

III Italian Consensus Conference on Malignant Mesothelioma of the Pleura. Epidemiology, Public Health and Occupational Medicine related issues

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Enrico Pira^{15,20} took part in the Consensus Conference activity but on April 8th asked not to sign the last version of the document, with no explanation.

SUMMARY

The III Italian Consensus Conference on Pleural Mesothelioma (MM) convened on January 29th 2015. This report presents the conclusions of the 'Epidemiology, Public Health and Occupational Medicine' section. MM incidence in 2011 in Italy was 3.64 per 100,000 person/years in men and 1.32 in women. Incidence trends are starting to level off. Ten percent of cases are due to non-occupational exposure. Incidence among women is very high in Italy, because of both non-occupational and occupational exposure. The removal of asbestos in place is proceeding slowly, with remaining exposure. Recent literature confirms the causal role of chrysotile. Fibrous fluoro-edenite was classified as carcinogenic by IARC (Group 1) on the basis of MM data. A specific type (MWCNT-7) of Carbon Nanotubes was classified 2B. For pleural MM, after about 45 years since first exposure, the incidence trend slowed down; with more studies needed. Cumulative exposure is a proxy of the relevant exposure, but does not allow to distinguish if duration or intensity may possibly play a prominent role, neither to evaluate the temporal sequence of exposures. Studies showed that duration and intensity are independent determinants of MM. Blood related MM are less than 2.5%. The role of BAP1 germline mutations is limited to the BAP1 cancer syndrome, but negligible for sporadic cases. Correct MM diagnosis is baseline; guidelines agree on the importance of the tumor gross appearance and of the hematoxylin-eosin-based histology. Immunohistochemical markers contribute to diagnostic confirmation: the selection depends on morphology, location, and differential diagnosis. The WG suggested that 1) General Cancer Registries and ReNaM Regional Operational Centres (COR) interact and systematically compare MM cases; 2) ReNaM should report results presenting the diagnostic certainty codes and the diagnostic basis, separately; 3) General Cancer Registries and COR should interact with pathologists to assure the up-to-date methodology; 4) Necroscopy should be practiced for validation. Expert referral centres could contribute to the definition of uncertain cases. Health surveillance should aim to all asbestos effects. No diagnostic test is recommended for MM screening. Health surveillance should provide information on risks, medical perspective, and smoking cessation. The economic burden associated to MM was estimated in 250,000 Euro per case.

RIASSUNTO

«III Conferenza di Consenso Italiana sul Mesotelioma Maligno della Pleura. Aspetti di Epidemiologia, Sanità Pubblica e Medicina del Lavoro». La III conferenza di consenso sul Mesotelioma Maligno della Pleura (MM) si è riunita il 29 Gennaio 2015. Questo rapporto presenta le conclusioni della sezione 'Epidemiologia, Sanità Pubblica e Medicina del Lavoro'. L'incidenza di MM nel 2011 in Italia è stata 3.64 per 100,000 persone/anno tra gli uomini e 1.32 tra le donne. I trends di incidenza nella popolazione sembrano non crescere ulteriormente. Dieci casi su cento sono associati ad esposizione non lavorativa. L'incidenza tra le donne è molto elevata in Italia, a causa sia di esposizione lavorativa sia non lavorativa. La rimozione dei materiali in amianto in opera procede lentamente, con esposizione residua. La letteratura recente conferma il ruolo del crisotilo nel MM. La Fluoenite fibrosa è stata classificata come cancerogeno (gruppo 1) dalla IARC, sulla base di dati relativi al MM. Un tipo di nanotubi di carbonio (MWCNT-7) è stato classificato 2B. Per i MM pleurici, dopo circa 45 anni dalla prima esposizione l'aumento dell'incidenza tra gli esposti rallenta, ma sono necessari studi di approfondimento. L'esposizione cumulativa è stima dell'esposizione biologicamente rilevante, ma non consente di distinguere se il ruolo principale dipenda da intensità o durata di esposizione e non consente neppure di valutare la sequenza temporale dell'esposizione. Studi hanno mostrato che durata ed intensità sono determinanti indipendenti del MM. La proporzione di MM con legami di parentela è inferiore al 2,5% in Italia. Il ruolo delle mutazioni genetiche di BAP1 sono limitate ai rari casi ascrivibili alla omonima sindrome familiare, mentre è irrilevante per i restanti casi. La correttezza della diagnosi è basilare; le linee guida concordano sull'importanza dell'aspetto macroscopico del tumore, e dell'esame istologico di sezioni colorate con ematossilina-eosina. I markers immunostochimici contribuiscono alla conferma diagnostica: la scelta dei marcatori dipende da morfologia, sede e diagnosi differenziale considerata. Il Gruppo di Lavoro suggerisce che 1) I registri generali di popolazione e le sezioni regionali (COR) del ReNaM interagiscano e confrontino sistematicamente casi di MM; 2) ReNaM dovrebbe presentare le casistiche di MM separatamente per certezza diagnostica e per modalità diagnostica; 3) Registri generali di popolazione e COR dovrebbero interagire con le unità di Anatomia Patologica

per garantire che siano impiegate le metodiche più aggiornate; 4) Autopsie dovrebbero essere effettuate, a scopo di validazione. Centri di riferimento esperti possono contribuire alla migliore definizione dei casi incerti. La sorveglianza sanitaria deve riguardare tutti gli effetti sanitari dell'amianto. Non sono disponibili tests diagnostici applicabili a scopo di screening. La sorveglianza sanitaria dovrebbe fornire informazioni su rischi, prospettive sanitarie, e cessazione del fumo. Il costo economico associato al MM è stato stimato in 250,000 Euro per caso.

FINAL DOCUMENT - EPIDEMIOLOGY, PUBLIC HEALTH AND OCCUPATIONAL MEDICINE' SECTION

Asbestos consumption, descriptive epidemiology and trend predictions

Italy was an important asbestos producer and user country until the ban in 1992, with an estimated total of 3,748,550 tons of raw asbestos consumption, peaking in the period between 1976 and 1980. MM incidence is correspondingly high: 3.64 and 1.32 per 100,000 person/years in 2011 in men and women respectively with 1,428 (1,035 in men and 393 in women) recorded incident cases (V ReNaM Report, in press, 2015). Data suggest that national incidence and mortality trends for MM are starting to level off. Data from other countries show that level off started earlier where asbestos control programs were enforced earlier.

Occupational and non-occupational asbestos exposure

Raw asbestos and asbestos-based products have been used in large amount in several industrial activities, such as asbestos-cement industry, construction and maintenance of railroad vehicles and ships, chemical industry, steel industry, metal works, building and others, as documented by reports of the National Mesotelioma Registry (ReNaM) (21), with an increasing relevance of a variety of unconventional circumstances of exposure. Incidence of MM among women is very high in Italy, because of both non-occupational (environmental and domestic) and occupational asbestos exposure; in particular the female workforce was very large in the textile industry and asbestos-ce-

ment production. The findings of Italian MM incidence surveillance system documented that 10.2% of MM cases are due to non-occupational exposure to asbestos (15). Non-occupational exposures to asbestos is more difficult to detect than the occupational but its relative importance is likely to increase. For a better assessment, interview information should be enriched by other parameters (such as historical reconstruction of asbestos pollution and biological markers of exposure). To date the definition of exposure relies on interview (50.3% direct to the patient 46.1% to proxies). Prompt notification of MM cases by physicians is recommended as a crucial issue for the efficiency of interview. The potential of sharing databases for case identification and for the assessment of exposure was noticed and the Working Group (WG) recommends its prompt and exhaustive implementation.

Background airborne asbestos fibers in the environment

Information from Italian regions is scanty: a recent monitoring campaign conducted in the city of Modena showed an average concentration around 0.1 ff/l, similar to the data reported in the IARC monograph n. 100 (10). WHO (26) estimated that for a continuous exposure to 0.4–1 ff/l (as measured with current methodology), a lifetime risk of MM would be from 4 to 10) × 100,000. Linear extrapolation to the 0.1 ff/l (current background level), would correspond to a lifelong excess in the order of one case (from 0.4 to 2.5) of MM every 100,000 persons. Local sources of contamination may determine higher levels of fiber concentration, that should be monitored for proper risk assessment.

Waterborne asbestos fibers

The presence of asbestos in water is becoming a matter of concern for a large part of the population, however there is no evidence of risk for pleural MM related to ingested fibers. Risk of exposure to airborne asbestos fibers because of the use of asbestos contaminated water can occur indoor and outdoor; in circumstances when an important level (millions/l) of fibers in water is detected, the possible increase of airborne fibers should be controlled and the level compared to the background.

Chrysotile

The recent literature confirms that chrysotile causes MM although with a lower potency than amphiboles.

Talc containing asbestos fibers

Epidemiological studies and case reports from ReNaM underlined the causal role of talc containing asbestos fibers. The need for greater understanding of this material, its source, where and how it was used in Italy, was acknowledged, with priority for epidemiological studies.

Current risk of exposure

There is still a risk of exposure for those employed in the construction industry. The removal of asbestos in place is proceeding too slowly and the entire process should be revised.

Association of MM and mineral fibers other than asbestos

Fibrous fluoro-edenite was classified as carcinogenic to humans by IARC (Group 1) on the basis of sufficient evidence including MM in humans (9). In Italy exposure is known in the area of Biancavilla (Sicily); it was found in other volcanic areas in Japan. Silicon Carbide (SiC) whiskers were classified as probably carcinogenic to humans (Group 2A), in absence of human data, but with clear evidence of MM in experimental animals (9). The

IARC Monograph took in consideration different types of Carbon Nanotubes (CNT), of which a specific type (MWCNT-7) was classified as 'possibly carcinogenic' (group 2B), while the classification could not be extended to other CNTs for lack of consistent data (group 3) (9). The group acknowledges the general concern on the possible health effects of CNTs, as their physical-chemical characteristics, in vitro data and several experimental animals outcomes suggest that some CNT types, albeit not all, might cause MM.

Does MM incidence increase indefinitely over latency time?

The mathematical model predicting MM incidence after exposure to asbestos in humans was adopted by the Second Italian Consensus Conference on Pleural MM, after considering the original literature and reviews then available. The model predicts incidence to increase indefinitely according to time since exposure, while studies with observation time longer than 40-50 years since first exposure suggested that, at such latency, model predictions were no longer correct and differences existed between pleural and peritoneal MM; results were imprecise because of the relatively small number of cases of interest. A recent pooled analysis (22) showed that in pleural MM, after about 45 years since first exposure, the trend in incidence and mortality increase is slowed down but the same is not observed for peritoneal MM. Further studies are appropriate.

Role of cumulative exposure in the dose-response relationship

After examining the results of a systematic literature review (15), the Second Italian Consensus Conference on Pleural MM concluded that risk of MM increased with cumulative exposure and lung fibre burden, and that time since exposure gives more weight to exposures that occurred early (19). In the study of MM epidemiology, the use of cumulative exposure to asbestos has a long standing tradition and cumulative exposure is a proxy of the relevant exposure.

The relevance of distinct exposure periods

MM cases commonly exhibit complex exposure patterns. It was suggested that the dose-response relationship may be used to assess the proportional causal weight of any distinct exposure period (15, 20). The Working Group noticed that it is necessary, however, to adopt assumptions about several key factors which are not precisely known in most instances, including among others, the relative potency of the different varieties of asbestos, the exposure intensity, and the duration of the preclinical phases of MM.

Is cumulative exposure a valid risk index?

To quantitatively investigate cancer etiology it is important to assess occurrence in relation to long-term exposure patterns, which often consist of a complex temporal sequence of exposure circumstances which are difficult to analyse separately disentangling the relative relevance of duration, intensity, and cumulative exposure (13, 23, 25). Cumulative exposure is a useful summary exposure index, successfully employed in various fields in cancer research (including etiological research and risk assessment), as it offers a solution to the difficulty of analytically dealing with complex exposure patterns (24). It is acknowledged that cumulative exposure does not allow to distinguish which of its components, duration or intensity, may possibly play a more prominent role, neither it allows to establish whether the temporal sequence of exposures is important (6). As regards separate analyses by duration and intensity, six different studies were found in a literature search and overall, these papers offered evidence that duration and intensity are independent determinants of MM occurrence.

Does exposure affect latency?

Even if the analysis of latency among MM cases is intuitively appealing, under the expectation of a shorter latency for the most exposed, it is fallacious because its results do not depend on the relationship between exposure and disease, but on the time

boundaries of the observation (18): the observation time is fixed (by the observer), and the dynamic of the distribution of exposures in the population from which cases originate had been historically determined. In cohort studies, furthermore, latency can be determined only for a minority of at risk individuals, due to the combined effect of administrative censoring and competing mortality (12). An increase in exposure causing an increase in incidence in the target population necessarily entails the acceleration of failure time (i.e. latency time), as the relationship between increase in incidence and acceleration of failure time is mathematically determined (3); nevertheless and contrary to what intuition might suggest, the average latency is unaffected¹.

Genetic factors in MM

The proportion of blood related MM cases in Italy is between 1.3 and 2.5%, considering only population based surveys (1, 2). In the population living or working in Wittenoom, blood related MM cases represented 7%, and a twofold increase of MM risk for blood relatives of cases was estimated, after adjustment for asbestos exposure (7). The role of BAP1 germline mutations is limited to the cases occurring in familial aggregations corresponding to the BAP1 cancer syndrome, while it is negligible (at most 1.4%) for sporadic MM cases (4). GWAS studies suggest a possible role of common genetic variants but results are still preliminary and agreement of different studies is limited (5, 16).

Evaluation of methods for diagnosis and for classification of MM under an epidemiological perspective

International guidelines underline the importance for the diagnosis of MM of the gross appear-

¹ Note: C. Bianchi did not agree and expressed the following comment, sent during the revision of the report: "Claudio Bianchi believes that an inverse relationship exists between intensity of asbestos exposure and length of the latency period".

ance of the tumour, in the context of appropriate clinical, radiologic, and surgical findings and of the hematoxylin-eosin-based histology. Immunohistochemical markers provide an important contribution to the diagnostic confirmation and to the interpretation of uncertain morphology. The selection of markers depends on the initial morphological evaluation. The role of immunohistochemistry varies depending on the histologic type of mesothelioma (sensitivity of immunomarkers is high in epithelioid and low in sarcomatoid types), the location of the tumor (pleural versus peritoneal) and the type of tumor being considered in the differential diagnosis (e.g. adenocarcinoma, squamous cell carcinoma, malignant melanoma, epithelioid hemangioendothelioma). Even if a large selection of immunohistochemical markers is currently available, not all MM cases can be definitely identified. Even after the diagnostic revision by a panel of expert pathologists, a proportion of cases is classified as probable or doubtful MM. Cancer registries adopt standard rules for the identification, coding, and registration of cases, as a prerequisite for analysis of incidence, and for geographic and trend analyses (8). Cancer registries do not diagnose cases but search them in the appropriate clinical departments or in the appropriate data files. Cases are accepted on the basis of the clinico-radiologic and pathological diagnosis, on the basis of the methods in use at the time of diagnosis. More severe selection procedures would cause a loss of cases. The Working Group suggested that 1) General Cancer Registries and ReNaM Regional Operational Centres (COR) interact and systematically compare MM cases; 2) ReNaM should report results presenting the diagnostic certainty codes and the diagnostic basis, separately; 3) General Cancer Registries and COR should interact with pathologists in order to assure that current diagnoses are made using the up-to-date methodology, including immunohistochemistry panels; 4) Necroscopy should be practiced at a larger extent, in order to validate *in vivo* diagnoses. Expert referral centres for the revision and confirmation of diagnoses could contribute to the definition of uncertain cases.

Health surveillance programs

Programs aimed to workers formerly exposed to asbestos or engaged in occupations with potential asbestos exposure are defined according to current laws [257/2006 and 81/2008]. Health surveillance should not aim at the prevention of a single disease but be planned with a broad perspective, in consideration of the different diseases associated to asbestos exposure and of the joint effect of asbestos and tobacco smoking on lung cancer. So far, no diagnostic test, including imaging and biochemical tests, has sensitivity and specificity high enough to be adopted for early diagnosis of MM in asymptomatic. Health surveillance activity should provide also information on risks and on medical perspective, collect information on occupational history, especially regarding asbestos exposures, and provide counseling for smoking cessation. For asbestosis, high resolution computer tomography (HRCT) is the recommended imaging technique, and International Classification of HRCT for Occupational and Environmental Respiratory Diseases. (ICOERD) standardized criteria should be used (17). Pneumococcal and influenza vaccination and early treatment of respiratory infection should be encouraged among exposed workers with lung fibrosis (17).

Given these considerations, health surveillance of asbestos exposed workers has: 1) To inform asbestos exposed subjects about their risk related to (present or past) asbestos exposures; 2) To inform relatives of asbestos exposed subject of their possible health risks; 3) To fully reconstruct occupational history, especially regarding asbestos exposures; 4) To provide information about diagnostic tools, therapy and forensic medicine perspectives; 5) To support claims for compensation; 6) To give counselling on smoking cessation and on other relevant matters related to health and life style.

Social and economic costs of MM

A reliable estimate of the economic burden associated to mesothelioma, including medical care, insurance and fiscal costs, and human capital costs related to productivity loss, provided an estimate of 250,000 Euro per MM case, as the sum of medical

(33,000), insurance (25,000) and productivity loss (192,000) costs (11).

Extrapleural Malignant Mesotelioma

The Working Group decided to expand its activity and to consider also MM in other sites, i.e. peritoneum, pericardium and vaginalis lining of the testis. MM can spread to the peritoneum and pericardium from the adjacent pleura and the reverse also can occur. The histology of extrapleural MM is not peculiar and the typical frequency distribution of epithelioid, fibrous, and mixed forms is observed, similar to the pleural location. In women, differential diagnosis between peritoneal MM and ovarian cancer can be challenging.

Cases of peritoneal MM are diagnosed and treated in different hospital wards than pleural MM cases. These difference are relevant for the organization of data collection from cancer registries, in particular for the specialized mesothelioma registries.

Incidence of peritoneal MM is lower (roughly 1/10) than pleural MM. In Italy, the IV report of the National Mesothelioma Registry (ReNaM) indicated 0.22 (/100.000 py) in men and 0.10 in women). Incidence of MM of the pericardium and vaginalis lining of the testis is further lower.

All types of asbestos fibres cause extrapleural, as well as pleural, MM (10). In addition to the internal body transport of inhaled fibres, the peritoneum can be exposed to asbestos fibres directly because of talc containing asbestos fibres used on surgical gloves or for personal hygiene. Prevalence of asbestos exposure appear lower for extrapleural, than for pleural, MM.

After asbestos exposure, risk of peritoneal MM shows a continuous increase, contrary to pleural MM, that shows a flattening of the increase of risk after 40-50 years of latency (22).

CONFLICT OF INTEREST

The report of conflicts of interest regarded the participants in the Consensus Conference for the 3 years period before the meeting (2012 – 2014). No authors reported economical or financial conflicts of interest. Out of Nineteen components of the Consensus Conference Group, two could

not contribute at any extent and are not considered here. Of the seventeen who actually contributed, ten have been asked to provide scientific information in criminal or civil court cases related to asbestos related diseases: six of them served as expert or expert witness for the court, nine for the public prosecutor, four acted as expert for the plaintiff(s), and three for the defendant(s). Seven were never involved in court cases in the period considered. A detailed report was provided to the Editor of "La Medicina del Lavoro".

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