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Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register

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ABSTRACT

Italy was an important producer of raw asbestos until 1992 (when it was banned) and it is now experiencing severe public health consequences due to large-scale industrial use of asbestos in shipbuilding and repair, asbestos-cement production, railways, buildings, chemicals and many other industrial sectors. Latency of malignant mesothelioma generally shows a large variability and the relationship with the modality of asbestos exposure is still not fully clarified. We present an analysis of latency period among the case list collected by the Italian mesothelioma register (ReNaM) in the period of diagnosis 1993–2001 (2544 malignant mesothelioma (MM) cases with asbestos exposure history). Exposure is assessed retrospectively by interview. Statistical univariate analyses were performed to estimate median and variability measures of latency time by anatomical site, gender

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and diagnosis period. The role of diagnostic confidence level, the morphology of the tumour and the modalities of asbestos exposure were verified in a regression multivariate model. We found a median latency period of 44.6 years increasing in recent years with a linear trend. Anatomical site, gender and morphology were not relevant for MM latency time whereas a shorter latency period was documented among occupationally exposed subjects (43 years) with respect to environmentally and household exposed ones (48 years).

1. Introduction

Malignant mesothelioma (MM) is a lethal tumour which arises from the serosal coverings of the pleura and, less frequently, of the pericardial and peritoneal cavities and from the tunica vaginalis of the testis. The relationship with asbestos exposure has been definitely demonstrated, but some aspects of biological mechanisms by which asbestos causes MM are still under scrutiny.[1] Latency time for MM shows a great variability and the relationship with the asbestos exposure intensity (and duration) is still not clarified. The range of latency period in the published study is exceptionally extensive and MM cases with a latency period shorter than 10 years are very rare. Some authors reported that latency has increased during the time due to less heavy exposure conditions,[2] but this remains a controversial issue.[3] Data regarding the influence of dose-response on latency are not frequent and there is no evidence about the putative role of other factors such as tumour site, asbestos fibre types and morphology.[4–7]

Italy was an important producer of raw asbestos until its ban in 1992. In-house production peaked at more than 160,000 tons/year between 1976 and 1979, then it went on with more than 100,000 tons/year up to 1987; additionally, importation exceeded in-house production from 1989 to 1991 (more than 60,000 tons/year). Italy is now experiencing severe public health consequences due to large-scale industrial use of asbestos, as it was extensively used in shipbuilding and repair, asbestos-cement production, railways, buildings, chemicals and other industrial sectors. In 2001, 797 men and 380 women deceased from pleural tumours and the national standardised mortality rate was 2.45 and 1.11 (×100,000 inhabitants) among men and women respectively. Historical Italian asbestos consumption curves and current MM mortality trends make a decrease of MM deaths in future years unpredictable.[8,9]

Since 1993, the National Mesothelioma Registry (ReNaM) has carried out a permanent MM epidemiologic surveillance, recently publishing figures for incidence, survival and asbestos exposure.[10–12]

The aim of the present study is to estimate the latency period (and its variability) in the large MM case list collected by ReNaM. The correlation between latency length and the modalities of asbestos exposure (professional, environmental or at leisure) are investigated, as well as the putative influence on latency of demographic and diagnostic factors (age at diagnosis, gender, anatomical site, cancer morphology, level of diagnostic certainty and incidence period).

2. Methods

ReNaM has a regional structure: a Regional Operating Centre (COR) has been progressively established in 18 Italian regions (out of 21) and one province, nowadays attaining coverage of almost the entire national territory (98.5% of the Italian population). Each COR acts independently applying standardised methods established by national guidelines. CORs collect incident malignant mesothelioma cases from health care institutions that diagnose and treat cases of mesothelioma (especially pathology and histology units, lung disease pneumology and chest surgery wards), and consult hospital discharge records and death certificates to verify for completeness of inclusion and information. Diagnostic criteria have been fixed by national guidelines and all cases of malignant mesothelioma are included and registered in ReNaM according to diagnostic certainty achieved (defined, probable, possible). Occupational history, lifestyle habits and residential hystory are obtained from the subject (48.3%) or next of kin (51.7%) using a standardised questionnaire administered by a trained interviewer. To obtain information on occupational and/or residential exposure, CORs consult local health and public hygiene offices, and regional occupational prevention, hygiene and safety agencies. An industrial hygienist classifies and codes the exposure, consulting the questionnaires and appling his own knowledge of industrial conditions. Occupational exposure was classified as definite, probable or possible. Definite occupational exposure is assigned to the subjects whose work has involved the use of asbestos or materials containing asbestos. Probable occupational exposure is assigned to the subjects who have worked in a firm or sector where asbestos was certainly used, but whose exposure cannot be documented, and possible occupational exposure to the subjects who have worked in a firm or sector where asbestos might have been used.[10] Data collected by each COR are then periodically transmitted to Renam and stored in a centralised database.

During the period 1993–2001, 5173 mesothelioma incident cases have been registered among the inhabitants of 12 regions (out of the 20 Italian regions): Piedmont, Veneto, Puglia, Tuscany and Emilia-Romagna provided cases since the beginning of the period, Liguria since 1994, Friuli-Venezia Giulia between 1995 and 1999, Marches since 1996, Sicily since 1998, Lombardy, Campania and Basilicata since 2000. In Friuli-Venezia Giulia, Campania and Basilicata, incident cases active research could not be considered completed. Data collection and trasmission from the remaining eight Italian regions is ongoing.

Latency time is here defined as the time elapsing between the beginning of asbestos exposure and MM diagnosis. For occupationally exposed subjects, the first year in the job activity involving asbestos exposure (certain, probable, possible) was considered the year of first exposure. For non-occupationally exposed cases, the whole residential and life habit history was evaluated to assess the first asbestos exposure among environmental, household and hobby-related ones.

Information about exposure circumstances were not available for 1621 cases (questionnaires could not be administered, generally because of the poor health of the patients). Asbestos exposure was unlike or unknown (i.e. questionnaires reported an incomplete job and/or residential history) for 809 cases. 2743 MM cases had (at least) an occupational and non-occupational asbestos exposure ascertained and were reliable, but 199 of them did not mention the year of first exposure, thus they were not considered. Finally, latency time analysis was conducted on the remaining 2544 patients: 2342 of them had experienced an occupational asbestos exposure and 202 exclusively a non-occupational exposure (household, environmental or hobbies-related).

Univariate analysis was performed to estimate mean and median latency period by anatomical site and gender. Range of variation, standard deviation of the mean and 5th and 95th percentiles were calculated to assess the variability of latency distribution. Differences among mean latencies with respect to the year of diagnosis have been tested by one-way analysis of variance (ANOVA) at a statistical significance level of 95%. Test for linear trend in ANOVA has been performed with respect to the year of diagnosis.

A multivariate analysis restricted to pleural and peritoneal mesothelioma (2537 cases) was conducted by way of a linear generalised regression model. Other anatomical sites (seven cases) were excluded so as not to reduce the degrees of freedom of the model. Region of notification has been found not relevant and excluded from the definitive model for the same reason. Diagnosis confidence level (definite; probable; possible MM), tumour morphology (fibrous; epithelioid; biphasic; not specified), asbestos exposure circumstances (professional; household; environmental; leisure), gender (male; female) and anatomical sites (pleura; peritoneum) were considered in the model as factors; age at diagnosis and year of diagnosis as covariates. To assess the significance of differences in latency time between occupationally and non-occupationally asbestos exposed MM cases, marginal mean adjusted for factors and covariates included in the model were estimated in the generalised model.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 15.0).

3. Results

The ReNaM dataset included 5173 new MM cases diagnosed during the period 1993–2001. Applying the selection criteria described above, 2544 patients (49.2%) came out to be eligible for latency analysis. The general characteristics of this cohort

Table 1 – Incident malignant mesothelioma cases with available first exposure to asbestos, recorded by ReNaM in the diagnosis period 1993–2001

Variable	Modality	Males	Females
Anatomical site	Pleura	2075 (95.8%)	360 (95%)
	Peritoneum	83 (3.8%)	19 (5%)
	Pericardium	2 (0.1%)	–
	Tunica vaginalis testis	5 (0.2%)	–
Age classes	⩽54	291 (13.4%)	61 (16.1%)
	55–64	623 (28.8%)	110 (29%)
	65–74	779 (36%)	122 (32.2%)
	⩾75	472 (21.8%)	86 (22.7%)
Diagnosis certainty	MM certain	1804 (83.3%)	310 (81.8%)
	MM probable or possible	361 (16.7%)	69 (18.2%)
Asbestos exposure	Occupational	2091 (96.6%)	251 (66.2%)
	Household	14 (0.6%)	70 (18.5%)
	Environmental	51 (2.4%)	47 (12.4%)
	Hobbies related	9 (0.4%)	11 (2.9%)
Morphology	Epithelioid	1089 (50.3%)	228 (60.2%)
	Biphasic	267 (12.3%)	46 (12.1%)
	Fibrous	169 (7.8%)	30 (7.9%)
	Not specified	640 (29.6%)	75 (19.8%)
Diagnosis period	1993–1997	686 (31.7%)	94 (24.8%)
	1998–2001	1479 (68.3%)	285 (75.2%)
Year of starting asbestos exposure	⩽1955	1080 (49.9%)	198 (52.2%)
	> 1955	1085 (50.1%)	181 (47.8%)
Total		2165	379

Figures by gender, anatomical site, age at diagnosis, period of diagnosis, exposure modalities, morphology and year of first exposure.

Table 2 – Incident malignant mesothelioma cases with available first exposure to asbestos, recorded by ReNaM in the diagnosis period 1993–2001

Anatomical site	Gender	Number of cases	Mean latency (±Standard deviation)	Median latency	Range of variation (min-max)	5°–95° percentile
Pleura	Males	2075	44.6 (±11.9)	44	6–84	26–64
	Females	360	45.2 (±13.6)	45	9–84	23–66
Peritoneum	Males	83	41.9 (±9.9)	42	23–63	25–59
	Females	19	36.8 (±10.2)	36	21–56	21–53

Mean, median and variability measures of latency time by anatomical site (pleura and peritoneum) and gender.

Table 3 – Incident malignant mesothelioma cases with available first exposure to asbestos, recorded by ReNaM in the diagnosis period 1993–2001

Variable	Modality	Adjusted mean latency by factors	Significance in the linear generalised model
Diagnosis certainty	MM certain	45.2	0.37
	MM probable	44.7	
	MM possible	45.9	
Exposure modalities	Occupational	43.4	<0.001
	Household	48.1	
	Environmental	48.0	
	Hobbies related	41.4	
Morphology	Epithelioid	45.2	0.31
	Biphasic	45.7	
	Fibrous	45.2	
	Not specified	44.6	

Adjusted mean latency time (years) and statistical significance (p value) of each variable included in the multivariate generalised linear model.

Model: latency = diagnosis certainty + exposure modalities + morphology + gender + anatomical site + age(covariate)* + year of diagnosis(covariate)*.

* Statistical significance of covariates: $p < 0.001$.

are reported in Table 1. Mean latency was 44.6 years (CI 95% 44.1–45.0), with a standard deviation of 12 years and a Gaussian distribution around the mean. The distribution of mean latency by anatomical site and gender is reported in Table 2. Among peritoneal MM female cases a mean latency of 36.8 years (CI 95% 32.3–42.1) was estimated. As described above, the relationship between latency time and the explicative variables was analysed using a generalised linear regression model to adjust for possible confounding factors. As shown in Table 3, the latency period is not significantly related to morphology: differences among fibrous, epithelioid and biphasic cases are not relevant such as the level of diagnosis certainty. Latency length appeared related to the age at diagnosis, the year of diagnosis and the modalities of asbestos exposure. Latency increased constantly during the observed period with respect to the year of diagnosis (Fig. 1): estimated latency period among pleural MM cases diagnosed in 1993 and in 2001 was 41.7 and 46.2 years, respectively, and the increase during this period is close to a linear trend (p ANOVA < 0.001; p ANOVA test for linear trend < 0.001). As expected, age at diagnosis is strongly related to latency length ($p < 0.001$ by ANOVA) and this finding suggests conducting a multi-way analysis. In the multivariate model, mean latency (after age adjustment) among household (84 subjects) and environmentally exposed cases (98 subjects) was 48.1 and 48 years respectively and it was significantly longer than the latency of 43.4 years observed among the occupationally exposed ones (2342 subjects).

Cases with a latency period shorter than 10 years are very rare (only four cases among the whole 2544). Mean latency time estimated among 20 cases with an exposure related to leisure activities (hydraulic and thermal areas, eternit handling) was significantly shorter (41.4). Concerning the economic sector of exposure for cases occupationally exposed, we observed a longer latency for workers of the shipbuilding and repair sector (46.3 years of latency after age-adjustment), a shorter latency in asbestos-cement industry (42.3) and latency almost equal to the general mean in the construction sector (43.7).

4. Discussion

It is widely agreed that mesothelioma latency is very long (up to 40 years and more) and with a great range of variability, but analyses of case lists from large national population-based registers are not frequently reported. The discussion on mesothelioma latency is a relevant issue considering the still unclear process of cancer causation from asbestos fibre inhalation[13] and the lack of encouraging progress in mesothelioma treatments.[14] Moreover, any prediction about the future burden of mesothelioma incidence and mortality in both industrialised countries, most of which have banned asbestos use[9,15–20] and developing countries, where asbestos is currently used,[21] is related with latency time estimation.

We have examined malignant mesothelioma latency over a large dataset produced from the national programme of malignant mesothelioma case collection, including all incident cases, in a diagnosis period of 9 years among a large part of Italian territory which included some areas with industrialised settlements and high incidence rates (in total, more than 240 million person/years of observations). Some preliminary issues regarding the characteristics of ReNaM dataset need to be discussed. We have considered eligible for the analysis about 50% of the whole case list collected (as described in the Methods section, questionnaires could not be administrated for 1621 MM recorded cases and, for 809 cases, questionnaires reported too poor information).

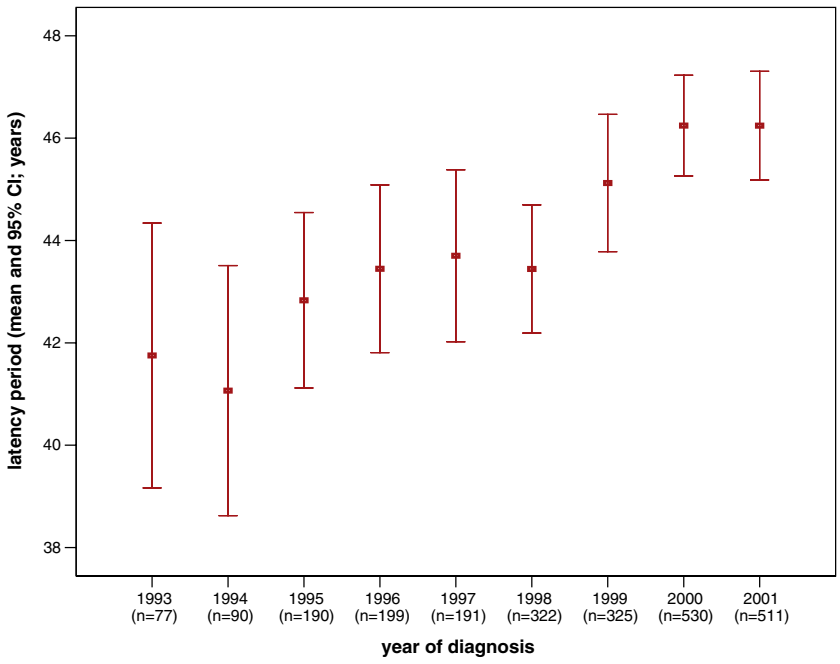

Fig. 1 – Incident pleural malignant mesothelioma cases with available first exposure to asbestos, recorded by ReNaM in the diagnosis period 1993–2001. Latency time (mean and 95% CI) by year of diagnosis.

This could represent a selection bias. Moreover, in the 'not eligible' group, the percentage of female cases (66.4% of 2629) is particularly high with respect to the analysed group (14.9% of 2544). The retrospective design of the study could 'miss' the cases with shorter latency thereby overestimating the mean latent period. The investigation of asbestos exposure modalities in ReNaM are defined only by analysing structured questionnaires. Quantitative measures of exposure in the workplace are not available (it is almost impossible to plan a reconstruction of quantitative assessment of exposure after the asbestos ban in 1992). Moreover, estimated measures of asbestos fibres in the lung (as exposure marker) are very rare in Italy and not available at all in this study. It is not easy to precisely determine the onset of asbestos exposure. In the present study, the beginning of occupational asbestos exposure was defined as the year in which the subject began the first job considered as related to the exposure. This assumption is not completely suitable with working conditions in the period of extensive consumption of raw asbestos (1950–1980). As a matter of fact, the beginning of a work period could not exactly correspond to the beginning of exposure to asbestos and it could lead to an overestimation of latency time. Cases of malignant mesothelioma reported in this study were collected in recent years; therefore, cases with relevant past exposures and short latency could be missing. From a methodological point of view it is necessary to underline that the limits of the observations in a population-based registry (i.e. the set registered cases since the beginning of registration limits at any point in time the upper range of dates of diagnosis that can be observed) combined with the fact that, in Italy, asbestos use declined and stopped in a well defined and limited calendar period, could be an estimated latency measure bias source. For MM cases of non occupational origin, the possible misclassification due to the beginning of the asbestos exposure period is an even more relevant issue. In these analyses, the first year of cohabitation (or the year of first exposure beginning for the cohabitant) was considered as the onset of exposure for cases with a household exposure and the residential history was used to define the onset of environmental exposure. In this latter case, the exposure onset was considered as the first year living near a potential environmental asbestos exposure source. The longer survival previously reported[11,22] and the shorter latency period for female peritoneal mesothelioma cases observed in this study, lead us to consider the possibility of a misclassification with female genital cancer. A variety of uncommon tumours of the peritoneum and of the ovary are closely related morphologically and histogenetically.[23–27] The possible diagnostic misclassification of female peritoneal mesothelioma[28,29] and the diagnostic utility of electron microscopy and immunohistochemistry as a gold standard in distinguishing between peritoneal mesothelioma and serous carcinoma, were recently underlined.[30–32]

Taking into consideration the previous issues, the most relevant findings of this study are an observed increase in latency period in recent years, with a trend close to linear, and a shorter latency period observed among occupationally exposed subjects with respect to those environmentally and household exposed.

Even before the Italian asbestos ban, measures to reduce exposure intensity were implemented in numerous workplaces, particularly in railway carriage construction plants, shipyards (construction area) and the asbestos-cement industry, where the use of sprayed crocidolite ceased during the 1970s. After that, during the 1980s, asbestos use ceased in most of the major textile plants as well as prevention measures being introduced in shipyards (maintenance area), in

the Military Navy and in the iron and steel industry, and even stricter security rules have been applied to the contract works of railway carriage decohibentation and maintenance of facilities for electricity production and distribution.

The increase in latency time by year of diagnosis revealed in this study could be due to some reduction of the intensity of asbestos exposure in most workplaces during the period before the asbestos ban or to the increased proficiency of CORs to detect the earliest asbestos exposure. Our results provide some evidence of a relationship between exposure intensity and length of latency, despite the absence of individual quantitative exposure estimates. Latency for MM cases with environmental or household exposures was significantly longer than for work-related cases (48 and around 43 years respectively) and it is reasonable to assume that occupational exposures entail on average considerably higher fibre levels. The short latency period observed among cases whose exposure was due to asbestos use during leisure activities need to be deeply investigated, also considering the limited sample size (only 20 cases) and the not easily determined onset of asbestos exposure. It could be observed that these activities carried out at home are limited in duration in comparison with a standard 8 h work-shift, but are performed without effective protective measures, such as local exhausts and personal protection devices.

The evaluation of the differences in mean latency period with respect to the specific job is a complex issue but some suggestions on the possible influence of exposure intensity on latency could stem. Limiting the analyses to few industries or occupations (those with at least 20 exposed cases), asbestos-cement workers in Italy have been exposed to fibre levels that, although poorly documented, were associated in some factories with a high risk of asbestos-related mortality[33]; their latency was lower than the average for occupational cases. Furthermore, it is strongly reliable that the year of job beginning and the onset of asbestos exposure are very close in the asbestos-cement industry, suggesting that the latency period in this sector is a very consistent estimated measure. Despite the fact that occupation in the shipbuilding and repair industry has determined very high exposures in some jobs, and that it is associated with the highest mesothelioma incidence areas in Italy, latency in this sector appears longer than average. The longer latency for workers exposed in these activities had been previously described in Italy, and it can be explained when considering the occurrence of competing diseases (asbestos related lung cancer and asbestosis) in the group with most heavy exposure levels.[5] The absence of historical fibre concentration measurements in these activities in Italy, makes it very difficult to further investigate the possible relationship between exposure level and latency.

Finally, the increasing trend in the latency length and the changes in the modalities of asbestos exposure during the period before the ban, induce expectations in the future of a MM case list affected, from an epidemiological point of view, by censored observations for competing causes of death.

Conflict of interest statement

None declared.

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