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Malignant mesothelioma and the working environment: the viewpoint of the occupational physician

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Key words

Occupational physician, working environment, etiological diagnosis, asbestos exposure assessment

Summary

Background: *Firm scientific evidence supports the causal association between malignant mesothelioma (MM) and occupational exposure to asbestos. Risk attributable to occupation varies from 30 to 80% across different populations. The existence of a threshold level below which there is no risk of MM is still debated. A prompt and thorough assessment of exposure is essential to evaluate and manage MM cases, from diagnostic and epidemiological points of view.* **Objectives and methods:** *To highlight the multiple areas of intervention by Occupational Physicians (OP) in MM evaluation and management, to describe an experience of OP in the province of Brescia.* **Results:** *The main areas of interest of the OP are exposure assessment, diagnosis (clinical, etiological), medico-legal issues, social consequences, preventive strategies, risk communication, scientific dispute/uncertainties. By means of an active search, the Brescia MM registry, managed by OP belonging to the local health authority observed 309 MM from 1977 to 2003; the local Institute of Occupational Health, hosted in a hospital of national relevance, evaluated about 200 MM in the last decade. The main outcomes of OP activity are the high percentage of direct interviews, individual case management, expert exposure assessment, etiological diagnosis, counselling, medico–legal assistance, better knowledge of occupational risks, enhanced cooperation among health professionals (oncologists, pathologists, surgeons, pneumologists, general practitioners and OP), important contribution to Registries and to epidemiology (estimates of attributable risks, incidence, survival rates), with positive social and scientific consequences (insurance agencies, trade union organizations, public events, teaching opportunities).* **Conclusions:** *This experience highlights the multifaceted role of OP in active research and evaluation of MM cases, in the context of a multidisciplinary approach.*

Riassunto

«*Mesotelioma maligno ed ambiente di lavoro: il punto di vista del Medico del Lavoro*». *È ben nota la relazione esistente tra mesotelioma maligno (MM) ed esposizione occupazionale ad amianto, molto diffusa in passato in numerosissimi settori industriali ed è ancora oggi presente in alcune attività lavorative. La stima del rischio attribuibile all'occupazione varia tra 30 e 80% a seconda della casistica e della popolazione considerata. È ancora oggi dibattuta l'esistenza di una dose-soglia al di sotto della quale non vi è incremento di rischio di contrarre MM. L'accertamento dell'esposizione occupazionale ad amianto è indispensabile per la valutazione del MM, sia dal punto di*

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vista diagnostico che epidemiologico, ed il medico del lavoro (MdL) riveste un ruolo fondamentale. È stata condotta una ricerca nella letteratura nazionale ed internazionale e sono stati sintetizzati i risultati dei principali studi epidemiologici che hanno indagato il rischio di contrarre MM tra i lavoratori esposti ad amianto. Inoltre, sono state affrontate le tematiche dell'accertamento dell'esposizione ad amianto, sottolineando il ruolo svolto dal MdL, e le problematiche correlate al nesso di causalità e all'attribuzione della neoplasia. Il contributo del MdL è evidenziato attraverso la descrizione dell'esperienza condotta in provincia di Brescia, un'area intensamente industrializzata del Nord Italia con un'incidenza annua di MM indicativamente pari a 2,5/10^5 nel periodo 2000-2003. Da molti anni e' stata avviata una ricerca attiva dei casi di MM dal Servizio di Medicina del Lavoro dell'ASL, condotta su scala provinciale in tutti i nosocomi nell'ambito delle attività del Registro Mesoteliomi della Provincia e dall'Istituto di Medicina del Lavoro dell'Università di Brescia, che opera in un ospedale di rilevanza nazionale per la diagnosi e la cura della neoplasia. Nel periodo 1977-2003, 309 casi di MM residenti nella provincia sono stati valutati ed inseriti nel Registro MM. Negli ultimi 10 anni, 200 soggetti affetti da MM ricoverati nel principale ospedale bresciano e provenienti da varie province, sono stati sottoposti ad accertamenti. Tra i principali risultati della ricerca attiva sono da annoverare la elevata percentuale di interviste dirette effettuate, l'efficiente gestione del caso individuale, con rilevanti approfondimenti per l'accertamento dell'esposizione, la formulazione della diagnosi eziologica, il counselling e gli adempimenti medico-legali. Inoltre, altre rilevanti conseguenze sono state la valutazione dei rischi occupazionali nella comunità locale (evidenziazione di clusters, eventi sentinella, esposizioni misconosciute) e l'attuazione di interventi preventivi negli ambienti di lavoro, la ricerca e collaborazione tra specialisti (pneumologi, patologi, chirurghi, medici di medicina generale, igienisti industriali e medici del lavoro) con conseguente sensibilizzazione ed accrescimento culturale. La ricerca attiva ha significativamente contribuito ai Registri MM (a livello regionale e nazionale) e alla epidemiologia (valutazione del rischio attribuibile, incidenza, sopravvivenza), con importanti ricadute sociali (rapporti con istituti assicurativi, patronati, organizzazioni dei lavoratori), scientifiche (ricerca, divulgazione) e didattiche. L'esperienza nella provincia di Brescia nel complesso ha evidenziato le molteplici aree in cui è fondamentale ed efficace l'intervento del medico del lavoro nella valutazione e gestione del MM, nel contesto di un approccio multidisciplinare.

INTRODUCTION

Malignant mesothelioma (MM) is a rare and aggressive tumour, which is most frequently located in the pleura. It is characterized by very poor survival, low background incidence (1-2 cases/million), high prevalence (5-10%) among subjects exposed to asbestos, with projections of an increasing incidence at least for the next 1-3 decades (Bertazzi, this issue). The attributable fraction estimated for occupational asbestos exposure is very high (30-80%), with no epidemiological evidence of a threshold below which there is no risk of developing MM and no epidemiologically relevant determinant factors other than asbestos exposure (with the exception of erionite exposure in selected geographical areas; Pasetto et al, this issue).

The disease has a significant impact both at the individual level and for society at large. In fact, many occupational health professionals are involved in the evaluation and management of MM cases for various aspects, such as those related to exposure assessment, clinical diagnosis, etiological attribution, medico-legal issues, planning and implementing of preventive strategies, risk communication, as well as various research questions mainly pertaining to dose-response assessment and mechanism of action. Among these professionals, the role of the Occupational Physician (OP) should be emphasized.

The aims of this paper are to explore the relationship between MM and occupational environment from the OP viewpoint, and to highlight the multifaceted contribution of the OP to the evaluation of MM cases within the framework of current scientific dispute and uncertainties, and through description of our experience on MM case-series arising in a highly industrialized area in Northern Italy.

Mesothelioma and occupational asbestos exposure: a glance at history and some epidemiological findings

The commercial term "asbestos" includes some naturally occurring mineral fibres having unique physical and chemical properties. During the Industrial Revolution, asbestos was used in a large variety of industrial activities and jobs, which reflect its great strength, heat resistance and flexibility. Manufacture and use of asbestos peaked in the late 1960's – early 1970's in Western Europe, North America, Australia. Workers were exposed to asbestos in many industrial areas, with a wide range of job tasks in hundreds of applications, such as manufacture of asbestos-containing tiles, roofing shingle, friction products, gaskets, coatings, sealants, reinforced plastics, pipes and flat sheets, tiles, textiles, insulation boards, fire-proof suits, blankets, gloves and shoe covers (17, 25).

As a consequence of global asbestos epidemics, by the early 1970's many industrialised countries began to legislate in order to restrict production and use of asbestos. Nowadays, the only relevant occupational exposure occurs in maintenance, removal or disposal of asbestos containing materials, especially railway carriages, building materials, heating/ventilating systems; the so-called in-place asbestos materials may also be a source of exposure, in selected circumstances. These situations are not the case for countries in transition, where significant production and uses still occur (30, 31, 36, 40, 41, 45, 56, 65).

The first systematic descriptions of MM attributable to asbestos appeared in the '50s. Wagner et al (1960) first reported 33 cases of pleural MM living in a circumscribed geographical area in South Africa, close to an asbestos mine: 8 of these subjects were occupationally exposed (64). In 1965, the International Conference on "Biological Effects of Asbestos" devoted a session to MM (55).

Since the mid-sixties, epidemiological surveillance of MM cases, on a population basis, has been progressively established in many countries worldwide. Identification of asbestos exposure for each case is a shared aim of MM Registries; however, methodology, data collection and exposure assessment/evaluation differ widely among nations. In particular, the Italian National MM Registry considers lifetime occupational history in terms of probability of exposure to asbestos and adopts the following categories of exposure: definite, probable, possible, domestic, environmental, leisure time, unlikely, unknown (for further details, see Nesti et al., this issue). Worldwide, national or local institutions of occupational health and various occupational health professionals are actively involved in MM registration and data analysis. Registries estimated that occupational exposure to asbestos occurs in about 60-80% of the MM cases (range 13-100%), with higher etiological fraction in men (about 90%) than in women (20-40%). About half of MM cases occurred among construction, shipbuilding and transport workers; about 5% were registered in the primary asbestos industry (2, 11, 12, 21, 29, 50, 57, 66).

Over the last three decades, overall firm scientific evidence supported the causal association between MM and occupational exposure to asbestos: the literature reported several case reports and epidemiological studies conducted in various occupational settings, or based on hospital records or routinely collected data from death certificates or cancer registries.

A number of cohort studies reported excess mortality risk of MM in various industries and occupations; most of these studies referred to the primary asbestos industry: $230/10^5$ person years (py) among employees in the asbestos textile industry, $143/10^5$ py in asbestos-cement workers, $124/10^5$ py in asbestos insulators, $28/10^5$ py in the friction materials industry, and between $13/10^5$ and $67,9/10^4$ py in asbestos miners. The incidence of MM, calculated as standardized incidence ratio (SIR), among workers exposed to asbestos in different industrial settings ranged from 1 to $52/10^5$/year (20-$52/10^5$ for manufacturers of asbestos products, 6-$7/10^5$ in railroad manufacture and sugar refineries, 2-$10/10^5$ among electricians, 2-$29/10^5$ in construction, $4/10^5$ wood and pulp industries, 2-$5/10^5$ plumbing and pipe fitters, 1-$6/10^5$ ship building, $3/10^5$ among seamen, 2-$4/10^5$ in the petroleum industry) (2, 11, 21, 29, 35, 38, 45, 50, 58, 62, 63, 66).

In case control studies from Germany, South Africa, USA, Canada, Italy, France, Spain, England and Australia, individual work histories were classified in terms of probability of asbestos exposure (definite, probable, possible, unlikely), with categories defined *a priori* or according to national or local industrial circumstances. Occupational asbestos exposure (definite and probable) was found in about 12-95% of MM cases and in 2 to 51% of hospital or population controls. For subjects with definite and probable exposure, the odds ratio were various orders of magnitude greater compared to control subjects with "unlikely" exposure. Excess risks were observed for occupations such as installation and removal of insulating material, sheet metal working, pipefitting, mechanics, fitters and plumbers, manufacture of non-metallic products, launderers, dry cleaners and pressers, engine and vehicle building industry, electricians and electrical fitters, machinery fitters and assemblers, industrial settings such as shipyard and primary asbestos industry, asbestos mining, asbestos-cement or friction material manufacture; in general, the highest relative risks were detected for insulation work (1, 14, 25, 27, 28, 37, 46, 48, 49, 57, 59, 61).

The estimate of the attributable risk to occupational exposure to asbestos ranged generally between 30% and 80%. Differences in study design, analysis of data and methods of exposure assessment are the main reasons for the wide variation of attributable risk (57, 60).

The epidemiological findings clearly show that different patterns of asbestos exposure may lead to different risks. Firstly, dose is a very important issue. A dose-response relationship was detected between cumulative asbestos exposure and MM, and with both probability and intensity of exposure (1, 28, 48). Threshold dose is still a controversial issue. While some authors claim that there is no evidence of a threshold level below which asbestos cannot cause MM, others suggested an approximate threshold of 5 fibres/mL/year (9, 10, 16, 22, 23, 26, 54, 55). Significantly increased odds ratio was found for a cumulative asbestos exposure below 0.15 fibers/year (1). Several cases of MM occurred after occupational or non-occupational exposure to asbestos characterized by a very short duration, such as a few weeks (20). In table 1, some examples are listed. Very brief exposure are rarely recorded or recordable in epidemiological studies; besides, information bias may largely affect the estimates and, depending on different circumstances, even relevant cumulative exposure to asbestos might be overloaded (26).

Moreover, it is well established that a specific mineral form of asbestos fibre leads to a different risk of MM. At exposure levels observed in occupational cohorts, the specific exposure risk of MM from the principal commercial asbestos types is broadly in the ratio of 500:100:1 for crocidolite, tremolite/amosite, chrysotile respectively (figure 1) (24; more details in Bertazzi and Pasetto et al, this issue). Cohort studies show different risks depending on type of industry, progressively decreasing for textile industry, asbestos-cement manufacture, friction products and mining (8).

Descriptive epidemiology showed that the incidence of MM has increased roughly with the increasing industrial use of asbestos, with a time lag of 25-40 years (16, 39). The mean MM induction period (calculated from the start of employment in the occupation at risk) has been repeatedly found to be between 30 and 40 years (range 5-72 years); more than 90% of MM were diagnosed more than 15 years after the first asbestos exposure (36, 65). However, MM cases were reported with very brief latency and epidemiological studies support the hypothesis that heavy asbestos exposure many result in a shorter induction period (Bertazzi, this issue). The consensus of international experts was that a minimum of 10 years from the first exposure is required to attribute MM to asbestos exposure (15); such criterion generally complies with current compensation, insurance and litigation issues in several countries (39, see also Langård, this issue).

THE ASSESSMENT OF OCCUPATIONAL EXPOSURE TO ASBESTOS

An accurate assessment of exposure to asbestos is essential in MM evaluation, from both diagnostic and epidemiological viewpoints. This represents a major challenge for the OP. In fact, retrospective

Table 1 - *Minimum occupational exposures by fibre type that have been associated with MM (from 26, modified)*

Author/Type of fibre	No of cases	Shortest duration (months)	Exposure conc (f/cc)	Dose (f/cc/y)
Amosite				
Seideman (1986)	14	6	50	26-46
Acheson (1981)	4	19	30	47
Crocidolite				
De Klerk (1989)	31	3	-	-
Jones (1980)	16	5	-	-
Jones (1987)	1	0.5	-	-
McDonald (1978)	9	4	-	-
Browne (1983)	144	0.75	50-100	3-6
Amosite-crocidolite-chrysotile				
Enterline (1987)	8	-	-	144
Hughes (1987)	8	5	11.2	4.5
Kolonel (1988)	8	12	-	-
Raffin (1989)	13	5	-	-
Amosite-chrysotile				
Hughes (1987)	2	4	13	4.5
Crocidolite-chrysotile				
Neuberger (1990)	5	60	1-10	5-50
Peto (1985)	47	9	5-28	4-21
Peto (1985)	4	-	-	-
Albin (1990)	13	-	-	>5
Chrysotile-tremolite				
McDonald (1983)	7	7-105	7-138	59-80

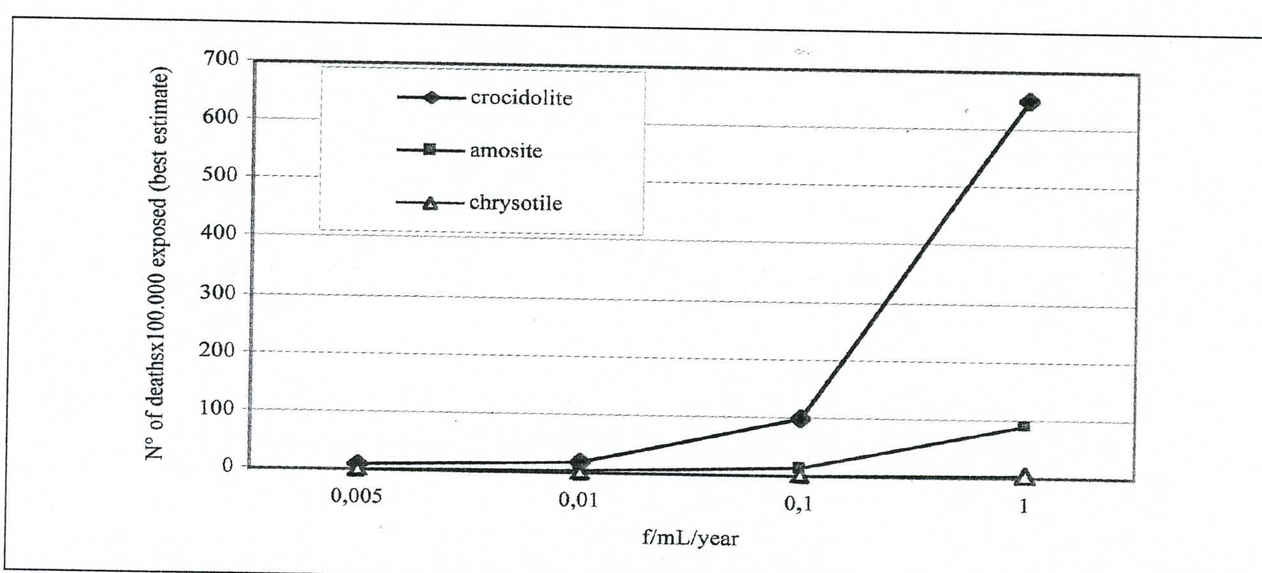

Figure 1 - Quantitative mesothelioma risks (best estimate of number of deaths per 100.000 exposed subjects) from asbestos exposure at different levels of cumulative exposure (f/mL per year) (from 24, modified)

exposure assessment is complicated by the very long latency period between the beginning of asbestos exposure and MM development. Moreover, MM may occur after brief, sporadic, intermittent or low level asbestos exposure. Recall and information bias may therefore frequently affect the evaluation.

The best reliable way for exposure assessment in the individual is probably through the collection of lifetime history by means of traditional anamnesis, taken with rigorous methodology (e.g. standardized questionnaires, checklists of jobs entailing asbestos exposure), preferably by the OP and possibly by means of direct interview, which is essential for quality assessments. Interview data might be supplemented with employment records and inquiries into workplaces (15).

Historical accounts by workers on working conditions and asbestos use and/or occupational histories or employment records should then be translated into estimates of existence and magnitude of past asbestos exposure (13). Examples are available in the international literature: semiquantitative estimates of asbestos exposure which are based on industrial hygiene monitoring are especially useful for historical exposure assessment (table 2) (13). Asbestos exposure may also be quantified using historical environmental monitoring data. However, such data are rarely available and are often characterized by questionable quality, related to sampling strategies and analytical problems, leading to uncertainties in interpretation (13).

One may go one step further and use expert evaluations, for example industrial hygienists' opinions, or personal experience and knowledge of the various professionals inside and outside workplaces. When no objective method of measuring exposure is available, the expert's judgment is most often considered the best exposure estimate, even if misclassification may still occur, especially in distinguishing between sporadic and irregular exposure (28, 59).

A number of tools are anyway available nowdays in order to obtain as reliable as possible estimates of asbestos exposure and the OP can certainly use and manage such tools.

Epidemiological studies on asbestos-related disease and database of exposure estimates in different workplaces and occupations at different calendar times might provide useful information to evaluate characteristics of asbestos exposure.

Retrospective assessment of asbestos exposure may be estimated by various surrogate parameters that may lead to cumulative exposure indexes. The main variables to take into account are probability, intensity, duration, frequency of exposure, fibre type (durability, dimension), calendar period (28, 29). Asbestos exposure estimates are often based

Table 2 - *Historical asbestos fibre concentration in Dutch occupations and jobs (from 13, modified)*

Occupation/job	Source of exposure	Exposure level (f/cc)	Year
Operator	Handling of raw asbestos in coating	1.5-2	1971
	Handling of raw asbestos in gunny bag	10-15	1971
Demolisher	Removal of furnace insulation	10	1971
Fitter/benchman	Finishing asbestos-cement products	6.2-18	1970
		50	1971
		0.2-0.7	1985
Warehouse worker	Handling asbestos-cement products	0.5-1	1971
	Raw asbestos warehouse	5.6	1973
		<0.3	1985
Insulator	Spraying of asbestos insulation	40	1971
Maintenance in chemical plant	Gasket removal	0.02	1996
Car mechanic	Brake servicing	0.01-5.7	1970-1984

on job exposure matrix (JEM), where estimates describing probability, frequency and intensity of exposure are not related to specific measurements but to expert evaluation of combinations of occupations, industries and calendar periods (48). Risk matrix for historical asbestos exposure in different occupation and exposure weighting factors are also available in the literature (tables 3 and 4) (13, 29). Recently, JEM have been published which estimate fibre type and length and relative exposure intensity for a wide range of manufacturing industries and jobs (table 5) (47). JEM can correctly be applied only by experts, taking into account possible historical and geographical differences in the asbestos consumption which may affect precision of estimates. The proper use of this options is also possible for OP; for example the correct evaluation of time patterns (29), especially when estimates or monitoring are referred to past decades. JEM and risk matrix are helpful instruments to refer to in individual MM case evaluation.

Another opportunity for the OP to assess exposure is provided by the availability of clinical data, for example by means of lung fibre burden analysis. Good dose-response relationships between occupational histories (duration of exposure) and pulmonary fibre burden have been described in the literature, but the correlation between lifetime cumulative exposure and fibre concentrations in the lung is not excellent (15, 23). The interpretation of necroscopic data should consider methodological issues, such as analytical techniques, lung distribution of fibres, biopersistence (e.g. taking into account short fibre elimination bias). Moreover, asbestos fibres can be found in most lungs and reference values by fibre type are not readily available, although the reader can be referred to the values reported by the so-called Helsinki criteria (15). Large case-series are described in the literature, median values for occupationally exposed subjects have been estimated; on the other hand, OP should be aware of the fact that low values do not outrule clear exposure history (15, 32, 33, 34, 53).

Finally, asbestos body counts in broncho-alveolar lavage or in sputum, as well as prevalence of pleural plaques or pulmonary asbestosis in the exposed population, may be useful for asbestos expo-

Table 4 - *Asbestos exposure weighting factors according to type of work and period of time (from 29, modified)*

Main activity	Exposure weighting factor	
	1976 and before	1977 and after
Installation of new pipes	2	1
Demolition of old pipes	5	5
Pipe insulation work	10	2
Electrical installation work	1	1
Ship repair work	5	5
Asbestos mining	10	-
Asbestos product manufacture	5	5
Brake and clutch repair work	1	1

Table 3 - *Risk matrix for historical asbestos exposure in Dutch companies and occupations (from 13, modified)*

Industry/Occupation	1946-1955		1956-1965		1966-1975		1976-1985		1986-1995	
Asbestos insulation	E3	P3	E3	P3	E3	P3	E-	Pna	E-	Pna
Asbestos textile	E3	P3	E3	P3	E3	P3	E2	P1	E-	Pna
Asbestos-cement	E3	P3	E3	P3	E3	P3	E2	P2	E1	P1
Asbestos friction materials	E3	P3	E3	P3	E3	P3	E2	P2	E-	Pna
Shipbuilding	E3	P2	E3	P2	E3	P2	E2	P1	E1	P1
Construction	E2	P1	E3	P1	E3	P1	E2	P1	E1	P1
Car service station	E2	P1	E2	P1	E2	P1	E1	P1	E0	P1
Furnace worker	E2	P2	E2	P2	E2	P2	E1	P1	E0	P0
Founder/caster	E2	P1	E2	P1	E2	P1	E1	P0	E0	P0
Electrician	E1	P1	E1	P1	E1	P1	E0	P0	E0	P0

Exposure category: E3 >5f/cc, E2 2-5 f/cc, E1 0,5-2 f/cc, E0 <<0,5f/cc

Probability of exposure: P3 each worker exposed, P2 each blue collar worker exposed, P1 specific blue collar worker exposed, P0 only few blue collar workers exposed; na=not applicable

Table 5 - *Asbestos job exposure matrix (from 47, modified)*

Manufacturning sector/product/job	Fibre type/length	Relative exposure intensity
Friction products	7C	3
Paint, coatings, sealants	7C	3
Heating boiler, domestic furnace, burner	3C, EL/L/S A	3
Industrial furnace ovens	3C, EL/L/S A	3
Ship operation (engine room, marine engineer)	3C, EL/L/S A	3
Textile (clothing)	3C	3
Asbestos mining	5C, T	2
Talc mining and milling	T, An	4
Construction: paint, paperhanging, decorating	5/6 C, T, An	3
Construction: tile, floor, terrazzo	3C	3
Construction: plumbing, heating and cooling	3C, EL/L/S A	3.2
Vehicle repair/maintenance	3, 7C	1

Fibre type: C=chrysotile, A=amosite, T=tremolite, An=anthophyllite, Cr=crocidolite
Length: chrysotile range 3 longest- 7 shortest; amosite, crocidolite: EL=extra long, L=long, M=medium, S=short
Intensity of exposure: 1 very low (< limit of detection, phase contrast microscopy), 2 low (<2f/cc), 3 medium (2-7,9 f/cc), 4 high (>8 f/cc)

sure assessment; such data are, in some cases, easy to collect and evaluate, e.g. from the clinical and radiological records of the patient. Consensus of international experts set sentinel values suggestive of high asbestos exposure both for ferruginous bodies per gram of dry lung tissue and for asbestos bodies in broncho-alveolar lavage or in sputum; there is also ample scientific consensus that analysis of pleural samples are of no use for asbestos exposure assessment (15).

The causation of malignant mesothelioma: some comments and controversial issues

In the OP daily practice, individual case management addresses the relevant question of etiologic diagnosis. The causal attribution of a disease to an occupational activity bears significant consequences for the affected individual, such as equitable compensation and assessment of liability either in civil action or criminal trials. Moreover, physicians have the legal requirement to report the occupational cancer to a registry and a local public health authority, leading to significant outcomes such as preventive interventions in workplaces, health surveillance, health education and risk assessment, since MM is a sentinel event.

Assessment of the etiology of a MM is based on a few generally accepted principles: asbestos is the only relevant etiologic agent for MM; causal association is well established and undisputed; the influence of other supposed determinants (such as pleural lesions, ionizing radiation) or lifestyle is negligible from a practical point of view.

The key issue is the documentation of exposure to asbestos "above the background level" in the individual case of MM. There should be no question about the fact that the OP has many tools available to try to document exposure, although with the above described limitations and particularities.

When it comes to scientific criteria for defining causation and apportionment, which are important issues for an individual approach, they appear to be surprisingly flexible, subject to variable interpretation by medical experts, and it seems there is insufficient research to define minimal requirements for MM causation (19, 33). One may accept that technical and scientific criteria (e.g., the well-known Bradford-Hill criteria, meta-analysis and reviews, evidence based risk assessment, International Boards evaluation) should help the interpretation and processing of workers' compensation claims, as well as attribution to asbestos. However, epidemiological concepts, such as the attributable risk, does not completely and always apply to the individual case. Some authors also stressed the difficulties of an epidemiological approach to evaluation of individual cases, with special reference to the probability of causation and apportionment (18, 19, 67). In fact, the concept of causation is different if examined from the epidemiological or the individual viewpoint and, also, considerable differences exist between scientific and trial debates, when generic questions (e.g., "can asbestos exposure cause the disease?") become specific (e.g., did "that" asbestos exposure cause "that" MM?) (67).

One more thing to stress is that, given sufficient evidence of significant asbestos exposure, different terminologies and semantics may be adopted in different contexts. The proposition commonly used in law courts regarding causation is "but for" ("but for exposure, the disease would have occurred later or would not have occurred"); i.e. the cause was necessary even if it was not sufficient, and final statements are guided by the principle of high probability of causation and "in dubio pro reo" (19). On the other hand, civil actions generally follow the principle "in dubio pro aegroto", which means that the "expert" does not need to provide scientific "certainty" but "a 51% level of confidence" and the words regarding the causation sound like "more likely than not" or "within medical probability" (33).

However, there are "guidelines" that can be used by the OP to define causation at the individual level, such as the Helsinki criteria. In fact, these criteria state that in the absence of markers of exposure (i.e., lung fibre count exceeding background range; pathological and radiological evidence of asbestos-related tissue damage, AB in histology sections), a history of "significant" occupational, domestic or environmental exposure to asbestos will suffice for attribution (15). At the same time, the term "significant" is not defined, and may well be brief or low level, but may give rise to different interpretations, being a general statement.

Assessing the role of low-level exposure might actually be a very difficult task, given scientific uncertainties on dose-response relationship. In fact, despite extensive research, there is no proof but only arguments to support the existence of a threshold: in fact, there is no documentation of asbestos exposure for several MM cases in different populations; MM may occur in very young people; time pattern of MM recorded in females (constant risk across birth cohort, constant age-adjusted rates); no MM seemed to occur among workers with very brief exposure (e.g., Australian miners with less than 3 months duration, North America insulators with less than 15 months asbestos exposure) (see Bertazzi, this issue). Therefore, truly unexposed populations are unlikely to be found in western countries, so definition of threshold of asbestos exposure useful to the OP for MM attribution could then be the exposure below which disease will not be epidemiologically detectable or an asbestos exposure level associated with a negligible incremental risk of MM (45, 52).

In an attempt to summarize, the definition of the minimal duration of exposure to asbestos needed to develop MM, whether a threshold exists and the minimum concentration of asbestos in tissues needed to cause MM still remain controversial issues and will still be debatable. In fact, there are no scientific data to answer these question consistently; it very much depends on fibre type and circumstances of exposure and it is not possible to identify the particular fibre or fibres involved in the genesis of an individual MM. It may well be that "experts" could attribute causation of MM to virtually any amount and any type of alleged asbestos exposure and all source of "significant" exposure (33, 53, 54).

In this respect, the OP might anyway be asked to evaluate non-occupational environmental exposures or asbestos exposure in various workplaces and different employers and to assess apportionment of causation. Here, reliable information might be exceedingly difficult to obtain; frequently, there are serious limitations in history collections as well as different interpretations of histopathology and fibre burden findings, when available; but evidence is needed to support the alleged asbestos exposure. Histopathologic findings or tissue fibre-burden analyses might be interpreted in conflicting ways and might not answer the need for objective evidence of "exposure above the background level" (56). However, occupational histories can be translated into estimates of past asbestos exposures, therefore transferring epidemiology towards the individual, provided that databases of industrial hygiene measurements are available over a broad range of jobs and time periods. On the other hand, no scientifically valid method to apportion causation of MM in instances of multiple sources of asbestos exposure have been established and this issue still remains controversial (33). The role of the OP in expert judgments on such occasions is valuable in balancing between scientific certainty (or uncertainties) and objective evidence in different contexts.

In conclusion, we agree with some statements by various authors that the research to define minimal requirements for MM causation seems nowadays insufficient and there is a growing need for objective guidelines, based on scientific evidence, that could be used in a consistent and fair manner in individual case management, litigation and compensation (16, 18, 19, 33, 53).

Malignant mesothelioma in the province of Brescia: an experience of occupational physicians

The province of Brescia has about 1.100.000 inhabitants and 490.000 workers and it is a highly industrialized area in Northern Italy. In the past, large numbers of workers were occupationally exposed to asbestos in various industries, such as construction, metallurgy, mechanical engineering and various manufacturing industries (asbestos-cement products, textiles, friction products, gaskets, ropes) – in plants that have been operating for several decades in different areas of the province. Since the late 1980's, the OPs belonging to the Occupational Health Unit of the Local Public Health Authority and the Institute of Occupational Health of the University of Brescia have addressed the problem of evaluation and management of MM cases.

For the purpose of this article, it is important to underline methodology as well as comprehensive results of the experience of OP's in this province.

Methods: the evaluation of MM cases

A rigorous methodology is essential for evaluation and management of MM.

The activity of a group of OP's in the province of Brescia belonging to different public Institutions was particularly focussed on the prompt referral of the patient to the OP, in order to collect the data directly from the patient, possibly avoiding, in the majority of cases, telephone or proxy interviews, which inevitably lead to inaccuracy or loss of information.

A network of several sources of cases was established by the local MM register to allow completeness of data collection (hospital registry and discharge records, general practitioners, death certificates) (figure 2).

Asbestos exposure was identified *via* a careful search of the detailed lifetime individual history. A semi-structured questionnaire, already used for data collection for Italian MM Registries, was administered. It includes sections on socio-demographic variables and education, lifetime smoking (quantity, duration), lifetime occupational history, leisure time activities entailing asbestos exposure (hobbies, military service), lifetime residential history, with specific reference to indoor and environmental sources of exposure, occupational history of relatives and co-habitants, with specific reference to asbestos exposure, clinical and histopathological data. As regards occupation, information regarded job title, plant activity, type of production, exposure to chemicals or heat sources, use of machinery, features and use of collective or individual protective devices, with detailed description of workplace and presence and characteristics of asbestos-containing materials. Additional sections for specific jobs/industrial activities (e.g., construction industry, shipbuilding industry, brakes, clutch and gasket production, plumbers, carpenters, fire fighters) are also used for selected cases.

Whenever needed, additional information on asbestos presence in certain workplaces were obtained by consultation with plant physician, occupational health authorities, industrial hygiene experts, technical personnel from specific plants and past environmental monitoring data; information from or linkage with co-workers affected by asbestos-related pathology was sometimes useful for interpretation of cases. Moreover, purchase orders of asbestos-containing materials from a number of local factories were carefully examined by the OP in order to record asbestos consumption; also, in a

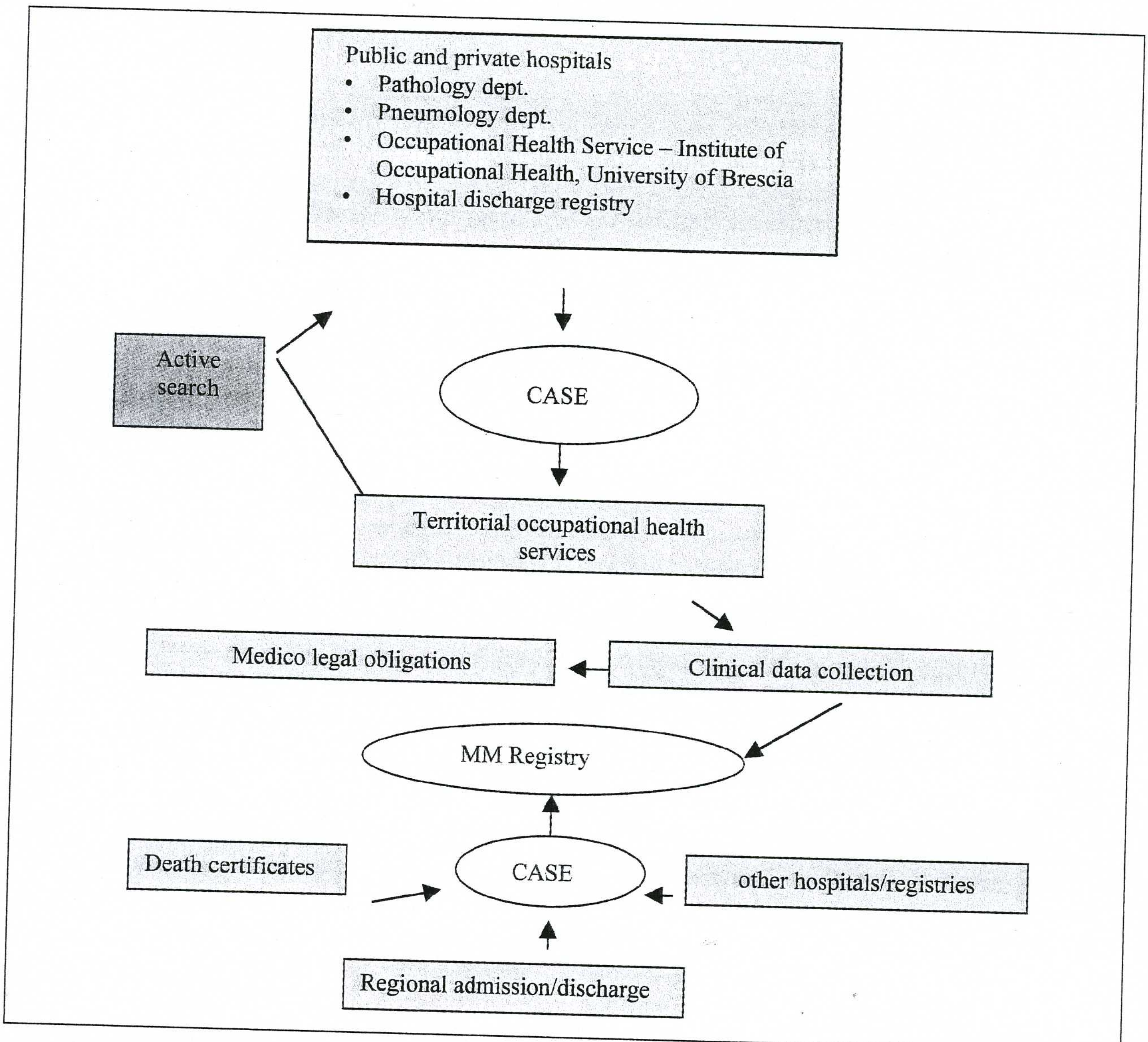

Figure 2 - Malignant mesothelioma registration: case collection and evaluation by the Occupational Health Unit, Department of Prevention, Public Health Authority, Brescia

few cases, environmental samples (various matrixes) were collected and analysed for asbestos fibre content.

Unusual or particular exposure conditions may occur and represent a challenge for the OP. Personal experience of the OP, historical knowledge of the local industrial milieu, dialogue with institutions or experts and use of modern tools, such as database and record linkage, as well as literature search, are very important in order to record asbestos exposure or other MM cases occurring in similar occupational settings.

Often, the joint X-ray reading by the trained radiologist and the OP allowed historical evaluation of a number of films (chest X-ray and/or HRCT), which was useful in looking for objective signs of other asbestos-related diseases, such as asbestosis or benign pleural effusion. In selected cases, research of asbestos bodies in sputum or other diagcho-alveolar lavage, were performed in order to evaluate lung fibre content or to check for pathological evidence of asbestos-related diseases.

The experience of Occupational Physicians in Brescia: outcomes

The local MM registry, instituted and managed by OP belonging to the Local Public Health Authority, has up to now filed 309 MM cases, collected retrospectively and prospectively from 1977 to 2003: 170 pleural MM among males and 102 among females, 33 peritoneal, 2 testicular and 2 pericardial MM. Since 2000, all cases have been routinely referred to the regional MM Registry (see Pesatori et al., this issue). Collection of incident cases allowed calculation of standardized incidence rates (SIR) for pleural and peritoneal MM (Italian population, census 1981). In the period 1996-99, SIR was 2.7 among males and 1.5 among females for pleural MM; 0.2 and 0.3 respectively for peritoneal MM. In the period 2000-2003 period, the annual incidence rates were still progressively increasing in males and females but only for the pleural site: 3.4 among males and 2.1 among females for pleural MM, 0.1 and 0.2 respectively for peritoneal MM. Rates of these last few years may change after verification of completeness of the collected data. For pleural MM, the male to female ratio was 1.6:1, which is similar to that recorded in Northern Italy.

Such OP database of MM cases also enabled the estimate of survival, which for pleural MM, 1 year after diagnosis was: 31.2% in males and 40.9% in females.

Also provincial areas with consistent environmental pollution derived from production of asbestos-containing ropes and gaskets were detected and were the object of specific multiple interventions addressing identification of all MM occurring among residents, estimation of MM incidence, collection of occupational histories of all cases, to evaluate previous exposures to asbestos.

Table 6 shows the Registry distribution of cases by categories of asbestos exposure. All lifetime histories were classified by a panel of OP with the aid of Industrial Hygienists, in terms of probability of exposure to asbestos, according to the Italian standard classification (see Nesti et al, this issue). 67.2% MM in males were attributed to occupational exposure to asbestos (definite, probable and possible), mainly in construction (25%), iron and steel foundry (18%), asbestos-cement/gasket production (10%). About half the females were registered with unknown exposure to asbestos; 29.1% MM cases were attributed to occupation, mainly in the textile industry.

Table 6 - *Malignant mesothelioma (MM) register of the province of Brescia (1977-2003): distribution of 309 cases in males and females, by type of asbestos exposure*

	MM in males N. (%)	MM in females N. (%)
Definite occupational	87 (45.8)	10 (8.4)
Probable occupational	10 (5.2)	7 (5.8)
Possible occupational	29 (15.3)	21 (17.6)
Domestic	1 (0.5)	3 (3.4)
Environmental	2 (1)	3 (2.5)
Extra-occupational	2 (1)	0 (0)
Not probable	8 (4.2)	6 (5)
Unknown	43 (22.6)	55 (46.2)
Not classifiable	8 (4.2)	14 (11.8)

Careful investigations allowed the documentation of previously unknown asbestos exposure in selected occupational areas (for example, in the textile industry).

In the last few years, a particular advance in exposure assessment was provided by lung fibre burden analysis in post mortem samples. Table 7 describes the results of analyses performed in 14 subjects after autopsy and analysed by means of SEM at the electronic microscope centre located at the regional environmental protection agency (ARPA) in Milan; notably, higher lung burden was recorded for MM caused by jute bag recycling and asbestos gasket manufacture. Further lung fibre analyses are ongoing for a dozen MM cases. Although the number of such analyses in Brescia province is still small when compared with larger series in the literature case (3, 34, 51), local OP experience stresses the importance of clinical/pathological data collection in selected cases, aimed at individual assess-

Table 7 - *Asbestos lung burden fibre analysis (SEM, 14 pleural MM cases)*

Industry/job	Occupational exposure		Mean lung burden (10^6 f/g dry tissue)	Mean length (mm)	Fibre type
	Type	Duration			
Jute bag recycling	Dir, dis	16	400±55	2.8	A+C
Asbestos gaskets manufacture	Dir, C	30	286±40	1-50	A+C+Cr
Asbestos-cement manufacture	Dir, C	23	130±18	17.1	A+C
		18	115±20	3.8	
		30	94±16	5.3	
		19	38±7	3.1	
Iron caster	P, ind	4	2.4 ±0.6	9.6	A+Cr+C
Teacher	P, ind	14	0.77±0.16	10.6	C
Machinery mechanic (rubber manufacture)	Dir, dis	5	0.69±0.16	4.3	AMF
Floor tile textile	Pos, dis	30	0.53±0.17	1.5	AMF+C
Auto-vehicle repair		5	<0.65	-	A+C
Iron repair; brewery (electrical fitter)	dis, dis	35	<0.71	7.6	AMF
Nylons	P, ind	35	<0.42	-	AMF
Various activities	unknown	-	<0.51	-	AMF

° A=amosite, Cr=crocidolite, C=chrysotile Amf=amphibole
Dir=direct; dis=discontinuous; C=continuous; Ind=indirect; Pos=possible; P=probable

ment of exposure, which is especially useful for medical/legal purposes.

The experience of the OP belonging to the Local Public Health Authority allowed exploration and verification, at local level, of incidence and causation of MM; the main methodological aspects and outcomes had already been published on journal of national relevance, where the reader may find further details (4-7).

Parallel important OP experience on MM evaluation and management comes from the Institute of Occupational Health of the University of Brescia, located in a large public hospital with an expert multidisciplinary team for diagnosis and treatment of MM, whose catchment area is of national significance. During hospital admission, every patient admitted at the Pneumology Department with histologically confirmed MM is systematically referred to the Institute. For the large majority of cases, a face to face interview is then carried out by the OP and/or a specialist in Occupational Medicine.

The evaluation, carried out basically with the same methodology reported above, is concluded with a detailed written clinical report where the causal relationship and medical/legal obligations are discussed and highlighted; the report is sent to a hospital referring physician, patient, local health authorities, MM Registries (provincial, regional, national), sometimes to law courts. Often, counselling is necessary or requested by patients or their relatives, family or plant physician, or other occupational health professionals.

In the last decade or so, 209 patients affected by MM (99% pleural and 1% peritoneal), 99% of which were histologically confirmed, were evaluated; half the subjects came from the province of Brescia and half from other provinces all over Italy. The detailed case series is described in table 8. One special advantage of this case-list is that more than 95% of the subject affected by MM were interviewed directly. In 89 (42,6%) cases, the etiology of the tumour was attributed to occupational exposu-

Table 8 - *Malignant mesothelioma (MM) caselist, Institute of Occupational Health, University of Brescia*

		MM caselist	MM attributed to occupation
Period 1990-12/2004	M	157 (69%)	88/157 (56%)
	F	71 (31%)	15/71 (21%)
	total	228 (100%)	103/228 (42.6%)
Age		Mean (range) median	Mean (range) median
	M	64 (42-81) 65	63.4 (42-81) 64
	F	65.5 (46-86) 67.5	68.2 (53-78) 70
Time since first exposure to asbestos (y)		-	41.7 (18-58) 42

3 (1,3%) MM attributed to environmental exposure (3 F); 2 (1%) peritoneal MM
* 41 (17, 9%) with asbestosis and/or benign asbestos pleural disease

to asbestos. Besides well-known sources of asbestos exposure, in some cases, the OP was able to identify unusual exposures, for example in a teacher or in a goldsmith (42).

Figure 3 show compensation outcomes (data from INAIL, which is the National Public Insurance Agency for workers) recorded for 67 occupational MM: 63% reported and evaluated cases were compensated, 9% are still under evaluation. The ratio of case presented/case compensated, as far as we are aware, is probably the highest recorded in Italy.

While we are aware of the very many aspects and questions pertaining to MM attribution, in particular from the insurance agency's viewpoint, we believe that the methodology adopted by the OP in individual case management suggests that strong efforts devoted to document asbestos exposure assessment and collect scientific evidence are effective.

Methodology and data from such case series had already been described and discusses in international congresses (43, 44).

Compensation outcomes			
Reported	Compensated	Rejected	Under evaluation
67 (100%)	42 (63%)	20 (30%)	5 (7%)

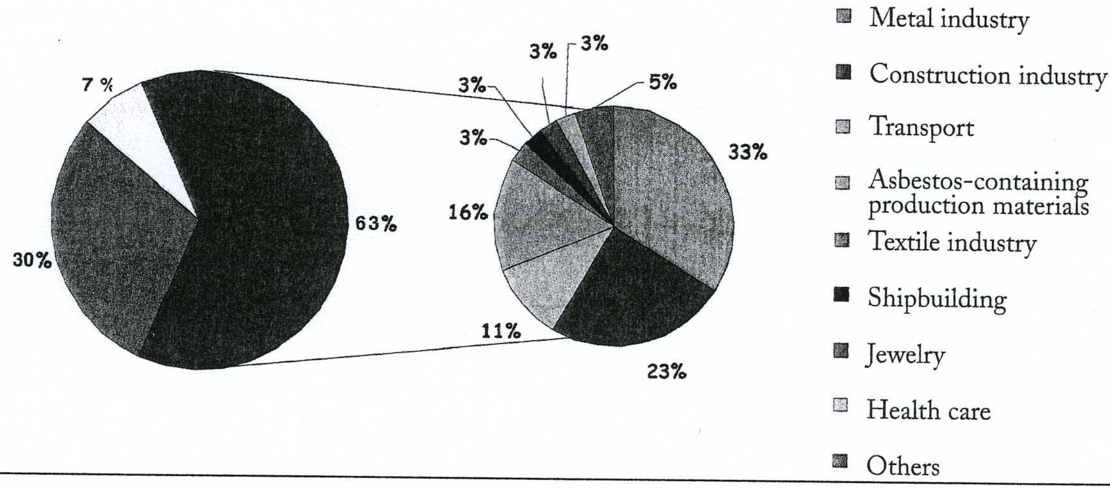

Figure 3 - Occupational malignant mesothelioma diagnosed at the Institute of Occupational Health, University of Brescia; distribution by compensation outcomes and by industry in compensated cases

Conclusive remarks

The experience of evaluation of MM in the province of Brescia highlighted the multifaceted contribution from the OPs.

Firstly, the OP played an important role in the management of individual case of MM, primarily by offering his knowledge of the occupational risk factors and his *expertise* in the differential diagnosis between occupational and non occupational diseases. The "active" search not only generated a high percentage of direct interviews, but also contributed to evaluate cases that would otherwise have gone misdiagnosed or under- or misreported.

Occupational exposure assessment, by means of modern tools and through the many sources nowadays available contributed to evaluate risk at low levels of exposure and to identify unknown, hidden or unusual asbestos exposures.

A number of etiological attributions of MM was defined. Etiological diagnosis had significant consequences from the medical/legal point of view, in order to set up compensation procedures for the case, and for epidemiological records of MM.

The OP actively contributed to local, regional and national MM registries. Systematic registration and data pooling led to relevant scientific outcomes, such as epidemiological studies aiming at, for example, definition of incidence rates in certain geographic areas or industrial activities, or survival analyses. A number of "sentinel events" was described in various industrial activities.

Better knowledge was gained regarding occupational risks at the local community level. Clusters of cases have been identified that allowed preventive interventions in specific workplaces and geographical areas. Often, specific health education or counselling activities or professional expert opinions were performed for exposed populations or individual subjects, trade union counselling, general attorneys and law courts, etc.

For many years, the OP's have been regularly cooperating with the organization of meetings, public events at local or national level on MM diagnosis, therapy, epidemiology and promotion of preventive interventions.

The OP played a key role in sensitizing different professionals inside and outside the working environment (such as government officials, trade unions, occupational health professionals, public insurance, media, pressure groups) and enhancing the culture of prevention and protection in the workplace. Of special value were the efforts of the OP to enhance cooperation among health professionals in the local medical community, mainly at hospital level and among general practitioners, as well as involvement in improving teaching opportunities, especially for local OP, general practitioners, training medical students and Occupational Health specialists. Furthermore, cooperation as well as discussion among the local OP improved over the years, leading to better MM evaluation and management.

Finally, the experience of the OP in Brescia highlighted the significant role of the "active" search of cases, especially for diseases with a high proportion attributable to occupation, such as MM.

It clearly appears that significant efforts devoted to establish and maintain a network of sources and to actively cooperate in etiological diagnosis are largely compensated by positive outcomes, from individual, social and epidemiological viewpoints.

Conclusions

In conclusion, the continuing appeal to maintain a high level of diagnostic and reporting practices as well as the availability and quality of scientific data, in the framework of legal requirements and individual and social rights are still issues for MM.

Only a real multidisciplinary approach will produce an effective strategy and close cooperation between different clinicians which generally formulate diagnosis of MM, such as oncologists, pathologists, surgeons, pneumologists, and the OP is essential to reduce under- or misreporting and misdiagnosis.

The OP is in a key position to significantly contribute to MM evaluation and management

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