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# Pleural Mesothelioma: Epidemiological and Public Health issues. Report from the Second Italian Consensus Conference on Pleural Mesothelioma

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**Parole chiave**
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**Summary**
*Malignant mesothelioma is closely connected to asbestos exposure, with epidemiological patterns closely reshaping the geography and history of asbestos exposure. Mechanisms of causation and of interaction of asbestos fibres with pleura are complex and currently not yet completely understood. Curative efforts so far provided little results. Italy shows one of the highest incidence of MM and developed a network of specialized cancer registries in order to monitor disease occurrence and describe its epidemiology in details. The second Italian Consensus Conference on Pleural*

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*Mesothelioma convened in Torino on November 24th-25th, 2011. Besides the main consensus report summarizing the contribution of the different expertises, that was published elsewhere, the participants in 'Public Health and Epidemiology' section decided to report in major details the evidence and the conclusions regarding epidemiology, causative mechanisms and the public health impact of the disease.*

**Riassunto**

***«Il Mesotelioma Maligno della Pleura: Quesiti Epidemiologici e per la Sanità Pubblica. Rapporto della Seconda Conferenza di Consenso Italiana sul Mesotelioma della Pleura».*** *Il Mesotelioma Maligno è strettamente associato all'esposizione ad amianto, tanto che la sua epidemiologia ripercorre strettamente geografia e storia dell'uso di tale sostanza. I meccanismi causali e di interazione tra tessuto pleurico e fibre sono complessi e non interamente conosciuti. Gli sforzi per individuare terapie non hanno finora sortito risultati adeguati. In Italia, dove l'incidenza della patologia è fra le più alte al mondo, si è formata una rete di registri specializzati per monitorare e descrivere l'andamento e le caratteristiche epidemiologiche della malattia. La seconda Conferenza di Consenso Italiana sul Mesotelioma Pleurico è stata riunita a Torino il 24-25 Novembre 2011. Oltre a contribuire insieme alle discipline degli altri gruppi di lavoro al documento globale di consenso, i partecipanti al gruppo di lavoro 'Sanità Pubblica ed Epidemiologia' hanno ritenuto opportuno riferire in maggior dettaglio le evidenze considerate e le conclusioni raggiunte relativamente ad epidemiologia, meccanismi causali ed impatto di sanità pubblica del Mesotelioma Maligno Pleurico in Italia.*

## The second Italian Consensus Conference on Pleural Mesothelioma

The second Italian Consensus Conference on Pleural Mesothelioma convened in Torino on November 24th-25th, 2011. Besides the main consensus report summarizing the contribution of the different expertises, that was published elsewhere (99), the participants in 'Public Health and Epidemiology' section decided to report in major details the evidence and the conclusions regarding epidemiology, causative mechanisms and the public health impact of the disease.

## Descriptive Epidemiology of Malignant Mesothelioma (MM)

The occurrence of MM showed an increasing trend in recent decades, more evident in industrialized countries, which was related to asbestos exposure and its temporal variation (16, 79, 93). In Italy incidence rate (age adjusted) of pleural MM estimated by the Italian Registry of Malignant Mesothelioma (ReNaM) in 2008 was 3.6 cases per 100.000 person-year in men and 1.3 in women (64). Corresponding rates for peritoneal MM were 0.24 and 0.12. Italy shows one of the highest rates in the world. Descriptive epidemiology data (in particular gender differences and geographic variation) correspond to the distribution of asbestos exposure (64, 66, 70, 71). In 2008 the overall number of incident cases of MM in Italy, as recorded by ReNaM, was 1,422 (64).

## Causes of MM

### Asbestos exposure

Asbestos is a trade name encompassing various fibrous silicates employed in several industries. Asbestos belongs to two groups: amphiboles (crocidolite, amosite, tremolite, anthophyllite, actinolite) and serpentine (chrysotile) (26, 33, 48, 90). The International Agency for Research on Cancer (IARC) and the National Toxicology Program – Report on Carcinogens (RoC) rated all asbestos types as human carcinogens; the tumour types caused by asbestos include MM (47, 48, 90). A general consensus exists that amphiboles are more potent in causing MM than chrysotile but the ex-

tent of the difference is still debated (28). In the case of asbestos, exposure is mainly determined by inhaled airborne fibres that deposit in the lung alveoli and further migrate to the pleura and to other organs. Exposure may be broadly classified as: i, occupational exposure in asbestos mining and in jobs involving asbestos fibres; ii, occupational exposure in trades using asbestos containing materials; iii, bystander exposure in workplaces where asbestos materials are present and possibly mobilized; iv, domestic exposure as family members of asbestos workers; v, environmental exposure consequent to dwelling in proximity of asbestos mining, dismissed asbestos industries or deposits of asbestos tailings; vi, environmental exposure to natural occurring asbestos (NOA); vii other exposures. The extension of asbestos exposure in industrial countries and its association with MM are at the basis for the call of a Global Asbestos Ban (113).

**Causal association of MM and other asbestiform natural mineral fibres**

Other naturally occurring fibrous minerals which share basic chemical composition and fibrous morphology with asbestos, are indicated as "asbestiform minerals" (48). They had no or limited industrial use. Some are causally associated to MM in humans. They include: erionite, a fibrous zeolite, which caused several MM cases in Cappadocia (Turkey) (9) but is also present in other areas (24); fluoro-edenite, recently discovered in the town of Biancavilla Etnea in Sicily, following the discovery of several cases of MM in a restricted area (22); asbestos contaminated vermiculite and a variety of asbestiform minerals (tremolite-actinolite, richterite e winchite) which caused a MM epidemics in Libby, Montana (USA), both in miners and in local dwellers (119).

**Causal association of MM and non-occupational exposure to asbestos or asbestiform mineral fibers**

Risk of pleural MM is increased after non-occupational exposure to asbestos and asbestiform mineral fibres. The evidence concerns both asbestos groups (chrysotile and amphiboles) (47, 51) and asbestiform minerals (zeolite, richterite, winchite and fluoro-edenite) (9, 22 119). An increased risk was detected following anthropic (47) and natural (91) environmental exposure, as well as domestic exposure (34, 45). ReNaM estimated that 8.3% of pleural MM in Italy are a consequence of non-occupational exposure, with wide variation among Italian regions (76).

**Man made mineral fibres (MMMF) and HARNs (High Aspect Ratio Nanomaterials)**

Various types of man made mineral fibres (MMMF) have been developed and produced as asbestos subtitutes. MMMF were classified by IARC (50) with various degrees of evidence for their carcinogenicity and possible causation of MM in humans. MM were observed in laboratory animals but not in epidemiological studies after exposure to ceramic fibres (52, 117). Incidence of MM was increased in rats after intra peritoneal injection of slag wool fibres (50). There is no evidence of MM induced after exposure to glasswool, both in animal and in epidemiological studies (50, 90).

Experimental animal studies on whiskers showed the occurrence of MM following airborne exposure to potassium titanate whiskers (1, 57) and after intrapleural injection of silicon carbide whiskers (1, 52).

As regards HARNs (High Aspect Ratio Nanomaterials) similarities between asbestos and carbon nanotube were reported but conflicting data were obtained in experimental studies. MM and peritoneal lesions were observed after intraperitoneal (101), intrapleural (111) and intrascrotal (107) injection with some kinds of carbon nanotubes. Opposite results were presented by a chronic toxicity experimental study that did not show association with cancer occurrence (83).

Asbestos exposure should be always suspected for MM cases. Occupational exposure is the most likely, but also non-occupational exposure should be thoroughly investigated, in particular when occupational exposure is unlikely. Contribution of asbestiform minerals or other fibrous materials must be considered.

## Mechanisms of asbestos carcinogenicity relevant for MM

Toxic effects of asbestos fibres are related to their dimension and surface properties. It was early shown in experimental studies that fibres longer than 5 μm and thinner than 0.1 μm have the higher potential to cause MM; (according to the early studies by Stanton relevant measures were length >8 μm and diameter <0.25 μm (110)). However, very short fibres were observed in pleural and pulmonary samples thus a possible role also of fibres shorter than 5 μm cannot be excluded (47, 89). The surface activity of fibres depends upon crystal structure, chemical composition, origin of the mineral, poorly coordinated metal ions contaminants. Iron ions appear to be the catalytic site for the generation of free radicals and reactive oxygen species.

Thin fibres can reach terminal bronchioles and alveoli. Alveolar macrophages can phagocyte the fibres shorter than 14-25 μm (i.e. macrophage diameter) but are damaged by longer fibres (frustrated phagocytosis) and eventually die, releasing pro-inflammatory cytokines and reactive oxygen species (ROS). Bio-persistent fibres (i.e. the fibres that are neither phagocytosed nor altered by physical-chemical actions) may pass through the bronchial epithelium, and attain the pleura, the peritoneum or even other locations. The fibres can interact with tissues for very long time (12, 47, 78). The mechanism of malignant transformation is incompletely understood: MM is clinically evident after an average period of three or more decades since the beginning of asbestos exposure: during this period a complex set of genetic and molecular alterations take place (46), which are still partially obscure (18, 25).

Several mechanisms of action of asbestos fibres have been hypothesized (54). Activation of alveolar macrophages causes a continuous release ROS and nitrogen reactive species (RNS) which cause mutations, DNA breaks and oxidization of DNA bases (46). Asbestos fibres interfere mechanically with the mitotic spindle, causing aneuploid or polyploid cells. Persistent inflammation and chronic oxidative stress have been associated to the activation of intracellular signal transduction, to the inhibition of apoptosis and to stimulation of cellular proliferation. ROS and RNS also cause tissue damage and genetic alterations.

The alteration at the molecular level that are relevant for MM pathogenesis in humans include autocrine stimulation of cell growth with the activation of the genes coding for growth factors and receptors (HGF/MET, EGFR, PDGF, IGF-1); inactivation of oncosuppressor genes, increased expression of VEGF and angiogenesis; increased resistance to apoptosis with activation and increased expression of AKT e BCL-X (6, 47, 84).

Epigenetic alterations including global DNA ipo-metilation and iper-metilation of the promoters of specific genes (which are inactivated) were observed. These effects may confer a competitive advantage to pre-neoplastic mesothelial cells in an environment characterized by continuous tissue microlesions and a chronic oxidative stress (27). The role of inflammation in causing neoplastic transformation of cells (8) is relevant for mesothelial cells too (62, 63, 120). Overall the processes and the alterations that favour the development of MM after asbestos fibres interaction with target cells and with macrophages can be summarized as follows: Microenvironment with persistent inflammation and chronic oxidative stress; direct and indirect genotoxic alterations; chromosomal alterations; epigenetic alterations. These alterations cause the activation of pathways regulating cell cycle, inactivation of oncosuppressor genes, resistance to apoptosis; acquired genomic instability and neoangiogenesis.

## Other causal factors for MM

### Ionizing Radiation

Research on causes of MM other than asbestos and mineral fibres focused on ionizing radiation and viruses. The cohort studies on Thorotrast exposed and on subjects medically treated with ionizing radiation showed an increased risk of MM, both pleural and peritoneal, depending on the body area that was treated (41). Exposure to ionizing radiation and to Thorotrast explains a minimal pro-

portion (1.7%-4.7%) of MM cases occurring each year in Italy.

### Viruses

Recent research no longer supports the hypothesis of a causal association with SV40 viral infection (39, 55, 59, 60, 109).

### Individual risk factors for MM

Family clusters of MM cases may suggest genetic predisposition but the likely hypothesis of common asbestos exposure must be carefully investigated (7, 116). In a study including over 1500 MM cases registered in three specialized MM registries, family clusters included only 1.38% of the cases (7).

Some studies carried on in Italy and in Finland on genetic risk for MM suggested a possible association between MM risk and polymorphisms of genes active in the repair of DNA damaged by oxydative stress. Risk of MM was increased between 2 and 4 times, in addition to the risk induced by asbestos (17, 40, 87). BAP1, an oncosuppressor associated to melanocytic neoplasms, was investigated in two studies on MM (20, 114). Testa et al (114) hypothesize a 'BAP1-associated neoplastic syndrome': in affected subjects, after asbestos exposure MM is the main disease.

## Relationship between asbestos exposure and MM occurrence

The main factors modelling MM risk include fibre type, exposure and time.

### Dose-response relationship between asbestos exposure and MM occurrence

A systematic revision of the studies presenting results on MM occurrence (mortality or incidence) by cumulative exposure dose (3, 15, 30, 36, 37, 51, 56, 58, 86, 96, 100, 102, 103) clearly showed a proportional relation of MM risk with dose [details in the supplementary material]. The study on the cohort of crocidolite miners in Wittenoom also presented results in respect to intensity and duration separately: proportionality was observed for both exposure metrics (85).

A further systematic revision was conducted on the studies presenting results on MM occurrence (mortality or incidence) by fibre burden (4, 72, 73, 82, 104, 105, 115) and proportionality of risk and exposure was also observed [details in the supplementary material].

Estimation of cumulative dose is difficult and errors may affect retrospective evaluation of exposure. Dose is a synthetic measure and any reported result should also separately evaluate intensity and its time variation. Assessment of fibre burden in electronic microscopy is complex because of technical difficulties and inter-laboratory comparability is limited. Moreover fibre burden at the sampling time may not represent accurately the life-long distribution of fibre burden relevant for the carcinogenic process. However little doubt remains about the proportional relation of cumulative dose and MM occurrence, both pleural and peritoneal (11, 19, 44).

### Temporal relation between asbestos exposure and MM occurrence (latency)

Incidence of MM after asbestos exposure increases proportionally to exposure multiplied by a power (3 or 4) of time since exposure (the interval since first exposure is usually called latency). Time since exposure gives more weight to exposures that occurred early. (19, 43, 88, 96-98). The Health Effects Institute (HEI) review (43), presents in details formulas relating MM occurrence with dose and time from exposure, according to duration of exposure (brief or extended) and constant or variable exposure. Some authors also included a minimum latency time (usually 10 years), corresponding to the shortest time assumed for the occurrence of a MM (43, 88, 97).

These models assume that MM incidence constantly increases with time since exposure, with no upper limit. They were based on the information provided by the early cohorts, with a follow-up of at most 40 years since first exposure (88, 97, 98). Recent reports include longer periods of observa-

tion, based on several cohorts followed-up for 50 years or longer. Regarding pleural MM the risk increase was not as expected by the traditional models but showed an attenuation; on the contrary a continuing increase was observed for peritoneal MM (14, 42, 58, 74, 108). Statistical models were presented either including a term for the reduction of asbestos fibres burden (10, 14) or based on the two stages and clonal expansion model (81, 112). The latter allows for the separate modellization of induction, clonal expansion and neoplastic progression.

### Biopersistence and clearance of the different asbestos fibres

Biopersistence of asbestos fibres depends on the efficacy of the elimination of fibres from pulmonary and pleural compartments and on physical and chemical processes, such as dissolution, fragmentation, transformation and translocation of fibres. Biopersistence in the lung is greater for amphiboles than for chrysotile. Clearance is faster for short fibres (macrophage clearance) than for long ones. Asbestos bodies formation is also a mechanism relevant for the neutralization of inhaled fibres, in particular for amphibole fibres. Some studies evaluated asbestos fibre clearance in human lungs, observing a reduction in asbestos lung burden with time since exposure cessation (pulmonary clearance), that was associated to fibre type (faster for the chrysotile fibres than for amphiboles) (5, 13, 29, 31, 35). As amphiboles are resistant to the chemical processes active in biologic tissues, the pulmonary clearance is associated also to translocation mechanisms, which are still incompletely known (78). Knowledge on the pathways and mechanisms for transportation of fibres into the pleural compartment and on the ratio between pulmonary and pleural concentration are still limited (21, 32, 92).

## Projections on future incidence of MM in Italy

Analyses to monitor the MM epidemics and to forecast future trends have been conducted in different countries. These analyses showed the association of MM and asbestos consumption trends (2, 23, 76, 81).

In Italy analyses carried on using different models agreed in predicting the epidemic peak: according to the first model it is expected between 2010 and 2020, with a maximum of about 1000 deaths per year (94, 95); according to a different model the peak will occur in 2012-2025 with a maximum of 800 deaths/year in males (68). Incidence trend analyses showed that the rate of incidence increase is slowing, in particular in the countries that first started asbestos reduction policies or adopted an asbestos ban. The change is more evident in younger age classes, that were less exposed (79). Available results are national averages and are not addressed to high exposure subgroups. Moreover Italian estimates are limited to pleural MM in men.

## Epidemiological surveillance of MM

A system for the epidemiological surveillance of MM and for the registration of MM cases is active in Italy, and notification is compulsory (DPCM n. 308/2002). It is organized in Regional Operational Units - aimed at the collection of MM cases and of their exposure information - and in the National Mesothelioma Registry (ReNaM) aimed at co-ordination and data analyses. ReNaM is located at the National Institute for Insurance of Occupational Accidents and Diseases (INAIL). The 4th report is published and freely available: in particular it presents data by region and type of exposure [http://www.ispesl.it/renam/Report.asp]. Specific results were presented in the scientific literature (65-67, 69, 77, 80). A critical issue in the organization of epidemiological surveillance of MM is the need to collect accurate information on exposure. ReNaM procedures include personal interview as the main source, therefore early notification of cases is mandatory. Moreover notification of MM to the compensation board is compulsory, as for occupational diseases in general (details available from INAIL and Local Health Authorities).

## Economical impact of MM

MM diagnosis and treatment represents an important cost for the National Health Service (106). Cost per case was estimated as € 15,000 in Scotland (118) and € 24,000 in Italy (75). Total annual cost in Italy is estimated in the order of € 25 million.

## Health surveillance of asbestos exposed and ex-exposed

In Italy health surveillance of asbestos exposed workers is compulsory and must continue after exposure cessation. At present, valid diagnostic tools for screening programs of MM or lung cancer are not available. The promising results of clinical trials on lung cancer screening in smokers using CT scan need verification in respect to asbestos exposure.

Therefore, the main aim of health surveillance should be: to provide assistance to formerly exposed workers for enquiries regarding health or compensation related issues; to promote an healthier life style and to keep attention on possible medical interventions. Moreover, health surveillance provides opportunities for collecting information on exposure history, useful for epidemiological research and for compensation evaluation.

## Survival

According to published data, in Italy median survival of cases diagnosed in 1990-2001 was 9.8 months, less than 10% of patients was alive after 3 years from diagnosis and 5% after 5 years (80). Survival of MM cases in Italy is as in other countries and in international studies (38).

Main determinants of MM survival are the histological type and the stage at diagnosis. In order to estimate survival variation correctly, individual prognostic information are needed and should be available in the clinical record according to a common data collection form to be used in all clinical centres.

## Disagreement note from E. Pira

Incidence of MM is function of the fibre type, approximately linear on dose and on the 3rd - 4th power of latency.

Some studies evaluated the concept of cumulative dose. The computation of cumulative dose as the product of dose by duration however is a gross simplification as the relevant time factor for MM is the latency and not the duration and the effect of latency is orders of magnitude higher than that of dose.

Nevertheless, MM risk increases according to a measure that compounds two factors (dose and duration, the latter taken as a proxy of the latency). Both factors are associated to MM incidence.

In conclusion, cumulative dose is a misleading metric and should be used only when data for distinguishing dose and time factors are not available.

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