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

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Final document - Epidemiology, Public Health and Occupational Medicine section. Detailed report

Introduction

The third Italian Consensus Conference on Pleural Mesothelioma convened in Bari on January 29th – 30th 2015. Besides the main consensus report summarizing the contribution of the different expertises, that was published elsewhere (Pinto et al), the participants in the 'Epidemiology, Public Health and Occupational Medicine' section decided to report in major details the evidence and the conclusions regarding epidemiology, causative mechanisms and the public health impact of the disease. The working group on Epidemiology, Public Health and Occupational Medicine focused its activity on several issues selected because of new evidence emerged after the II Consensus Conference. The Group members proposed a selection of topics and the final program was agreed on during

the first preparatory meeting (Dec 12th, 2014). The group agreed also on the inclusion of a summary on peritoneal MM.

Asbestos consumption and descriptive epidemiology of malignant mesothelioma (MM)

The International Agency for Research on Cancer definitively stated that all forms of asbestos are carcinogenic for humans. There is sufficient evidence that asbestos causes MM (arising from the serous membranes of the pleura and, less frequently, of the peritoneal and pericardial cavities and from the tunica vaginalis of testis) and lung, laryngeal and ovarian cancers. Positive associations have been also observed between exposure to all forms of asbestos and pharynx, stomach and colorectal cancers [IARC, 2012].

More than 30 million tons of asbestos in all forms were produced worldwide during 20th century and production exceeded five million tons per year in the peak period, around 1975-1978. Worldwide asbestos consumption declined after that and so far 55 countries have banned its production. Asbestos is still extensively used in many parts of the world including Russia, China, India and Brazil, notwithstanding the fact that the main international organizations involved in occupational safety and health (International Labour Organization - ILO, World Health Organization - WHO, International Commission on Occupational Health - ICOH) have issued calls and recommendations for the international ban [ILO, 2006; WHO, 2014b; ICOH, 2013]. WHO report on the elimination of asbestos related diseases (ARD) estimated 125 million people exposed to asbestos worldwide at the present, 43,000 MM and 107,000 ARDs deaths per year worldwide [WHO, 2014].

In Italy from the end of the Second World War to the asbestos ban in 1992, 3,748,550 tons of raw asbestos were used, reaching a peak in the period between 1976 and 1980 at about 160,000 tons/year. Incidence standardized rate of pleural malignant MM by Italian National Mesothelioma Register (ReNaM) was 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]. Mortality rates for MM in 2011 (C45 code in ICD X revision) were 2.74 and 0.83 in men and women with 1107 deaths (786 and 321, respectively).

MM predictions

According to the strong causal association, the trends in incidence and mortality for MM follow the trend in asbestos consumption, with a lag of 30–40 years. As a result, many Western countries are currently suffering from a MM epidemic, which reflects the relevant use of asbestos occurred between the 1940s and 1980s [Lin, 2007]. Forecasts of MM incidence or mortality predicted a steady growth of the number of cases among industrialized countries, following a plateau or decline in consequence of the restriction in the use of asbestos [Montanaro et al, 2003]. While in countries such as the United States, Australia, the United Kingdom and the Nordic European countries asbestos consumption levelled off during the 1960s and 1970s and then decreased, in Italy, Spain and France, asbestos productions and imports gradually decreased from the 1980s only, and consequently the decline in MM occurrence started correspondingly later.

Forecasts of MM mortality have been published in Europe for Great Britain [Hodgson et al, 2005; Tan, 2010], France [Gilg Soint Ilg et al, 1998; Banaei et al, 2000; Le Stang et al, 2010], Italy [Marinaccio et al, 2005], The Netherlands [Segura et al, 2003], Denmark [Kjaergaard et al, 2000], Norway [Ulvestad et al, 2003], Spain [Pitarque et al, 2008; Lopez-Abente et al, 2013]. Outside Europe, analyses of the peak MM trend are available for United States [Price et al, 2009], Australia [Leigh et al, 2003], Japan [Myojin et al, 2012; Murayama et al, 2006] and other Asiatic countries [Le et al, 2001]. All predictions have been developed either using national asbestos consumption as proxy of exposure or according to age-period-cohort models. In addition to the delayed effects of asbestos, the increasing trend in MM may be explained by factors concerning the increasing awareness of the clinicians in identifying MM and the improvements in diag-

nosis, leading to improved sensitivity and specificity of MM diagnoses [Husain et al, 2009]. The group noticed however that total asbestos consumption is a crude indicator of population exposure. For a better estimation of time trends, factors such as changes in fibre type, introduction of dust control systems in some industrial sectors, size of exposed workforce, the technology in use and others should be taken into account.

For Italy the observed trend of MM mortality (since 2003 based on ICD X coding system) overlaps with predicted male pleural MM deaths [Marinaccio et al, 2005]. Trend data suggest that national incidence and mortality trends are starting to level off.

Regional analyses on MM trends and predictions have been performed recently, based on the availability of historical MM incidence data from local registries. In the Veneto Region, based on the dataset of incident cases in the period 1987-2010, it was predicted that the trend will decrease after the incidence peak observed in 2010 [Girardi et al, 2014]. In Lombardy, based on 2000-2011 incidence data, an increase is expected until 2020 with about 11,000 cases in the period 2000-2030 [Consonni et al, 2015].

Occupational sectors involved in asbestos exposure in Italy

Occupations interested by asbestos exposure have been reported by analytical (case/control or cohort) studies and by MM surveillance systems in different countries [Leigh et al, 2003; Goldberg et al, 2006; Yeung, 1999; Marinaccio et al, 2012].

In Italy, 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 ReNaM reports [ReNaM, IV report, 2012].

The analysis of asbestos exposure for MM patients in Italy shows changing patterns over time. The proportion exposed in activities with asbestos use as raw material is reduced in recent years, with an increasing relevance of unexpected circumstances and sources of exposure, in a wide spectrum of activities, mainly related to maintenance [Binazzi, 2013; Baldassarre et al, 2012].

At present, the main economic sector for number of MM cases in Italian MM surveillance program, is the construction sector [ReNaM, IV report, 2012], which is composed of a wide array of different jobs, with ample variations in the asbestos exposure profile. Asbestos has been largely used as fireproofing and soundproofing in various building materials, mixed with cements or resins (such as vinyl flooring) with consequent potential risk of exposure during maintenance and refurbishing activities even after the asbestos ban [Olsen et al, 2011].

The increasing weight of the unconventional exposure circumstances must be underlined for the implications with respect to exposure prevention measures and public health policies. Prompt notification of MM cases by physicians is recommended as a crucial issue for the efficiency of anamnestic interview. [Marinaccio et al, 2012].

MM in women

As a consequence of the occupational origin of the disease, gender ratio (ratio between male and female number of cases) for MM is particularly high. As stated in a recent worldwide mortality analysis [Delgermaa et al, 2011], gender ratio is 3.6 for all MM deaths recorded worldwide in 1994-2008. Variability of this parameter is high: from 1.9 in middle-income countries to 5.7 in the United Kingdom and 5.4 in Australia. In Italy it was 2.4 in the same period. Similar results were observed for incidence data. Gender ratio for incident pleural MM cases recorded by the Italian National Mesothelioma Register in the whole observation period (1993-2011) is 2.6, with little time variations [V ReNaM Report, in press, 2015]. In Australia and France, where similar experience of MM incidence registration are currently active, gender ratio is significantly higher (6.8 and 4.2 respectively) [Hyland et al, 2007; Goldberg et al, 2006]. The relevant number of MM cases and the high incidence among women in Italy reflected both non-occupational (environmental and domestic) and

occupational asbestos exposure, in particular the large size the female workforce in the textile industry and asbestos-cement production.

MM due to non-occupational asbestos exposure

Asbestos pollution outside the workplace contributes significantly to the burden of some asbestos-related diseases, in particular MM and pleural plaques. Regarding MM, significant sources of risk are the cohabitation with an occupationally exposed patient and the residence near a source of asbestos pollution. Asbestos exposure during leisure time activities is difficult to identify and probably underestimated.

Environmental exposure from naturally occurring asbestos contamination of the soil has been documented in rural areas of Turkey [Bayram et al, 2013], Greece [Sakellariou et al, 1996], Corsica in France [Boutin et al, 1986], New Caledonia [Goldberg et al, 1994], China [Luo et al, 2003], California in the USA [Pan et al, 2005]. In Italy such occurrence was observed in the Sicilian town of Biancavilla (Italy) because of a mine in the town surroundings, where fluoroedenite-contaminated gravel was extracted, for construction and road paving [Bruno et al, 2006]. Clusters of MM and other ARDs were reported in Basilicata [Musti et al, 2006] and Piedmont [Mirabelli et al, 2002] because of natural asbestos contamination of the soil. Soil contamination determines both environmental and occupational risk, due to the human activities such as agriculture and construction: the analysis of environmental and personal sampling showed significant exposure from in operations involving earthmoving and soil disturbance [Massaro et al, 2012].

Risk of MM associated with local industrial sources was repeatedly demonstrated for neighboring populations [Kurumatani et al, 2008; Tarrés, 2013]. In Italy, MM incidence and mortality risk increased for residents near asbestos-cement plants in Casale Monferrato [Magnani et al, 2001], Bari [Musti et al, 2009], Broni [Mensi et al, 2015] and for residents near navy shipyards and steel industry in La Spezia [Dodoli et al, 1992] and Taranto [Baldassarre et al, 2013]. The MM risk in Casale Monferrato decreased with increasing distance from the factory [Maule et al, 2007]. The exposure for people resident in the neighborhood of plants using asbestos as raw material, depends on different factors, such as working modality, containment of asbestos diffusion from the factory, storage and use of processed and rejected materials, and also on personal habits, such as outdoor activities. In Casale Monferrato area, asbestos-cement workers wives showed a large excess of pleural MM, attributed to soiled work clothes brought home [Ferrante et al, 2007] but MM risk was also increased for other relatives, most notably for the offspring [Magnani et al, 2001]. The role of improper use of asbestos containing discarded materials is known but is not precisely quantified so far.

The Italian MM incidence surveillance system (15,845 incident MM cases and 12,065 individuals interviewed from 1993 to 2008), documented that 10.2% of MM cases are due to non-occupational exposure to asbestos. Specifically 4.4% of cases are due to familial exposure (they lived with a person who was occupationally exposed), 4.3% to environmental exposure (they lived near sources of asbestos pollution) and 1.6% are due to asbestos exposure during hobby-related or leisure activities [Marinaccio et al, 2015].

Airborne asbestos exposure in the environment

The so-called "natural background" up to about 150 years ago was limited to the fibres from natural outcrops. Since then it largely increased with the industrial massive use of raw materials, the emissions being cast during activity of manufacture companies, the widespread presence in means of transport, including railway carriages and vessels [ReNaM 2010], the wearing of friction pads and braking systems [Paustenbach et al, 2004], the widespread asbestos cement roofing [Spurny et al, 1989], and other similar sources. Several studies have been conducted to define the quantitative and qualitative concentration of airborne fibres [Chiappino et al, 1991] even in the absence of or at a safe distance from point sources. The IARC Monograph No. 100 reports that: "*In studies of asbestos concentrations in outdoor air, chrysotile is the predomi-*

nant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m^3). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure." [IARC, 2012].

WHO [2000] estimated that for a continuous exposure to 0.4–1 ff/l (as measured with current methodology), a lifetime MM risk 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 MM case (from 0.4 to 2.5) every 100,000 persons. Information on airborne asbestos concentration from Italian regions is scanty. A monitoring campaign conducted by ARPA Emilia Romagna in the city of Modena [Silvestri S, personal communication], showed an average concentration around 0.1 ff/liter (100 ff/m3*),* similar to the one mentioned in the IARC monograph n. 100 for urban locations (IARC, 2012).

Mainly the MM cases classified with environmental exposure incurred in areas with well known sources of asbestos pollution [Conti et al, 2014; Maule et al, 2007; Musti et al, 2009; Pasetto et al, 2004; Mirabelli et al, 2010]. Local sources of contamination may determine higher levels of fibre concentration, that should be monitored for proper risk assessment. To date no case exclusively attributable to living nearby areas with large presence of asbestos cement roofing has been identified by ReNaM. To date no systematic surveys on the occurrence of MMs exposed to natural background have been performed. Small clusters reported in relation to natural outcrops of asbestos in Basilicata and Piedmont were discussed earlier.

Removal of asbestos material in place should be improved, also for Asbestos Cement materials, in order to both reduce the risk of exposure for construction related workers and to avoid release of asbestos fibres in the environment. It is estimated that since 1992 only 1% of the national tonnage was removed per year [Silvestri, 2012]. The so called "asbestos way-out" at this rate of cleaning up, is definitively too slow, and new policy to rediscuss the entire process is needed.

Waterborne asbestos fibres

The presence of asbestos in water is becoming a matter of concern for a large part of the population.The relevance of water transported asbestos is because of the ingestion and also because the air suspension and possible inhalation of fibres. Water intended for human consumption is conveyed in Italy by asbestos cement pipes from nearly a century. It is estimated that the extension of the national water network using asbestos cement conducts might have a total length of around 80,000 km. In the Tuscany region 2000 km of asbestos cement pipes are still in use. The Circular of the Ministry of Health n. 42 1/8/86 (Official Gazette n. 157 of 07/09/1986) and the DM 14/05/1996 indicated, as a risk factor for the erosion of the inside surface of the pipes, the level of aggressiveness of the water transported, which is inversely proportional to pH, (total alkalinity and calcium hardness). Water can also be contaminated by natural presence of asbestos minerals. Studies on water contamination by asbestos fibres have been performed since a long time ago in various parts of the world [Toft et al, 1981; Cook et al, 1974; Cotruvo, 1983] and also in Italy [Cherubini et al, 1998; Fiorenzuolo et al, 2013]. The US Environmental Protection Agency recommended a threshold limit of 7 million fibres per liter on the number of fibres in drinking water [U.S. EPA, 2010]. Contaminated water can increase the indoor background level of airborne fibres in the premises served [Webber et al, 1988]. No reports of increased risk of developing MM following water contamination by asbestos fibres are known to us. One epidemiological study on lighthouse keepers reported a possible cancer risk for other organs, but not for MM [Kjarheim et al, 2005]. The conclusion of IARC Monograph 100C [2012] of possible association between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum were not related to waterborne asbestos exposure.

Chrysotile

The recent literature confirms that chrysotile causes MM although with a lower potency than amphiboles [IARC, 2012; WHO, 2014a]. Recent

updates include: the incidence of MM in the workers of the chrysotile mine of Balangero and in the population living nearby [Mirabelli et al 2008] and the mortality for MM in a cohort of friction materials workers [Finkelstein et al, 2010]. In Italy a wine cellar workers developed MM after exclusive exposure to chrysotile asbestos used for wine filtration [Nemo et al, 2014]. A second similar case was reported to the group [Silvestri S. personal communication].

Talc containing asbestiform fibre

The IARC evaluated talc containing asbestiform fibres as carcinogenic for humans (group 1) [IARC 2012]. The recent occurrence of a cluster of MMs with exclusive and well-defined exposure to contaminated talc powder [COR Piemonte, Mirabelli D. personal communication] underlines the need for greater understanding of this material, the industrial divisions where it was employed and the type of use. In particular, it is a priority to produce a map of the Italian talcum mines and of their mineralogical characteristics with particular regard to contaminants such as amphiboles [IARC, 2010; Marconi et al, 1986; Finkelstein 2012]. Cohort studies of workers exposed to contaminated talc are also a priority for future research, in consideration of the widespread use of the material.

Current risk of exposure in the construction industry

The widespread presence of Asbestos Cement Materials (ACM) in the construction industry determines a risk of asbestos exposure, particularly for those who carry out refurbishment of dwellings, even though planned removal of large quantities is normally carried out by specialists [Silvestri, 2012]. The relevance of ACM for the environmental background of asbestos fibres was discussed earlier.

Illegal import of asbestos and asbestos containing material

The Working Group expressed its concern about the possible illegal import of asbestos containing material and the possible fibre contamination of materials legally imported, such as talc or vermiculite.

Association of MM and mineral fibres other than asbestos: an update

Some mineral fibers differing from asbestos and originated in areas different from those geologically known to host asbestos, have been responsible for the development of MM in humans. The evidence for some of these fibres was presented in the II Consensus conference. The working group for IARC monograph 111 [Grosse et al, 2014] convened in 2014 and, among other materials, evaluated Fluoro- edenite, the fibrous mineral from the Etna volcano near Biancavilla (Italy). The mineral was also identified in the Kimpo volcano (Japan), leading to a possible presence close to other volcanic areas. Use of the quarry material for unpaved roads and as building material caused a marked excess of MM in the Biancavilla population, most prominent in young adults, suggesting an environmental rather than occupational cause [Comba et al, 2003]. Fluoro-edenite fibrous amphibole was classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that exposure causes MM. Sufficient evidence of carcinogenicity was also reported in experimental animals [Belpoggi et al, 2014].

Possible association of MM to Artificial Fibres and High Aspect Ratio Nanomaterials (HARNs)

Some newly commercialized fibrous materials bearing characteristics close to asbestos may turn out to be a potential cause of MM in the exposed population. The working group for IARC monograph 111 [Grosse et al, 2014] evaluated Silicon Carbide (SiC) and Carbon Nanotubes.

SiC particles are manufactured mostly by the Acheson process, with SiC fibres being unwanted by-products. The product arising from the Acheson process was classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that it causes lung cancer (but not MM), while fibrous SiC was classified as possibly

carcinogenic to humans (Group 2B), based on limited evidence in humans that it causes lung cancer.

SiC whiskers are produced as durable industrial substitutes for asbestos; they are monocrystalline with dimensions similar to asbestos amphiboles. In experimental animals, there was sufficient evidence for the carcinogenicity of SiC whiskers, with MMs observed in rats treated by intrapleural implantation, intrapleural or intraperitoneal injection, and in one inhalation study [Johnson and Hahn, 1996]. In the absence of human data SiC whiskers were classified as probably carcinogenic to humans (Group 2A).

Carbon nanotubes (CNT) are prepared either as single graphene cylinder (SWCNTs) or as multiple concentric graphene cylinders (MWCNTs). CNTs (nanometric diameters but variable length up to tens of micrometers) exhibit variable physical and chemical characteristics. Their physicochemical properties may be modulated by varying the method of synthesis and by applying post-synthesis treatments. Therefore, a large variety of CNT forms may be produced that exhibit different chemical reactivity from each other.

CNTs exhibit high thermal and mechanical resistance, electrical conductivity or semiconductivity. Such properties make CNTs interesting in a variety of industrial applications including improving the structural properties of fabrics, plastics, rubbers, electronics, composite materials energy-storage devices, solar cells, sensors, and in mechanical applications as a filler in polymeric composites [Grosse et al, 2014; Donaldson, 2011; Fubini et al, 2011]. The highest release of CNTs, usually as entangled agglomerates which can be respirable, is observed during production and handling, and in cleaning the production reactor [Grosse et al, 2014].

Biopersistent straight CNTs have been reported by Donaldson and coworkers as potentially similar to asbestos in causing MM [Donaldson, 2011], however, not all fibers are equally toxic, as toxicity also depends upon several other physical-chemical factors [Fubini et al, 2011]. No human data on CNT carcinogenicity are available.

Several tests in rodents reported peritoneal MM (10-12), however because of discrepancies, and of the variability of CNTs production procedure, only one type - MWCNT-7 - was classified as possibly carcinogenic to humans (Group 2B). The lack of coherent evidence across the various distinct CNTs precluded generalization to other types of CNTs [Grosse et al, 2014]. Mechanistic studies also suggest carcinogenicity but the data are too sparse and contradictory. Measurement of occupational exposure is limited, and consumer exposure was not quantified [Grosse et al, 2014].

A new study appeared after October 2014, also reporting peritoneal MM in rats following intraperitoneal injection of CNTs. In a two-year carcinogenicity study, with a protocol where granular dusts were negative, with amosite asbestos as positive control a tested MWCNTs (four types) caused MM [Rittinghausen et al, 2014]. Highest frequencies and earliest appearances after treatment occurred with the rather straight MWCNT types. Later on during the two-year study, mesotheliomas were found also in rats treated with the most curved type of nanotubes. MM induced by intraperitoneal injection of different MWCNTs and of asbestos were histopathologically and immunohistochemically similar, and were also similar to MM in humans, suggesting similar pathogenesis. The group acknowledges the general concern on the possible health effects of CNTs, as their physical-chemical characteristics, in vitro data and several experimental animal studies suggest that some CNT types, albeit not all, might cause mesotheliomas.

Improving asbestos exposure information for MM cases

To date the definition of exposure relies, for the vast majority of the MM cases, on the interview. Interviews are available for 74.1% of cases listed in the ReNaM [IV rapport, 2012] and were administered to the patient (50.3%) or to proxies (46.1%). Under-reporting of MM cases from hospital departments and delays because of inadequate management of the cases in the CORs are the main causes of the loss of direct interviews. It is useful to remember that delays and consequent loss of information might damage compensation for the patient and scientific research. Years of experience in

epidemiological surveillance teach that the best way for reducing delays is an organization which allows to overcome the human factor. Successful experiments of web networks among Regional Administrations and other public bodies ("Cooperazione Applicativa") could provide a solution for prompt case notification. The creation of a computer network sharing information and files from INAIL, INPS, Camere di Commercio, SDO archives, ISTAT and others, requires a strong political decision, however. These archives today are accessible only through complicated bureaucratic procedures, or are not accessible at all. Information coming from the direct interview could be enriched by other parameters able to increase the scientific level of exposure assessment.

Temporal relation of asbestos exposure and MM risk

Does MM incidence increases indefinitely over latency time?

A mathematical model to predict MM incidence after exposure to asbestos in humans was suggested by Newhouse and Berry [1976] and subsequently modified by others. The expression of the model proposed by Peto et al [1985] was widely adopted.

It was adopted also by the Second Italian Consensus Conference on pleural MM, even if it was noticed that the model predicts incidence to increase indefinitely according to time since exposure, while some authors had advanced alternative formulations, which do not impose such a constraint [Pinto et al, 2013]. The Working Group document, in particular, noticed that studies in which observation time extended beyond 40-50 years from the beginning of exposure suggested that, at such latency, model predictions were no longer correct and differences existed between pleural and peritoneal MMs [Magnani et al, 2013a]. The following studies had been taken into account:

- North-American insulators [Selikoff et al, 1991]
- Crocidolite miners at Wittenoom, Western Australia [Berry et al, 2012]
- Workers included in the Great Britain Asbestos Survey [Harding e Darnton, 2010]
- Workers producing crocidolite gas masks in Nottingham, UK [McDonald et al, 2006]
- Asbestos-cement workers in Casale Monferrato, Italy [Magnani et al, 2008].

A common limitation of these studies was the relatively small number of cases observed at 40 / 45 years of latency and beyond, due to the shrinking size of the cohorts. The ensuing statistical uncertainty of risk estimates made it difficult to rule out, in the individual studies, that variation in incidence (or mortality) could be due to chance. An up-date of the mortality study of Australian crocidolite miners was published after the second Consensus Conference, providing confirmation of previous results, but their statistical instability could not be completely overcome.

To increase the statistical power, a pooled analysis was carried out by combining several cohorts, including Wittenoom miners and Eternit workers [Reid et al, 2014]. Results show that: (1) in pleural MM, after about 45 years since first exposure, the trend in incidence increase (or mortality) slowed down; (2) the same did not happen with peritoneal MM.

Role of cumulative exposure in the dose-response relationship (co-authored by Milena Maule)

In the II Consensus Conference, after examining the results of a systematic literature review, the Working Group concluded that no doubt existed about the proportionality between cumulative dose and occurrence (mortality or incidence) of pleural and peritoneal MM. This conclusion had been criticized on the grounds that the mathematical model adopted by the Working Group did not contain a cumulative dose term [Zocchetti, 2013]. For each brief exposure, this model predicted mesothelioma incidence at time t to be function of a constant, k characterizing asbestos variety, of exposure intensity f (that, to simplify calculations, was assumed to be constant) and of the third power of time since exposure. In case of non-instantaneous exposures, integration over time makes incidence proportional to k, f and the difference be-

tween the fourth power of time elapsed since exposure start ($t - t_1$) and end ($t - t_2$):

$$I(t)=1/4 \cdot k \cdot f \cdot [(t-t_1)^4 - (t-t_2)^4]$$

The Working Group replied that indeed such model implies a role for cumulative exposure, in agreement with the empirical evidence provided by their systematic review of the literature [Magnani et al, 2013b] After considering that time since exposure end ($t - t_2$) equals the difference between time since exposure start ($t - t_1$) and duration ($t_2 - t_1$) and simplifying the notation, by putting $(t - t_1) = L$ (as latency) and $(t_2 - t_1) = d$ (as duration), it was shown that the following expression is obtained:

$$I(t)=1/4 \cdot k \cdot f \cdot d \cdot (4 \cdot L^3 - 6 \cdot L^2 d + 4 \cdot L d^2 - d^3)$$

where the product of duration and intensity (whether constant or average) is cumulative exposure.

It may be interesting now to move a step forward and analyse the meaning of the polynomial, perhaps less easy to grab than that of cumulative exposure. To do so, we consider that duration d may vary between a minimum, equalling an ideally instantaneous exposure, and a maximum equalling latency, as it cannot exceed latency.

If d takes on its minimum value we must go back the base-model expression:

$$I(t) = k \cdot f \cdot d \cdot L^3$$

When d is at its maximum, then $d = L$. As a consequence:

$$I(t) = 1/4 \cdot k \cdot f \cdot d \cdot L^3$$

Incidence is thus always function of k , the constant for asbestos variety, exposure intensity f, duration d and the third power of latency L, times a coefficient that may vary between a maximum value of 1 (when exposure duration is at its minimum) and a minimal value of 1/4 (when exposure duration is at its maximum). At intermediate values of duration, the coefficient value depends on the ratio between duration and latency. By defining the ratio

$$\rho = \frac{d}{L}$$

And $d = \rho L$, then:

$$I(t) = 1/4 \cdot (4 - 6 \cdot \rho + 4\rho^2 - \rho^3) \cdot k \cdot f \cdot d \cdot L^3$$

The figure 1 graphically shows how the coefficient varies according to ρ

In practical terms, the dose-response model predicts that the cumulative exposure determined by an intensity kept constant from exposure start to time t would cause MM incidence at t to be equal to one fourth of that caused by the same exposure concentrated at the initial moment. This highlights that timing of exposure affects incidence, but at lower extent compared to what might be thought at first on the grounds that incidence is proportional to the third power of latency. In the study of MM epidemiology, the use of cumulative exposure to asbestos has a long standing tradition, as shown by our systematic review of the literature, and is a proxy of the relevant exposure.

The relevance of distinct exposure periods

MM cases quite commonly exhibit complex exposure patterns. A typical case with multiple, different and overlapping, occupational and non-occupational exposures, was discussed by Mastrangelo et al [2014].

The dose-response model adopted by the Second Consensus Conference and further explored above does not imply the existence of no-risk thresholds for duration, intensity or cumulative exposure. It does not imply either any threshold beyond which further increases in these factors would cease to increase MM incidence. Even with regard to latency, defined as time elapsed since exposure start, no threshold was established – unless a minimum value for latency is introduced, to account for the pre-clinical phase of tumour development, as suggested by some authors [Newhouse e Berry, 1976; HEI, 1991].

Nevertheless, the model does not assign the same strength to all exposures, as this is a function

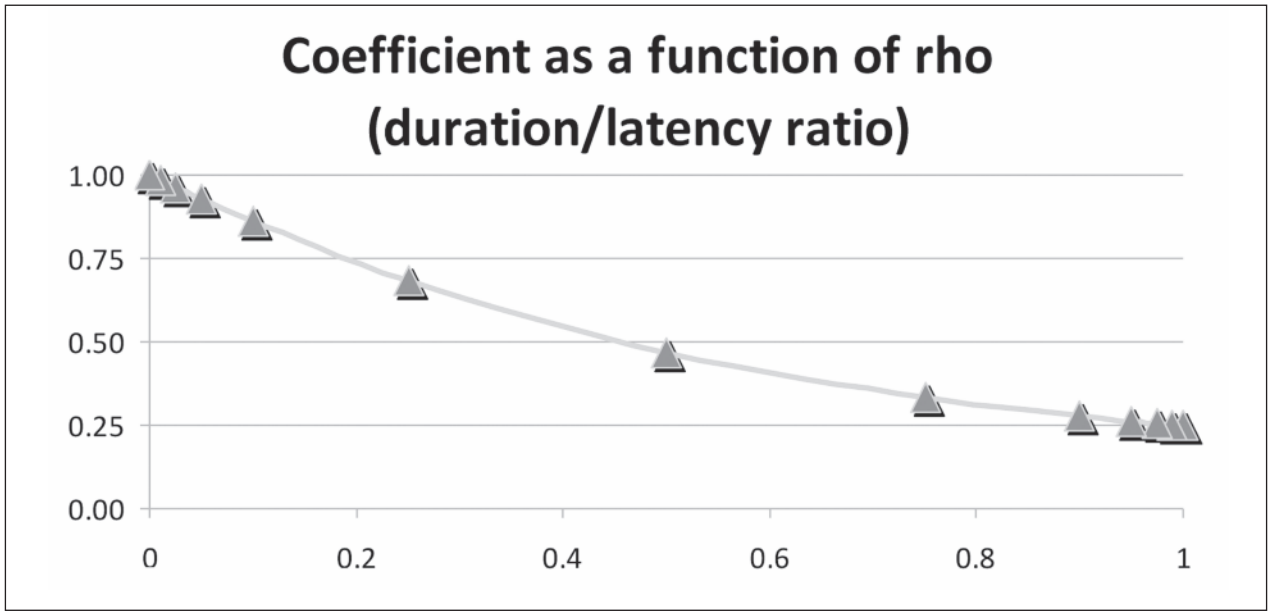

Figure 1 - The figure shows how the coefficient d (= ρ L) varies according to ρ

of: asbestos variety, intensity, duration and time since exposure. These factors do not have the same meaning. The first three - asbestos variety, intensity and duration - are the causal determinants of MM, amenable to modification by preventive interventions. The fourth - time since exposure - is simply the extension of disease-free life; it cannot be modified; it is stopped by the occurrence of MM or the death from a competing cause.

It has been suggested that the dose-response relationship may be used to assess the proportional causal weight of any distinct exposure period, if its characteristics are known or can be estimated [Price e Ware, 2005]. The feasibility of this approach to quantitatively assess the contribution from different exposure circumstances to causation of individual MM cases was shown by Mastrangelo et al [2014a]. Price and Ware [2005] estimate individual risk from the model developed using data from epidemiological studies [HEI, 1991]. 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?

The report issued by the Second Consensus Conference mentions the objection from one Working Group member, that cumulative dose is a misleading measure of exposure and an over-simplification. As (i) the time-related factor relevant for MM risk is latency and not duration, (ii) duration is a proxy for latency and (iii) cumulative dose is determined (also) by duration, cumulative dose would be spuriously associated with MM risk [Magnani et al, 2013].

The respective roles of duration and latency in the mathematical model for MM incidence has been clarified in a previous paragraph pointing out, in particular, that duration of exposure is a determinant of incidence.

Cumulative exposure does not allow to distinguish which of its components, duration and intensity, may possibly play a more prominent role, neither it allows to establish whether the temporal sequence of exposures is important [Checkoway et al, 2004]. To quantitatively investigate cancer etiology it is in theory important to assess long-term exposure patterns, which often consist of complex temporal sequences of different exposure circumstances.

From a practical point of view, however, this may prove hard to accomplish when exposures last long. Even if in certain studies efforts were made to disentangle the relative relevance of duration, intensity and cumulative exposure, they are limited to specific examples - lung cancer and either cigarette smoking or ionising radiation - with precise exposure assessment at the individual level [Lubin & Caporaso, 2006; Vlaanderen et al, 2013; Richardson et al, 2012]. Cumulative exposure, therefore, has long been, and still remains today, 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 [Thomas, 2013].

Moreover, in the case of asbestos six papers relating to five different studies also reported separate results by duration and intensity. The first is the cohort study on the Australian crocidolite miners, where mortality from pleural and peritoneal cancers was analysed in a nested case-control study [de Klerk et al, 1989] as well as through a traditional cohort analysis with internal reference [Musk et al, 2002]. The second is a nested case-control study on MM mortality in the cohort of Ontario (Canada) asbestos-cement workers [Finkelstein, 1991]. The third investigation is the mortality study of Wittenoom (Australia) residents [Hansen et al, 1998]. The fourth one is a population-based case-control study based on incident cases of pleural MM registered by the French "*Programme National de Surveillance sur le Mésothéliome*" [Lacourt et al, 2012]. Lastly, the mortality of workers employed in some plants in Calvados (France), where asbestos textiles and other asbestos goods were produced, was studied by Clin et al [2011]. In the study by Hansen et al [1998], only duration of exposure was found to be related with mesothelioma incidence. In the cohort of Calvados asbestos workers only average intensity, on the opposite, turned out to be significantly associated with mesothelioma mortality [Clin et al, 2011]. In the remaining studies, mesothelioma occurrence was a function of both intensity and duration. Overall, these papers offered consistent evidence that duration and intensity are independent determinants of MM occurrence.

Does exposure affect latency?

A number of studies were planned to provide an answer to the following research question: "Does an increase in exposure cause an anticipation of the occurrence of MM among asbestos-exposed subjects, as well as an increase in incidence?'". Commonly, however, this question has been confused and substituted with another one, that appear identical but, as we will show, is completely different "Does an increase in exposure shorten latency?" [Bianchi e Bianchi, 2009; Frost, 2013; Marinaccio et al, 2007; Neumann et al, 2001; Yeung et al, 1999; Zocchetti, 2013]. A further question asks whether an increase in exposure is paralleled by a younger average age at disease occurrence and, as a consequence, at death from MM [Metintas et al, 1999; Neumann et al, 2001]. We will consider here latency, age at diagnosis and age at death to be equivalent entities. The term "average" will be used here in a broader sense, including any central index of distribution.

Most authors decided to investigate the relationship between exposure and acceleration of failure time by analysing the latency of MM cases registered in population cancer registries [Bianchi e Bianchi, 2009; Marinaccio et al, 2007; Neumann et al, 2001; Yeung et al, 1999,] or occurring among cohort members [Metintas et al, 1999, Frost, 2013; Frost, 2014]. The average latency was compared among groups of cases with different exposures.

As an example of registry-based study we mention Neumann et al [2001], who compared the average age at diagnosis between cases with pleural and peritoneal MM, to infer a relationship between asbestos exposure level and anticipation of disease occurrence. In cohort-based studies, analyses of latency included only MM cases, as latency is known only for cases [Metintas et al, 1999; Frost, 2013]. This strategy of analysis is wrong because it does not take into account the population originating the cases [Thomas, 1987; Thomas, 1988; Langholz et al, 1999]. As to age at diagnosis, already in 1937 Austin Bradford Hill cautioned on the danger of considering age at diagnosis [Hanley e Foster, 2014; Hill, 1937; Hill, 1967]. The fundamental flaw of this kind of analysis was demon-

strated by Pike and Doll [1965], and has been described in textbooks [Colton, 1974; Rothman, 2012; Rothman, et al 2008; Weiss, 2012; Everitt, 2006; Kravitz, 2005] and papers [Consonni, 2013; Consonni et al, 2014; Hanley e Foster, 2014; Mirabelli e Zugna, 2014].

Cases reflect the characteristics of their population of origin: cases in a closed cohort (e.g. who were employed in industries no longer using asbestos because of ban) will necessarily have a progressively longer latency because the cohort is no longer in a steady state condition.

Latency and age at diagnosis, furthermore, are not known for individuals not affected by MM, generally constituting the large majority of cohort members [Consonni et al, 2014; Mirabelli e Zugna, 2014; Thomas, 1987 and 1988]. To overcome these fundamental limitations the survival analysis methods were developed. These are based on the risk-set concept, that is the inclusion in the analsysis of all individuals at risk of disease, not only of cases [Thernau e Grambsch, 2000; Thomas, 1987], as highlighted by Mirabelli and Zugna [2014].

Two further factors worsen the fallacy of case-only analyses: 1) the first, almost invariably present, is late entry at observation, as the fact that cohort members start exposure during different calendar periods [Consonni, 2013] depends on historical determinants, such as general socio-economic dynamics (the rise and decline of asbestos industrial activities); 2) the second is left censoring, that occurs when the study subjects are not observed since their first exposure, but only starting at some later time, as in the cohort studied by Frost [Farioli et al, 2014; Frost 2013; Frost, 2014]. Whereas in a cohort study all of the above mentioned factors may be at work, in dynamic populations, such as those served by cancer registries, late entry is likely to play a major role.

In conclusion: the analysis of latency based on a period approach, as from population registry data, is fallacious because its results do not depend on the relationship between exposure and disease, but on the material boundaries of the observation: the observation time is fixed [by the observer) and the distribution of exposure in the population had been historically determined. Analyses based on a cohort approach are also fallacious, as failure time can be determined only for a minority of at risk individuals, due to the combined effect of censoring and competing mortality.

The correspondence between an increase in incidence, e.g. due to an exposure, and acceleration of failure time was illustrated in handbooks of epidemiology (see, for instance, chapter 3 in Rothman et al, 2008). It has been also observed in experimental studies of animal carcinogenesis [Guess e Hoel, 1977]. It has been pointed out: "*The inappropriateness of trying to distinguish between earlier onset and more onsets is particularly relevant for tumours with onset rates which increase steadily with age. Such tumours include the majority of all human tumours and the majority of animal tumours elicited under conditions of chronic exposure…*" [Peto et al, 1980].

The figure 2 shows incidence during an observation time of fixed duration (40 years) after continuous exposures, at two levels of exposure of a causal factor for a disease (line marked with squares: high exposure, alternative scenario, versus line marked with triangles: low exposure, reference scenario). The difference in incidence corresponds to an anticipation of the time needed to reach a specified incidence rate (horizontal arrows). The two dimensions cannot be disentangled.

The cases that occur during the observation period in the reference scenario, in the alternative scenario are anticipated (as represented by horizontal arrows) because of the exposure. Further, a number of apparently additional cases occur (represented by vertical arrows). Indeed, also these additional cases are anticipated, but with respect to a failure time that cannot be observed in the reference scenario, as it falls beyond the end of follow-up. As a consequence of this phenomenon the distribution of the failure times that can be observed during follow-up and their average are basically identical in the two scenarios. Neither the average value of latency, therefore, nor any other parameter of its distribution may change, if not by chance.

In summary: the idea that the acceleration of failure time can be estimated using the average latency is perhaps intuitively attractive, but wrong. Similarly, it is wrong to infer that when no change in latency is observed, no acceleration of failure

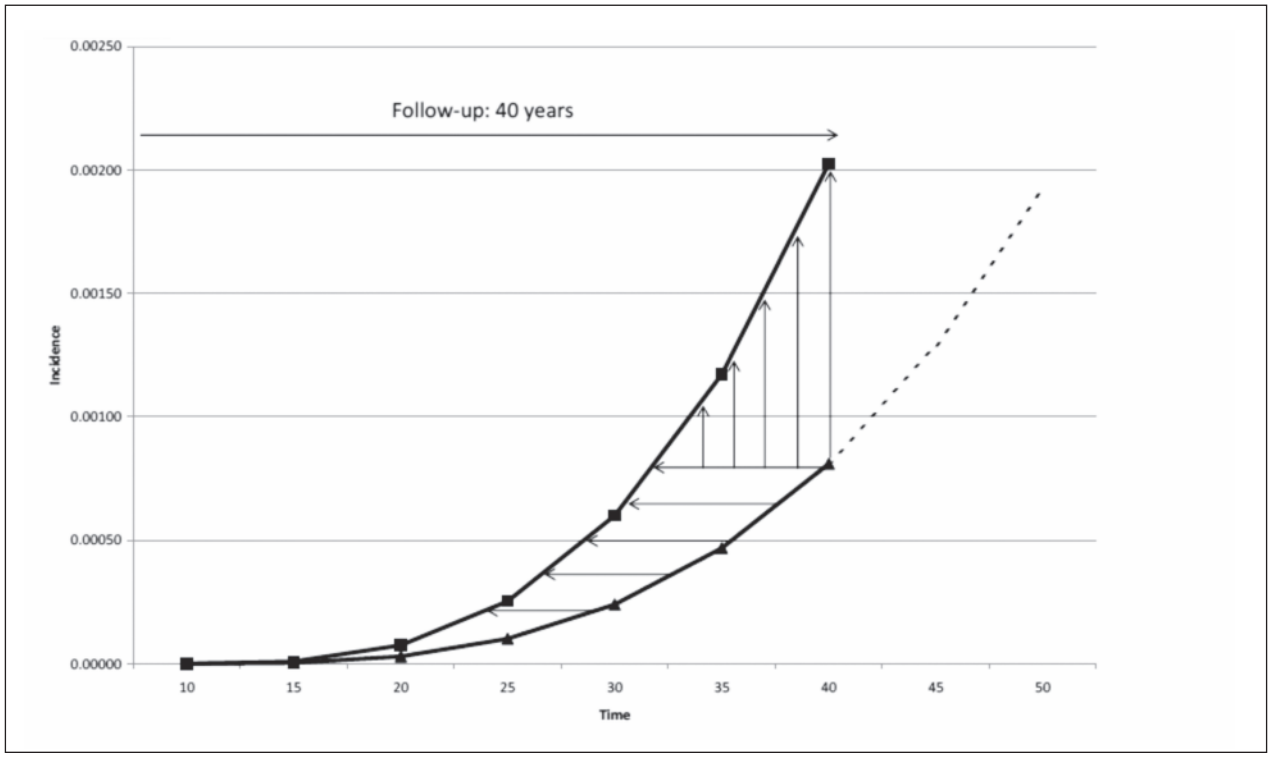

Figure 2 - The figure presents the variation of incidence during an observation time of fixed duration (40 years) after continuous exposures, at two levels of exposure of a causal factor for a disease
line marked with squares: high exposure, alternative scenario
line marked with triangles: low exposure, reference scenario

time occurred. An increase in exposure causing an increase in incidence in the target population necessarily entails the acceleration of failure time, as the relationship between increase in incidence and acceleration of failure time is mathematically determined [Berry, 2007]. Nevertheless and contrary to what intuition might suggest, the average latency would be unaffected[1].

Genetic factors in MM (co-authored by Irma Dianzani

The final document approved in the II Italian Consensus conference on Malignant Mesothelioma (MM) evaluated the scientific evidence on familial risk and on genetic risk factors for MM. In summary, it was noted that the proportion of MM cases in familial aggregations was very small (in the order of 1-2%) and studies were reported on the possible association with genetic polymorphisms in the DNA repair and with mutations of the BAP1 gene.

New epidemiological observations were reported on the familial risk in the Wittenoom cohorts [deKlerk et al, 2013] and on familial MM clusters in an Italian region [Ascoli et al, 2014]. deKlerk et al [2013] in the Wittenoom cohort observed that, given the same asbestos exposure, first and second degree relatives of MM cases have an increased risk (OR= 1.9) to develop a MM. The risk was not increased for spouses, and the authors underlined genetic characteristics as the most likely interpretation. The study included 27 (7%) familial out of a total of 369 MM cases. Ascoli et al [2014] measured the frequency of MM familial clusters in the

[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".

Mesothelioma Registry of Latium in 2001-2012 and in a large pathology based registration in the same area in 1980-2000. They observed 34 MM cases, corresponding to 3.4% of total registration (14/206 in 1980-2000 and 20/791 (2.5%) in 2001-2012), forming 13 familial clusters. The Working Group noticed that the very high frequency in 1980-2000 may be determined by selection bias, and also that frequency in 2001-2012 was higher than that observed from the same authors [Ascoli et al, 2007] in other Italian regions. The authors did not comment on the latter observation; the Working Group noticed that the most recent work may have been more sensitive in the identification of familial relations of cases. Out of 34 MM cases, 13 had experienced occupational asbestos exposure (in 7 families), 10 household exposure (2 families), 4 environmental (1 family), while for the remaining either no exposure was detected (5) or could not be classified because of limited information (2). A previous observation was published by Bianchi et al [2004], who observed in a highly 40 familial cases, out of 610 pleural MM (6.6 %), all exposed to asbestos.

BAP1 is an oncosuppressor gene, that is frequently inactivated in MM tumor genome (somatic mutation). Several studies were published on BAP1 mutations in families at high risk for MM (families with 2 or more cases) [reviews in Carbone et al, 2013 and Betti et al, 2015]. The rare BAP1 cancer predisposition syndrome includes MM, uveal and cutaneous melanoma, renal cell carcinoma, as well as other tumor types [Betti et al, 2015]. Preliminary data suggest that the type of tumor is related to the exposure to specific carcinogens. Carriers of the germline mutation are at risk for a second mutation, according to Knudson's two-hits model. Early referral to cancer genetic clinics is recommended on the suspicion of the syndrome. After the initial report by Testa et al [2011], the occurrence of genetic (germline) mutations in sporadic MM cases was measured by Betti et al [2015] in Italy, Rusch et al [2015] in Switzerland and Sneddon et al [2015] in Australia. Results on the frequency of BAP1 germline mutations in sporadic MM were: Testa et al [2011]: 2 / 26 (both affected by uveal melanoma also); Rusch et al [2015]: 1 / 78 (brother affected by leukemia); Betti et al [2015]: 0 / 103 and Sneddon et al [2015]: 0 /115. Therefore, prevalence of BAP1 mutations in sporadic MM can be estimated between 1/296 (0.36%) and 3/322 (1.4%). The lowest figure corresponds to all the studies published after the initial report by Testa et al [2011] while the highest corresponds to all the studies published in extenso. We are not aware of estimates of the prevalence of BAP1 mutations in the general population, and we deem it very rare indeed, based on these figures and on similar figures from the studies on uveal melanoma [review in Betti et al, 2015].

Regarding low penetrance genetic factors, two GWAS were conducted in Italy [Matullo et al, 2014] and in Australia [Cadby et al, 2014]. Results of GWAS studies are of difficult interpretation:

- Both studies discovered genetic variants (SNPs) with different prevalence for cases and controls;
- The two studies do not show the same genetic variants as in association with MM risk, albeit the results overlap for some of the associated regions;
- Replication of the results was limited;
- Some genetic variants and some regions correspond to genes with known functions related to pathogenetic mechanisms of interest for MM.

In summary, genetic predisposition was observed for MM, as for other neoplasms, but its role is very limited. Association with low penetrance (common variants) and high penetrance genetic factors (rare variants) was investigated. Knowledge is more limited regarding low penetrance factors: results from the two GWAS deserve further investigations, with larger studies. The high penetrance factor more investigated so far is BAP1 gene, that is involved in a cancer syndrome including different tumor types. Current data are too limited for the estimation of the risk of MM attributable to genetic factors in the population. Prevalence of BAP1 germline mutations in the population is unknown. However, the low frequency of such a mutation in sporadic MM cases (between 0.34 and 1.4%) is a reason to believe that it is a rare condition. Occurrence of blood related MM cases is also rare: in the two Italian studies it was between 1.3 and 2.5%, based on the pop-

ulation based registry data. The range is a preliminary basis for estimating the fraction of MM cases in familiar clusters in the population, with consideration to the fact that asbestos exposure is determinant for the pathogenesis of cases in familial clusters. Early referral to cancer genetic clinics is recommended on the suspicion of familial syndromes, such as blood related MM cases.

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

Procedures currently used for diagnosis as well as for therapeutic and prognostic assessment are discussed elsewhere in the consensus document. This Working Group agreed on limiting the evaluation to epidemiology relevant aspects, regarding: i) population estimation of incidence, mortality and survival; ii) medical and epidemiological research regarding MM.

International guidelines underline the importance for the diagnostic process of MM of the gross appearance of the tumour, in the context of appropriate clinical, radiologic, and surgical findings and of the hematoxylin-eosin-based histology [Husain et al, 2009; van Zandwijk et al, 2013].

Recent consensus documents underline the importance of multiple biopsies (at least 5 samples) for the diagnosis of MM [Husain et al, 2012; Pinto et al 2013]. The pathological diagnostic process begins with the evaluation of gross appearance and routine hematoxylin-eosin staining. "Most MMs are readily identified or strongly suspected on routine hematoxylin-eosin staining where they exhibit a variety of histologic subtypes, broadly divided into epithelioid, sarcomatoid, or mixed (biphasic) categories" [Husain et al, 2012]. "The current reference diagnostic method is mainly based on light microscopic examination of tissue samples stained with conventional hematoxylin–eosin and immunohistochemical stains" [Pinto et al, 2013].

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. "A definitive diagnosis of MM requires a workup including immunohistochemistry and in some cases, histochemical stains for mucin. 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 (adenocarcinoma, squamous cell carcinoma, malignant melanoma, epithelioid hemangioendothelioma)" [Husain et al, 2012]. Consensus conferences agreed on the evaluation that, even if a large selection of immunohistochemical markers is currently available, not all MM cases can be definitely identified [Husain et al, 2012; Oksa et al, 2014]. Sarcomatoid and desmoplastic MMs may be completely negative for markers of mesothelial differentiation and their diagnosis may be posed on clinico-radiologic features, negativity for non-mesothelial markers and lack of alternative diagnosis.

Markers of interest present high sensitivity and specificity, as evaluated for each marker, but this does not exclude a sizable proportion of false positive or false positive diagnoses. Husain et al [2012] suggest that selected markers should present at least 80% sensitivity and 80% specificity, values that implicitly admit up to 20% of false positives and false negatives. Immunohistochemical markers are more useful for epithelioid than for mixed or sarcomatoid MM [Pinto, 2013]. Standardized procedures are needed in order to reduce intra and inter-laboratory variability, for both single markers and for panels of different markers. Even after the diagnostic revision by a panel of expert pathologists, a proportion of cases is classified as probable or doubtful MM [Betta, 2012; Husain,2012].

Identification and classification of MM cases for epidemiological surveillance

In Italy, population based registration of MM is carried on by the General Cancer Registries and by the special MM registries, at the national (ReNaM) and regional (COR) level of organization. Details were provided elsewhere [Pinto et al, 2013; ReNaM, 2012].

Cancer registries in general must adopt standard rules for the identification, coding, and registration of cases, as a prerequisite for analysis of incidence, and for geographic and trend analyses [Esteban,1995]. Standard rules were developed by cancer registries in the Italian Association of Cancer Registries (AIRTUM), following international guidelines. Data of interest include personal data of the subject and clinical and pathological data of the tumor (site, morphology, behavior, therapy and prognosis) [http://www.registri-tumori.it/cms/]. Standard rules were defined for the same purposes by the ReNaM and COR special MM registries [update 2003: http://www.ispesl.it/ReNaM/LineeGuida.asp].

Cancer registries, either general or specialized, do not diagnose cases but search them in the appropriate clinical departments or in the appropriate data files. Cases are then classified and entered in the Cancer Registry files according to the above mentioned standardized procedures. Cases are accepted on the basis of the clinico-radiologic and pathological diagnosis, based on the methods in use at the time of diagnosis. More severe selection procedures would cause a loss of cases.

Classification of tumor type takes into consideration morphology, site and diagnostic procedures. International Classification of Disease for Oncology (ICD-O) is the current standard for General Cancer Registries. ReNaM uses a composite code including the summary evaluation (MM certain, MM probable, MM possible) and the diagnostic basis [ReNaM 2003]. A comparison of MM cases incident in 2000- 2004 in the General Cancer Registries and in the corresponding ReNaM regional registries (COR) showed a good agreement on MM cases classified as certain (from 67 to 100% of MM cases were corresponding) [Nicita et al, 2014]. Better agreement was obviously observed when the registries active on the same area shared procedures and data evaluation. Differences in the date of diagnosis were observed, that may reflect on annual incidence rates or on survival analyses.

On this basis the Working Group suggested that 1) General Cancer Registries and 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. 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.

Identification and coding of MM for medical research purposes

In general, for research it is mandatory to use the most accurate diagnostic procedures [Allen, 2013), but according to the different study design, either completeness or diagnostic certainty may be the most relevant issue. Moreover, studies with retrospective data collection must take into consideration the diagnostic procedures in use at the time of the diagnosis of the cases. If only the more recent methods were used, some cases would be wrongly excluded.

In clinical trials, cases must be diagnosed using the most accurate methods. Misclassified cases would determine errors in the study conclusions and in the estimates of efficacy.

In analytical epidemiology studies, diagnostic requirements change according to the study type.

In cohort studies, completeness is mandatory, as in descriptive epidemiology studies. These studies compute rates or compare the observed and the expected number of cases. The loss of cases would systematically correspond to a lower risk estimate. In the case of studies with a very long period of observation, diagnostic methods are likely to improve over the study period but the diagnostic procedures in use at the time of the diagnosis of the cases should always be used. Best evidence studies are also an option, but appropriate statistical methods are needed.

In case-control studies, accurate selection of cases is more important than exhaustivity, as in clinical trials. Common selection criteria include pathological diagnosis, with supplementary investigations and panel verification. These methods may

not be always applicable in ordinary activity, because of costs or lack of tissue samples.

Health surveillance of asbestos exposed and ex-exposed subjects

Early diagnosis of MM

Tools for early diagnosis and effective screening programs regarding MM are not available so far. Chest radiography was early evaluated as ineffective in screening for MM in asbestos-exposed workers [Harries et al, 1972]. More recently low dose computer tomography (CT) was also found ineffective in detecting MM in early stage [Fasola et al 2007; Robert et al, 2009]. Use of positron-emission tomography (PET) as screening tool for MM is strongly limited by false positive results due to inflammatory lesions [Orki et al 2009]. Magnetic resonance imaging (MRI) frequently suffers from artefacts due to motion, has limited spatial resolution and the adverse reactions to contrast medium limit its routine use [Helm et al, 2010]. Some CT studies aimed at lung cancer and ARD detection in asbestos exposed groups also identified MM cases [Tiitola et al, 2002; Roberts et al, 2009], however to date no evidence supports the introduction of CT for early diagnosis of MM [Oksa et al, 2014].

Several soluble biomarkers has been evaluated in pleural fluid for early diagnosis of MM, including cytokeratin fragment 21-1, tissue polypeptide antigen (representing fragments of cytokeratins), cell surface antigens (CA 15-3, CA 19-9), carcinoembryonic antigens (CEA), and hyaluronic acid [Greillier et al, 2008], none of them with sufficient sensitivity and specificity. Levels of C-C motif chemokine (CCL2) has been observed to be higher in MM patient than in subjects with metastatic adenocarcinoma or nonmalignant pleural effusions, however its low specificity prevents the use as early diagnostic tool [Gueugnon et al, 2011]. Recently, combinations of CCL2, galectin-3, and soluble mesothelin-related peptides (SMRP) were proposed as screening tools [Blanquart et al, 2012; Canessa et al, 2013], however further studies are needed before their use in clinical routine. Moreover the analysis of pleural fluid is appropriate in the context of early diagnosis of symptomatic cases with pleural effusion but not in screening of non-symptomatic subjects.

Among proposed serum biomarkers for MM early diagnosis, SMRP and osteopontin are those that have been most evaluated. To date none of them showed useful in early diagnosis of MM [Oksa et al, 2014]. High levels of fibulin-3 were observed in serum of patient with pleural MM [Pass et al, 2012], but also this result deserves further validation studies before been proposed as an early diagnosis tool and more recent investigations do not support the first positive results [Creaney et al, 2014]. Encouraging results were observed for some microRNA (miRNA) in plasma, serum and peripheral blood [Kirshner et al, 2012; Weber et al, 2012; Tomasetti et al, 2012; Santarelli et al, 2011], though, as others biomarkers, they are not available for clinical and routinely purposes, at present.

Furthermore, no evidence of a positive impact of an early diagnosis of MM on mortality is available at present. Scarce evidence showed a limited increase in survival in patients diagnosed with MM at early stage [Sugarbaker et al, 1999; Nakas and Waller 2014], and further studies are needed. The psychological impact of an early diagnosis without an effective treatment that improves quality of life or survival could be devastating and has to be avoided. More generally, health surveillance of asbestos current and former exposed should be targeted to all ARD, and not only MM.

Health surveillance programs

The precondition of effective health surveillance programs is the identification, as precisely as possible, of the real (current or former) exposed workers. With the exception of validated list of workers in asbestos using industrial settings, sensitivity and specificity of the rosters of asbestos exposed workers must be assessed. Moreover, it is desirable to develop programs that monitor the fruition of all those entitled, to detect any differences among beneficiaries.

The health surveillance for current workers with potential asbestos exposure is compulsory in Italy,

being regulated by the laws 257/2006 and 81/2008. These workers have to undergo a medical examination, at least once every three years, including pulmonary function tests if requested by the occupational physician. Thorax standard radiography or CT are not included among first step approaches for health surveillance, due to the uncertainty of their cost-benefit profile, and they have to be considered case by case by the occupational physician. Continuation of health surveillance at the end of working activity is recommended [law no. 81/2008, art. 259], in particular for workers who have been included in the Registry of asbestos exposed workers.

Recently the updated Helsinki Criteria [Oksa et al, 2015] recommend that health surveillance has to be carried out on current and former asbestos workers "*according to the intensity and duration of exposure*" and "*priority should be given to workers with high cumulative asbestos exposure*". Follow-up should be prolonged for at least 30 years after exposure cessation. For exposure assessment, questionnaires are reliable tools and can be used also to record current symptoms. Estimated cumulative exposure in fibre-years is an appropriate estimation of worker's exposure [Oksa et al, 2014]. Serial medical examinations and spirometry are recommended at 3-5 years interval time, depending on exposure level, time from cessation of exposure, and age. Carbon monoxide alveolar-capillary diffusion should not be used as a screening test.

Even if cigarette smoke is not a risk factors for MM, smoking habits have to be collected, including age at start, number of cigarettes smoked per day, length of smoking habits and cessation date, given that the health surveillance regards prevention of asbestos related diseases, most notably lung cancer. Exposed workers must be aware of the increase in risk due to smoking and asbestos exposure, and anti-smoking counselling programs should be part of the clinical health surveillance. Regarding the CT screening for asbestos-related lung cancer the Authors of Helsinki Criteria recommend LD-CT screening for the following: i. asbestos exposed workers with a smoking history equal to the entry criteria of the NLST study; ii. workers with asbestos exposure with or without a smoking history, which alone or together (asbestos and smoking interaction) would yield an estimated absolute risk of lung cancer equal to that in the entry criteria of the NLST study [NSLT team, 2011].

For asbestosis, high resolution computer tomography (HRCT) is the recommended imaging technique, and ICOERD standardized criteria should be used [Oksa et al, 2014].

Pneumococci and influenza vaccination and early treatment of respiratory infection should be encouraged among exposed workers with lung fibrosis [Oksa et al, 2014].

In recent years, several studies have been conducted with the use of non-invasive techniques such as the electronic nose (e-nose) and the exhaled breath analysis in order to detect biomarkers of early signs of asbestos-related diseases and of their progression [Lehtonen et al, 2007; Pelclova et al, 2008; Dragonieri et al, 2009 and 2012; Carpagnano et al, 2014], small airways pathologies [Lehtimaki et al, 2010; Dragonieri et al, 2012], or other biomarkers as mesothelin-related peptides/proteins, osteopontin, microRNA, and epigenetic changes, as described in the updated Helsinki criteria [Oksa et al, 2014]. For these methods further investigation is required before their routine use in current or former asbestos populations.

On the occasion of health surveillance, in particular for former exposed workers, patients should be informed about their health risks and their rights to claim compensation for asbestos-related disease.

Given all these considerations, health surveillance of asbestos exposed workers has:

- To inform each subject about his own risk related to (present or past) asbestos exposures;
- To inform relatives of asbestos exposed subject of their possible health risks;
- To fully reconstruct occupational history, especially regarding asbestos exposures;
- To provide information about diagnostic tools, therapeutic and forensic medicine perspectives;
- To support claims for compensation;
- To give counselling on smoking cessation and on other relevant matters related to health and life style.

Not least, the health surveillance of asbestos exposed workers should be structured to provide data

for scientific studies, both epidemiological and clinical, to improve knowledge about asbestos-related diseases, especially MM.

Social and economic cost of MM

To provide a reliable estimate of the economic burden associated to MM, it is necessary to include medical care, insurance and fiscal costs, and human capital costs related to productivity loss. With this comprehensive econometric approach, an estimate of 288,000 euro per MM case has been recently provided as the sum of medical (33,000), insurance (25,000) and productivity loss (230,000) costs for the society [Iavicoli et al, 2014]. The economic benefits of improving health and safety at work, eliminating asbestos exposure in work and living places, must to be underlined and further studies are recommended to keep economical evaluation updated.

Extrapleural Mesothelioma

In addition to the chest, other body cavities are lined by a mesothelium layer, corresponding to the peritoneum the pericardium and the tunica vaginalis of the testis. Mesothelioma can occur in these locations as well as in the pleura. Peritoneum and pericardium can also be interested to MM spreading from the pleura, and spreading to the pleura of peritoneal MM can also occur.

As regards morphology, extrapleural MM presents the same morphological characters as pleural MM, with epithelioid or sarcomatoid or mixed morphology. Epithelioid MM is the most frequent form.

Early symptoms can be non specific (asthenia, fever) or related to the location, pain and effusion being the most common. In women differential diagnosis between peritoneal MM, in particular of the epithelioid tubular-papillary histology, and ovarian cancer can be challenging, because of the common embryogenesis of the interested tissues. Misclassification bias is likely to cause the loss of the rarer disease in favour of the more common, with a consequent underestimate of incidence rate of peritoneal MM.

Diagnosis and treatment of peritoneal and pleural MM usually involve different medical specialties, the former being more often treated in general medicine or abdominal and gynecological surgery wards. These differences are cumbersome in the data collection of a mesothelioma registry and if not properly considered can cause a loss of cases.

In Italy in 2008, incidence was: 0.22 x 100000 in men and 0.10 in women for peritoneal MM (age adjusted, using only data from the areas with the highest standards of data collection, and limited to the 'certain' diagnoses), and 0.01 x 100.000 for MM located to the vaginalis of the testis. It could not be computed for MM of the pericardium, however, in men, estimated incidence, including also the 'doubtful' diagnoses, was 0.003 x 100000. In 1993-2008, the Italian Mesothelioma Registry (ReNaM) included a total of 12,329 MM cases (certain diagnoses only), of which 834 were peritoneal MM, 30 pericardial, and 47 of the vaginal lining of the testis [ReNaM, 2012]. Incidence by age shows an anticipation for peritoneal compared to pleural MM [Marinaccio et al, 2010]. Incidence rates of peritoneal MM measured in other countries (Eurocim for Europe and SEER for US) are similar to the data observed in Italy. International incidence trends are stable or increasing [Boffetta 2007].

According to IARC Monograph 100 C [*IARC, 2012*] and to WHO "*Chrysotile Asbestos*" document [*WHO, 2014*], all mineralogical types of asbestos are carcinogenic for humans. Cohort studies of workers exposed to asbestos showed excesses of peritoneal MM after exposure to amosite, crocidolite and chrysotile asbestos, as well as to mixed asbestos fibres [Boffetta, 2007].

After inhalation, asbestos fibres are transported to other organs through lymphatic or haematic circulation [Dodson et al, 2000; Kahn et al, 1980; Miserocchi et al, 2008]. As regards peritoneal MM, it was reported that abdominal surgery, and use of talc containing asbestos fibres for personal hygiene, or on surgical gloves causes the transport of asbestos fibres to the peritoneum and to the ovary [Huncharek et al, 2011; Bounin et al, 2014]. Epidemics of MM, including peritoneal MM were

caused by erionite in Turkey and Mexico [Baris et al, 2006; Ortega-Guerrero et al, 2015].

Pleural and peritoneal MM are also associated to radiation exposure for medical use. Exposure to Thorotrast, a diagnostic X-ray contrast medium used in the '50s and emitting alpha radiation caused cases of peritoneal MM [Travis et al, 2003; Pinto et al, 2013]. External irradiation of abdominal lymphonodes (e.g. for the treatment of lymphoemopoietic or prostatic cancer) was associated to peritoneal MM [Farioli et al, 2013]. Similar results were reported for pericardial MM after irradiation of the mediastinum [Bendek et al, 2010].

Occurrence of peritoneal MM has been associated to high asbestos exposure, corresponding to the observation of high lung asbestos burden of peritoneal MM cases [Dodson et al, 2000; Barbieri, 2011]. In Italy the areas presenting high frequency of pleural MM also show high frequency of peritoneal MM [Bruno et al, 1990].

The proportion of cases with asbestos exposure is lower for peritoneal than for pleural MM [Boffetta et al, 2007; Marinaccio et al, 2010; RENAM, 2012]. In ReNaM, the proportion with definite asbestos exposure was 70% for peritoneal MM vs 80% for pleural MM [Marinaccio et al, 2010]. Prevalence of exposure for cases of MM of the pericardium or the vaginalis of the testis is even lower, and evidence of the association with asbestos is also based on case reports [Gorini et al, 2005; Marinaccio et al, 2010; Mensi et al, 2011, Mensi et al, 2012].

After asbestos exposure, risk of peritoneal MM shows a continuous increase, contrary to pleural MM, that show a flattening of the increase of risk after 40-50 years of latency [Reid et al, 2014].

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