [17] measured asbestos concentration in different city areas using Scanning Electron Microscope (SEM) with fiber identification. Fiber counts resulted in the range of 0.4 (detection limit) to 19.1 f/l. Mean values were 4.5, 5.5, 4.0 and 1.0 in the four sampling points in the city; the lowest figure was measured in the city area farthest away from the plant. The authors observed that while most asbestos fibers were chrysotile, a relevant proportion (in the range 15% to 30%) was classifiable in the calcium-rich amphibole group [18]. Further studies were conducted from 1990 by the LHA and by the Regional Agency for Environmental Protection of Piedmont (ARPA). In March 1990 - July 1991 the LHA in cooperation with the National Institute of Health measured asbestos fiber concentration monthly in 12 sampling sites in the town; fibers were counted by Transmission Electron Microscope (TEM) and identified by energy dispersive X ray analysis. Annual averages were below 1 f/l (only fibers longer than 5 μ are considered), this threshold being exceeded in 12% of samples. The highest concentration was 8.4 f/l. Between 20% and 50% of fibers were of the amphibole type (Internal report, LHA of Casale Monferrato). ARPA measured asbestos concentration in the town area and in surrounding areas with repeated campaigns from 1999. Results showed a progressive reduction in fibre concentration, with values that now are lower than 0.2 f/l [www.comune.casale-monferrato.al.it/flex/cm/pages/ServeBLOB.php/L/IT/IDPagina/3315 and www.comune.casale-monferrato.al.it/flex/cm/pages/ServeBLOB.php/L/IT/IDPagina/1902].

Other researchers investigated asbestos exposure in early '90s with different sampling methods, of limited comparability with LHA and ARPA surveys, however they also confirmed that asbestos concentration in Casale Monferrato was higher than in the other Italian cities considered in the survey [19].

Besides the emission from the plant, a relevant source of exposure in the city was the dispersion of production tailings, in particular from lathing of pressure pipes (so called *polverino* - "fine dust"). The material was given freely to whom was interested and was used mostly for thermal insulation in buildings and hardening of footpaths and courtyards.

Lung burden of asbestos fibers was measured in 41 persons died in 1985-88 in Casale Monferrato hospital. Out of 10 occupationally exposed subjects, 8 showed more than 1000 asbestos bodies/gram (ab/g) dried lung tissue. Of subjects without occupational exposure, 6/31 exceeded 1000 ab/g and 12/31 showed between 500 and 1000 ab/g [20].

Although the results of the cohort study showed an impressive excess of mortality from pleural cancer, it was clear that occupational exposure in the factory explained less than the 50% of the cases in the area. Therefore, further studies were planned for assessing environmental exposure and defining the extent of risk caused by domestic and environmental exposure.

First, a cohort of wives of asbestos cement workers was started to assess the burden of domestic exposure. It included 1740 women who were married to an asbestos cement worker and never worked in the plant. In the most recent update (follow-up period 1965-2003), 21 cases of pleural malignancies were observed, for a Standardized Mortality Ratio (SMR) of 18.0 ($p < 0.01$). No other causes showed a statistically significant increase [21].

Incidence of mesothelioma in the area of Casale Monferrato has been monitored since 1980, first with a retrospective survey and since 1990 by the Piedmont Mesothelioma Registry. Descriptive studies served both for monitoring incidence and as the basis for conducting analytical studies on the local causes of the mesothelioma epidemic.

The first survey of mesothelioma incidence conducted in the period 1980-91 identified 126 cases, of which 75% were accepted at pathological revision. Excluding the cases with occupational exposure, a trend was observed, with the highest rate for Casale Monferrato (8.2/100 000 person-years in men and 5.1 in women), intermediate in the adjacent towns (3.4 and 0) and lowest in the municipalities further away (0.6 and 0.7, similar to reference rates) [22]. This result confirmed the interest on environmental risk factors for mesothelioma in the area and the first suspects of non-occupational mesothelioma cases raised by medical doctors working in the Casale Monferrato Hospital [23].

Three case control studies have been conducted in the area of Casale Monferrato, including the town and the rest of the LHA. These studies confirmed, with different methods and a progressive refinement of the investigations, the association of mesothelioma risk with living closer to the asbestos cement factory, with domestic exposure and with cumulative exposure to asbestos. The



first study included the cases of pleural mesothelioma incident in 1987-93, retrospectively identified. Pleural mesothelioma risk was greatly increased for Eternit workers, with odds ratio (OR) = 52.5 and 95% confidence interval (95% CI) = 12.5-220. Once such occupational cases were accounted for, however, ORs in Casale Monferrato were inversely associated with residential distance from the Eternit factory: they decreased from 27.7 (95% CI: 3.1-247.7) at less than 500 m to 22.0 (95% CI: 6.3-76.5) at 500 to 1500 m, to 21.0 (95% CI: 4.9-91.9) at 1500 to 2500 m, and to 11.1 (95% CI: 1.8- 67.2) at more than 2500 m. Further analyses showed that until a distance of 9 km from the plant, the risk was significantly increased, suggesting other sources of diffusion of asbestos exposure besides airborne transport. The study also showed an increase of the risk for domestic exposure, defined as living with an asbestos exposed worker, and for having attended a grammar school in Casale [24, 25]. Data collection was repeated prospectively in 2001-2006 for a better assessment of exposure and for confirmation of the results. Main results confirmed the previous observations and showed an increase of mesothelioma risk with cumulative asbestos exposure, both including all subjects and in analyses limited to non occupationally exposed subjects [26].

Supporting results were provided by the analysis of exposure histories of cases, carried out according to Re-NaM guide-lines. Interviews and exposure assessment were available for 847 (82%) out of 1039 registered cases of mesothelioma from the Casale Monferrato area, 125 of whom had been employed at the Casale Monferrato Eternit plant (15% of cases with known exposure). Overall, 475 cases (56%) had been considered occupationally exposed, whereas 357 (42%) had been classified as non-occupationally exposed, mostly due either to residential proximity to the asbestos-cement factory ("environmental" exposures: 200 cases) or to living with factory workers ('familial' exposure: 144 cases). Such figures highlight the overwhelming and persisting impact of asbestos contamination in the work-place and in the general environment from asbestos-cement production.

Collection of information on exposure must be accurate and exhaustive and interviews are very demanding for patients and their care-givers. They induce cases to re-examine their life, including their family and domestic environment, with deep emotional involvement and questions on exposures that should have been avoided. A sense of outrage is common, as discussed in other contributions in this issue [27]. Malignant Mesothelioma Registry interviewers expect, by experience, such reactions, but are neither trained nor qualified to detect and meet possible needs of psychological assistance for patients and care-givers, which require dedicated resources. Proper advice on medico-legal aspects regarding recognition and compensation of the disease should also be provided early as part of patients' management by attending clinicians and LHA officers.[28]

The results from Casale Monferrato on the risk for malignant mesothelioma after occupational and environmental asbestos exposure and on the dose response relation with cumulative exposure are in agreement with

other case control studies conducted in other countries. They are a strong documentation of the association of mesothelioma with asbestos exposure in Casale and also provide important scientific and operational information of interest for all asbestos contaminated communities.

A NATIONAL SURVEILLANCE SYSTEM OF PLEURAL MESOTHELIOMA MORTALITY IN ITALY

The publication of the first Casale Monferrato study, the occupational cohort, in 1987 [14] had a major impact in the country because of the size of the mesothelioma excess; further concern in the public opinion was determined in the same years by other unexpected findings, namely those resulting from the epidemiologic studies on railway carriages construction and repair [29] and on non-asbestos textile industry where rags were packed in previously asbestos-containing jute bags [30]. These unexpected findings contributed to the decision of the Italian Parliament to ban the use of asbestos, and also triggered the implementation of a permanent epidemiological surveillance of pleural mesothelioma mortality in Italy, covering 20 Regions, 100 Provinces and over 8000 municipalities [6].

The first report on pleural mesothelioma mortality covered the time-window 1980-87 [31], the subsequent reports covered, respectively, the years 1988-92, 1988-97, 1995-2002 and 2003-09 [32-35]. The recently published last report covered the time-window 2003-2014 [12]. These reports updated the mesothelioma mortality rates at national level and for each Italian municipality, showing temporal trend and highlighting the areas with excess risk, sometimes not previously detected. The most recent report showed, in 2003-2014 period, 13051 deaths for pleural mesothelioma (9397 men and 3654 women), corresponding to an annual standardized rate of 1.77/100 000 inhabitants (2.98/100 000 in men and 0.86/100 000 in women).

The two main findings of this sequence of studies have been the detection of two previously unrecognized clusters of pleural mesothelioma. The first one was located in Broni, in the Province of Pavia (Lombardy), where a major plant for the manufacture of asbestos-cement products had been operating from 1932 through 1993. Broni still now shows a 20-fold excess of mortality from pleural mesothelioma with respect to the Lombardy Region reference population [12]. An occupational cohort study [36] detected an 18-fold excess mortality from mesothelioma. About half of mesothelioma cases detected in Broni are due to environmental exposure, mainly associated with the use of "polverino", a dusty byproduct of the asbestos-cement widely used, in the past decades, as an insulating agent in dwellings or as a material suitable to pave courtyards and country roads [37]. Subsequent to the initial detection of the mesothelioma outbreak in Broni, the town was recognized as National Priority Contaminated Site, and environmental clean-up actions are in progress.

The second major finding of the mortality surveillance concerned the previously unrecognized cluster of mesothelioma in Biancavilla, a rural town located at the slopes

of Etna volcano in Sicily. Subsequent to the detection of a statistically significant excess of malignant pleural cancer mortality in 1988-92 (when the 9th Revision of the International Classification of Diseases was still being used), based on 4 observed cases, an *ad hoc* study confirmed the diagnoses of the causes of death, detected further cases occurred after 1992 and excluded occupational asbestos exposure for most subjects [38]. A substantially equal number of men and women was present in the case-series, and the average age at diagnosis was lower than usual [38]. Amphibolic fibers detected in a quarry located close to the center of Biancavilla, from which material used in the local building industry was extracted, were initially classified as an intermediate phase between tremolite and actinolite, and subsequently as a new mineral fiber, fluoro-edenite [39, 40]. Since 2002, Biancavilla was recognized as a National Priority Contaminated Site [41]. This implied a major environmental clean-up intervention, including termination of quarrying activity, covering quarry area with spritz-beton, paving with asphalt roads previously paved with quarry's by-product material and removal of construction industry waste material close to unfinished buildings in the new districts of Biancavilla. A subsequent study based on 26 mesothelioma cases (13 men and 13 women) diagnosed in the years 1998-2011 and collected by the Sicily Region Operational Centre of the National Mesothelioma Register, showed an overall 5-fold excess mesothelioma incidence over the Sicilian population, that resulted in 20-fold excess incidence among subjects under 50 (based on 5 observed cases, with respect to 0.23 expected) [42]. In the meanwhile it had been shown that fluoro-edenite fibers cause mesothelioma after pleural and peritoneal injection in rats [43]. IARC evaluated as "sufficient" the available evidence of carcinogenic risk to humans [44] and fluoro-edenite was allocated to IARC Group 1 "Carcinogenic for human". In this frame, it is important to notice that the previously summarized environmental clean-up action caused a significant reduction of airborne fiber concentration in the central area of the city [41]. A major public health response of the Sicilian Regional Authorities has integrated the environmental monitoring and clean-up activities. All these interventions have been object of a communication process with the affected community, local administrators, local *media*, school and other stakeholders [45].

Besides the outstanding detection of the two towns of Broni and Biancavilla, both eventually included in the National Priority Contaminated Sites so that environmental clean-up and public health actions might be implemented, the epidemiological surveillance of mesothelioma mortality has pinpointed a number of critical situations in areas characterized by past presence of several asbestos-cement factories, and by naval shipyards including Navy installations, oil refineries, petrochemical plants, steel production, railway carriages production and repair plants, textile industries, power plants including geothermal facilities, warfare chemical industries [12]. The information produced by this surveillance system is helpful in order to estimate the burden of asbestos disease in Italy 25 years after the asbestos ban, to detect "active" sources of asbestos

fibers for which environmental clean-up still has to be implemented and, last but not least, to address mesothelioma patients to the best treatment centers, and to concurrently assist them in terms of access to compensation and legal support in cases of civil litigations or criminal trials.

NATIONAL SURVEILLANCE SYSTEM OF MALIGNANT MESOTHELIOMA INCIDENCE AND EXPOSURE ASSESSMENT

In addition to mesothelioma mortality surveillance, since 2002, an epidemiological surveillance of mesothelioma incidence has performed in Italy by the National Register of Malignant Mesotheliomas (Registro Nazionale dei Mesoteliomi, ReNaM in Italian).

The epidemiology of mesothelioma incidence in Italy can be described by the means of figures provided by the National Register of Malignant Mesotheliomas (ReNaM). The structure of the network, the procedures for retrieving cases and for assessing exposure are briefly described forward, with the principal aim of underlying the faculty of improving the level of health protection for workers and general population.

ReNaM is a national surveillance system of mesothelioma incidence, active with force of law since 2002, devoted to identify cases and to assess asbestos exposure modalities. An Operating Centre in all 20 Italian regions (COR, *Centro Operativo Regionale*), works applying standardized methods, as described in the national Guidelines [46]. CORs retrieve information about incident malignant mesothelioma (MM) cases from health care institutions potentially involved in diagnosis (chest surgery wards, pathology and lung care units) and classify the reliability of diagnoses according to 3 classes of decreasing level of certainty: certain (if histological confirmation is available), probable (if cytological confirmation is available) and possible MM (only radiological and clinical evidences). The complete diagnosis coding system has been described extensively elsewhere [47]. The circumstances and categories of industrial activities implying asbestos exposure are routinely defined by the means of a standardized questionnaire, administered to the patient (or to the next of kin) by a skilled interviewer. The reliability of the assessment of occupational exposure is qualitative and classified as definite, probable or possible. The non-occupational modalities of exposure considered are: environmental exposure (due to the residence near a source of asbestos pollution without work-related exposure), familial exposure (when patients have lived with a cohabitant occupationally exposed) and leisure activities exposures (other non-occupational exposures like those due to leisure-time activities).

Between 1993 and 2015, ReNaM has collected 27 356 incident MM cases. Certain MM represent around 80% of detected cases. Incident case list for 2015 is ongoing. More than 90% of collected cases are localized in the pleura (93%), peritoneal MM cases are 6.5% (5.3% and 9.4% in men and women respectively) and pericardial and tunica vaginalis testis MM cases are very rare (58 and 79 collected cases respectively among the entire ReNaM archives). The modalities of exposure to asbes-

tos have been investigated for 21 387 MM cases (78% of detected cases). An occupational exposure has been defined for around 70% (14 818) of cases investigated by the anamnestic questionnaire. Non-occupational exposure is still relevant with 4.9% of cases for which a familial exposure has been detected and 4.4% of cases with an environmental exposure. The epidemiological findings have been extensively described and discussed in ReNaM reports [48].

The epidemiological surveillance of malignant mesothelioma incident cases, by the means of a national register estimating the occurrence of the disease and identifying the circumstances of asbestos exposure, is a relevant tool for preventing asbestos exposure, for estimating reliable epidemiological figures and for identifying possible sources of contamination still in place after the ban. The forecast scenarios for MM epidemic curve have been evaluated according to a model including asbestos consumption before the ban [49], estimating the peak of disease trend in the period 2015-2020. The territorial clustering of incident cases have been identified and discussed, based on collected cases and asbestos exposure qualitative assessment provided by CORs [10]. The geographical distribution of MM cases is a sort of map of the industrial use of asbestos before the ban in 1992, demonstrating that a higher than expected incidence of mesotheliomas has been observed in areas with direct use of asbestos as the naval shipyards, asbestos-cement plants and other industrial activities, such as railways carriages maintenances. Nevertheless, asbestos exposure in civil buildings, such as public offices or schools, where subjects have no awareness of contact with asbestos-containing material, could be a still real concern, such as occupational exposure due to unexpected sources of contamination [50]. Recently an extensive analysis of MM incidence in Italian national priority contaminated sites (NPCSS) has been performed [51], showing an overall excess of 1531 cases in these areas, in the period 2000-2011. It is remarkable that mesothelioma occurrence resulted higher than expected also in sites for which asbestos was not explicitly cited as contaminant in the official documents. The estimate of the financial burden of mesothelioma is a public health topic and it can enforce the awareness regarding the economic advantage of the ban in countries with still a current use of asbestos. According to an inclusive econometric model, elsewhere described in details [52], an estimate of 33 000 and 25 000 euros per patient for medical care costs and for insurance and compensation costs respectively, has been provided. The most relevant extent of indirect costs, generally neglected, refers to productivity loss that can be quantified around 200 000 euros per patient.

The systematic epidemiological surveillance of asbestos related diseases incidence and the analyses of asbestos exposure modalities is a relevant tool for increasing the effectiveness of insurance and welfare system. The substantial proportion of workers with tumors of occupational origin who do not seek compensation and the consequent underestimation of the occupational cancer burden in insurance statistics is a real concern in many countries [53]. The crucial role of epidemiologic find-

ings to support and stimulate the reliability and effectiveness of the insurance system has been shown [54]. ReNaM has repeatedly provided evidences of the extent of mesothelioma epidemic in Italy and the forecast scenarios of the disease trend and peak have been discussed in an epidemiological framework. These figures have been critically discussed in comparisons with data from the public insurance system, improving the awareness of the occupational origin of the disease.

Furthermore, the distribution of economic sectors involved in exposure has been made available in ReNaM reports and research papers, underlying the wide spectrum of occupational circumstances of possible exposure. Italy was one of the main asbestos producer and user country until the ban in 1992 and the range of economic activities with a risk of exposure for workers is not only related to the industries with a direct use of asbestos as raw materials, but includes a great variety of economic sectors, sometimes unexpected and remarkable. In this context, one of the roles of epidemiological surveillance, providing evidence of this large spectrum of activities involved, is to improve the capacity of the welfare system to recognize all possible circumstances of asbestos exposure. More in details, the heavy asbestos exposure suffered, before the ban, by workers during the maintenance and disposal of insulation from railway carriages is well known. The asbestos-cement industry and shipbuilding and repair provide the most detailed published studies on account of the number of plants involved and exposed workers in Italy. Workers in these sectors, clinicians and public opinions are well informed about the occupational origin of the disease. In contrast, where workers have been exposed to asbestos in unexpected and scarcely recognized occupational circumstances – such as maintenance workers in the chemical industry and construction workers – the probability of seeking (and receiving) compensation is much smaller.

Consequently, the systematic dissemination of information regarding all occupations involved in asbestos exposure, as provided by ReNaM, is a relevant tool for contributing to improve insurance system effectiveness. In the countries that have banned asbestos, the majority of asbestos-related diseases are caused by occupational exposure that occurred before the ban. Nevertheless, the assessment of the effects of non-occupational asbestos exposure is great point of attention for the public interest. ReNaM data demonstrate, confirming to previous reliable findings of analytical epidemiological studies, that living with asbestos workers or close to asbestos mines or manufacturing plants, or in asbestos-insulated buildings represent a source of health risk. Asbestos pollution outside the workplaces significantly contributes to the burden of asbestos related diseases [55] and the evaluation of a framework for dealing with compensation rights for MM cases induced by non-occupational exposure to asbestos needs to be carefully undertaken from the economic, ethical and insurance points of view. Recently in Italy a special fund for asbestos victims (without any occupational exposure) has been implemented. A large presence of women among mesothelioma cases in Italy has been documented by ReNaM. The relevance of non-occupational exposures



and of the historically high female workforce participation in several industrial settings such as non-asbestos textile sector has been discussed as the causal factors [56]. The awareness of occupational or environmental origin of mesothelioma in women could improve the efficiency of the public compensation system and the prevention policies, redefining the tools for investigating asbestos exposure in a gender perspective.

TAKING CHARGE OF MESOTHELIOMA PATIENTS: THE CASALE EXPERIENCE AS A MODEL AT NATIONAL LEVEL

The experience of Casale Monferrato with respect to taking charge of mesothelioma patients has evolved over time. Its current configuration is characterized by an interinstitutional liaison between Casale hospital and the hospital of Alessandria, the chief town of the Province where Casale is located. This approach has been designed and tested in the frame of a project by the Centre of Disease Control of the Italian Ministry of Health (CCM 2012 "Modello Operativo per la presa in carico globale del paziente affetto da mesothelioma": www.salute.gov.it/imgs/C_17_notizie_2456_listaFile_item-Name_7_file.pdf).

The aims of the project were to shorten the time needed for the diagnostic process, to provide psychological support to patients and their families, and to follow them for all the therapeutic path in cooperation with general practitioners and no-profit organizations. A dedicated information system allows data collection, retrieval and analysis.

The specialists of the network include pneumologists, thoracic surgeons, radiologists, pathologists, nuclear medicine specialists, oncologists, radiotherapists, pain therapy and palliation specialists and psychologists. All cases are collegially followed. The network of specialists also defines the strategy for communicating with the patients and their families. Palliative care specialists are present since the early stages of therapy (simultaneous care).

A thorough presentation of these aspects of the model can be found in the website MAIDASOLI (www.meso.ospedale.al.it/). This model has been shown to improve self-management of patients, compliance with treatments and quality of life in general. At the same time, the model has been shown to be beneficial for the health system itself, in terms of capacity building and support to research activities. In the frame of the same CCM 2012 Project, this model has already been tested in a different context characterized by a somehow similar epidemiological setting previously discussed in this paper, namely the town of Broni, in Lombardy Region, where a large asbestos-cement facility operated for many decades thus determining a major mesothelioma outbreak. In that case, the organization was in charge of the interinstitutional Oncologic Department of the Province of Pavia (DIPO).

In more general terms, as it has been extensively discussed in the frame of the Third National Asbestos Conference held in Casale Monferrato 24-25 November 2017, this model should be replicated at a national level, of course taking into account local specificities,

with a priority for those areas where overt outbreaks of mesothelioma, or in any case high numbers of patients, are observed.

CONCLUDING REMARKS

The experience of Casale Monferrato represents a lesson in several terms, from the epidemiological surveillance to the health care of the victims and the relationship between epidemiologists, victims, their relatives and residents in contaminated areas. The studies performed in Casale have contributed to the implementation and interpretation of mesothelioma registration, temporal and spatial analyses of mesothelioma occurrence, analytical epidemiological investigations, health care planning, support to asbestos victims and community empowerment throughout all of Italy.

Registration of mesothelioma cases, has performed in Italy since 2002 by the system of the National Register of Malignant Mesotheliomas (ReNaM), with the Regional Operating Centers (COR). It provides good epidemiological indicators of the disease, including temporal trend and survival indicators; the latter allow to have indicators of effectiveness and efficiency of the health care system for mesothelioma cases. The compensation and public health insurance for environmental exposed cases are still rare. The peak of disease trend has been estimated to be in the period 2015-2020, according to a model including asbestos consumption before the ban; poor data on asbestos elimination trend make difficult an estimation of the time for a complete elimination of asbestos-related tumors, based on epidemiological models.

The most recent report of the national mesothelioma mortality surveillance plan showed, in Italy, 13051 deaths for pleural mesothelioma, in the time window 2003-2014. A number of alerts have been produced over the years by this activity, leading in a series of circumstances to detecting sources of previously unrecognized asbestos exposure, to be object of prevention interventions.

Analytical *ad hoc* studies and mortality and incidence mesothelioma surveillance plans, with their integrated interpretation, have been, and still are, a useful instrument for the protection of public health and rights of workers and general population. These studies also contribute to defining social support actions for asbestos victims and science based criteria to be used in the Courts.

The Italian experience, like as that of Casale for Italy, could represent a model for the countries where the use of asbestos is still allowed or the management of the ban is still on-going.

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Conflict of interest statement

There are no potential conflicts of interest or any fi-

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