Survival of pleural malignant mesothelioma in Italy: A population-based study

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A median survival time of about 9 months is generally reported among malignant pleural mesothelioma cases. Recently, better results in terms of survival and performance status have been reported in clinical trials that included highly selected patients. We describe the survival of pleural mesothelioma patients and the factors predictive of survival in an unselected, population-based setting. Pleural mesothelioma cases (4,100) registered from 1990 to 2001 by 9 Italian regional mesothelioma registries contributing to the network of the National Mesothelioma Registry were followed until December 31, 2005. Univariate (Kaplan-Meier) and multivariate (Cox proportional hazards regression) analyses of survival were carried out according to selected individual characteristics, including limited information on treatment in a subset of 578 cases. The median survival time was 9.8 months (95% confidence interval: 9.4–10.1). In multivariate analysis, younger age at diagnosis and epithelioid histotype were associated with significantly reduced hazard ratios. Positive effects of gender (women) and being diagnosed in a hospital with a thoracic surgery unit were of border-line statistical significance. No association with calendar period of diagnosis or asbestos exposure was present. Treatment was not associated with a statistically significant improvement in survival. This is the largest population-based study on survival in patients with pleural mesothelioma to date. Results regarding the effect of treatment were disappointing but may be useful to assess the future impact, at the population level, of recently introduced therapies.
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Malignant pleural mesothelioma (MPM) is a highly lethal tumour induced by asbestos exposure. Although asbestos industrial uses have almost completely stopped in Europe, incidence and mortality are still increasing and no reversal of this trend is expected in the near future, even if the rate of increase is beginning to slow down in some countries.[1–3] On the basis of the current and past national mortality figures and past asbestos consumption statistics, a decrease in mortality is not expected in the next 20 years in Italy.[4] Public concern due to the relentless breakthrough of new cases is amplified by the absence of a consensus on treatment and of confidence on its effectiveness.[5] The relative rarity of this neoplasm has limited research opportunities, and only a few clinical trials have been done or are on-going.[6–8]

Recently, favourable results in terms of survival and performance status have been reported in some trials, based on highly selected patients.[7,8] Survival analyses performed on a population basis suggested that the median survival time was about 9 months.[9,10]

This study describes the survival of MPM patients registered by 9 Italian regional mesothelioma registries participating in the network of the National Mesothelioma Registry (ReNaM) and assesses the prognostic value of certain personal characteristics, based on data systematically collected in this population-based context.

Material and methods

Italy was an important producer and importer of raw asbestos until the ban issued in 1992.[4] Population-based registration of mesothelioma cases was started independently in the late 1980s at several research institutions, each covering a regional population, to support epidemiological investigations on the aetiology of the neoplasm. On the basis of this experience, ReNaM was established in 1993 at the National Institute for Occupational Safety and Health, in compliance with the 1991 Act that made mesothelioma cases registration compulsory.[17] Currently, 18 regions out of 20 participate in registration through the use of regional registries—Regional Operating Centres (CORs) of ReNaM—covering about 98.5% of the Italian population. Each COR, on the basis of standard guidelines,[18] identifies incident cases, collects the relevant clinical documentation as well as information on exposures, usually through personal interviews based on a standardised questionnaire, and assesses exposures. As incidence estimation and aetiology investigation are the primary objectives of ReNaM and of its network, the follow-up of cases and survival estimation are not mandatory. However, they were carried out on a routine basis by

TABLE I – CHARACTERISTICS OF THE REGIONAL OPERATING CENTRES (CORS) OF ReNaM CONTRIBUTING TO THE STUDY

COR	First year of registration	Population (2001)	Number of cases		Men		Women	
			Total	Mean annual	SIR[1]	95% CI	SIR[1]	95% CI
Piemonte[2]	1990	4,214,677	1,177	98	28	(26–30)	15	(13–16)
Veneto[2]	1990	4,527,694	637	53	18	(16–20)	6	(5–7)
Liguria[3]	1994	1,571,783	664	83	71	(65–77)	15	(12–18)
Emilia Romagna	1993	3,983,346	452	50	17	(15–19)	6	(5–7)
Toscana	1990	3,497,806	435	36	16	(14–17)	3	(2–4)
Marche	1996	1,470,581	113	19	18	(14–22)	6	(4–8)
Puglia	1993	4,020,707	264	29	13	(11–15)	4	(3–5)
Sicilia[2]	1998	4,968,991	192	48	18	(15–21)	4	(2–5)
Brescia province[2]	1992	1,108,776	166	17	21	(17–25)	11	(8–14)

SIR: standardised incidence rate, 95% CI: 95% confidence interval.–[1]Per 1,000,000 person-years. Standard: Italian population at 2001 census.–[2]CORs contributing data on treatment for part of their cases.–[3]Registration limited to the Genoa municipality in 1994 and to the Genoa province in 1995.

several CORs. Analyses of incidence, asbestos exposure (including latency), and survival have been published.[13,19–21]

The present study is based on data from 9 CORs that provided survival information for MPM cases diagnosed up to December 31, 2001. Cases first diagnosed after January 1, 1990 were included in the analysis. The CORs that started their activity after 1990 contributed for part of the study period (Table I). Only CORs that could ensure complete registration of cases for their coverage period and that had followed their cases until December 31, 2005 were included.

Case registration and survival estimate

Notification of new diagnoses of asbestos-related mesotheliomas is compulsory.[17] However, mesothelioma cases, irrespective of their possible causal relationship with asbestos, are mainly identified by active search strategies, according to the national guidelines.[18] Enquiries are made at the most relevant hospital departments, such as chest surgeries and oncologic referral centres, the files of all pathology units in public and private hospitals are searched, and the records of hospital discharges, available since 1995 at every regional Health Authority, are perused. For every possible case, the relevant clinical information is abstracted and evaluated to assess the confidence in the diagnosis of MPM and to establish the date of diagnosis. The diagnosis is classified as: (i) "definite" when morphological and, if available, immunophenotypical features are typical of malignant mesothelioma, as judged by the referring pathologist; (ii) "probable" when they are not typical, but compatible with malignant mesothelioma; and (iii) "possible" when supported only by clinical assessment and radiological imaging. The date of first diagnosis (incidence date) is established according to the rules adopted by the European Network of Cancer Registries.[22]

Vital status is ascertained, following a standard procedure in Italy, by enquiring at the Town Office of the last known municipality of residence and, if the patient moved, by repeating the enquiry until the vital status is known. Date of death or of last follow-up is recorded.

Exposure assessment has been fully described elsewhere.[20,21] In this study, cases were classified as ever occupationally or nonoccupationally exposed to asbestos, never exposed, or unknown.

Data on treatment could be provided by 4 CORs (as in Table I) for a fraction of their registered cases. Cases were classified as either ever receiving/never receiving treatment, or of unknown status. Data on treatment, abstracted from the original clinical records, were limited to the information that surgical procedures had been carried out (type and date of intervention), or that courses of chemo- and/or radiotherapy had been given (including date of treatment start).

Data on smoking habits, of possible interest given the relationship between tobacco smoking and comorbidities that can affect survival, are not generally available and could be provided only by the Liguria COR.

All patients who survived more than 4 years were re-examined by the notifying COR. Cases with a histopathological diagnosis expressed as "well differentiated papillary mesothelioma" or "malignant mesothelial hyperplasia" (i.e., lesions of uncertain biological behaviour) were excluded from analyses.

In the period 1990–2001, 4,546 new cases of MPM were registered. Our study was restricted to 4,105 cases with microscopically evaluated specimens (i.e., those with a "definite" or "probable" diagnosis). After further exclusion of 5 persons who had lesions of uncertain biological behaviour, 4,100 patients were included in the present analyses.

Statistical analysis

The prognostic effect of the following personal characteristics (predictive variables) were investigated: gender (men vs. women), age at diagnosis (categorized as: <55, 55–64, 65–74, 75+), calendar period of diagnosis (4 consecutive 3-year periods, from 1990–1992 to 1999–2001), diagnosis confidence (definite vs. probable), morphology (epithelioid, fibrous, mixed, unspecified), asbestos exposure (ever exposed, never exposed, unknown), type of hospital where the diagnosis was made (hospital with thoracic surgery, hospital without thoracic surgery, unspecified), and COR (Piemonte, Veneto, Liguria, Emilia-Romagna, Toscana, Marche, Puglia, Sicilia, Province of Brescia). Information on treatment was used to identify a treated group [i.e., patients receiving: (i) a surgical procedure of therapeutic, nonpalliative intention, such as radical or cytoreductive exeresis of neoplastic lesions, (ii) a cycle of chemo- or radiotherapy, (iii) either treatment (i) or (ii)], an untreated group (consistent information that these patients were never treated), and a group of unknown treatment status (due to incomplete clinical records).

Survival time was computed starting from the incidence date up to death or last follow-up date; observations were censored at 72 months after incidence due to the very small fraction of individuals surviving longer. Observed survival was assessed using the Kaplan-Meier method (univariate analyses), and differences in survival curves by category of each predictive variable were assessed by the log-rank test. Differences in the distribution of long- and non-long-term survivors (cutoff: 48 months) across categories of the predictive variables were assessed by the χ² test.

Multivariate analyses were carried out through Cox modelling of proportional hazards, by fitting first the full model, i.e., the model including all of the aforementioned variables. The subsequent search for a simpler model was limited to assessing the effect of deleting those predictive variables that were not in the list of "a priori" interest, which included gender, age class, morphology, asbestos exposure, and calendar period of diagnosis. The effect of model simplification was assessed by testing the log-likelihood ratio. The assumption of hazards proportionality was assessed graphically.

Analyses restricted to the 3 subsets (surgery, chemo-/radiotherapy, and surgery or chemo-/radiotherapy) of treated versus untreated cases were similarly carried out, as well as an analysis

TABLE II – CHARACTERISTICS OF ALL CASES AND OF LONG-TERM SURVIVORS (SURVIVAL TIME ≥48 MONTHS).

Characteristics	All cases Number	All cases (%)	Long-term survivors Number	Long-term survivors (%)	p^*
Gender					0.024
Men	2,995	(73)	175	(67)	
Women	1,105	(27)	86	(33)	
Age at diagnosis					<0.001
<55	560	(14)	64	(25)	
55–64	1,129	(27)	86	(33)	
65–74	1,436	(35)	79	(30)	
≥75	975	(24)	32	(12)	
Calendar period					0.004
1990–1992	326	(8)	12	(5)	
1993–1995	732	(18)	45	(17)	
1996–1998	1,338	(33)	70	(27)	
1999–2001	1,704	(41)	134	(51)	
Diagnosis					0.046
Definite	3,432	(84)	230	(88)	
Probable	668	(16)	31	(12)	
Morphology					<0.001
Epithelioid	2,199	(54)	174	(67)	
Mixed	554	(13)	18	(7)	
Fibrous	353	(9)	19	(7)	
Unspecified	994	(24)	50	(19)	
Asbestos exposure					0.757
Yes	2,204	(54)	146	(56)	
No	122	(3)	7	(3)	
Unknown	1,774	(43)	108	(41)	
Hospital					<0.001
With thoracic surgery	2,083	(51)	163	(63)	
Without thoracic surgery	1,458	(35)	69	(26)	
Unspecified	559	(14)	29	(11)	
COR (residence)					<0.001
Piemonte	1,177	(29)	49	(19)	
Veneto	637	(15)	44	(17)	
Liguria	664	(16)	34	(13)	
Emilia Romagna	452	(11)	38	(15)	
Toscana	435	(11)	58	(22)	
Marche	113	(3)	12	(5)	
Puglia	264	(6)	1	(1)	
Sicilia	192	(5)	14	(5)	
Brescia (province)	166	(4)	11	(4)	
Total	4,100	(100)	261	(100)	

p^*: Cases surviving ≥48 months *versus* cases surviving <48 months.

restricted to cases registered by the Liguria COR, for whom data on smoking habits were available (cases were classified as current-, former-, and never-smokers).

Tests for statistical significance were 2 sided. All analyses were conducted in Stata 9.2.[23]

Results

The personal characteristics of the 4,100 patients retained for the analysis are reported in Table II. The male:female ratio was about 3:1, most patients had ages between 55 and 74 (62%), a "definite" diagnosis of mesothelioma was present in more than 80% of cases, epithelioid morphology accounted for more than 50% of cases, about 50% were diagnosed in a hospital with a thoracic surgery unit, and slightly more than 40% were diagnosed during the most recent observation period (1999–2001).

Long-term survivors (survival time ≥48 months), in comparison with the other patients (survival time < 48 months), included a larger fraction of women, of younger people, of "definite" diagnoses, and of cases diagnosed in hospitals with thoracic surgery (Table II). All differences were statistically significant. The fraction of long-term survivors increased in the most recent calendar periods, reaching 8% in 1999–2001 *versus* 3.7% in 1990–1992.

Univariate analysis

The median survival time was 9.8 months (95% confidence interval: 9.4–10.1). Less than 10% of patients were alive 3 years after diagnosis, and 5% were alive after 5 years.
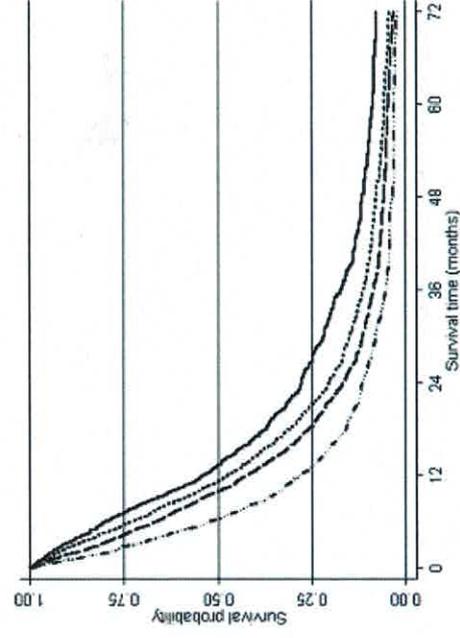

FIGURE 1 – Survival (Kaplan-Meier) by age-class in pleural mesothelioma. Age classes: <55, solid line (——); 55–64, short-dashed line (- - -); 65–74, long-dashed line (– – –); 75+ dashed and dotted line (–·–).

All variables, except sex, showed significant effects (details not shown). Better survival was observed in younger patients (Fig. 1), and in those with epithelioid morphology (Fig. 2), those who underwent treatment (Fig. 3), those who were exposed to asbestos,
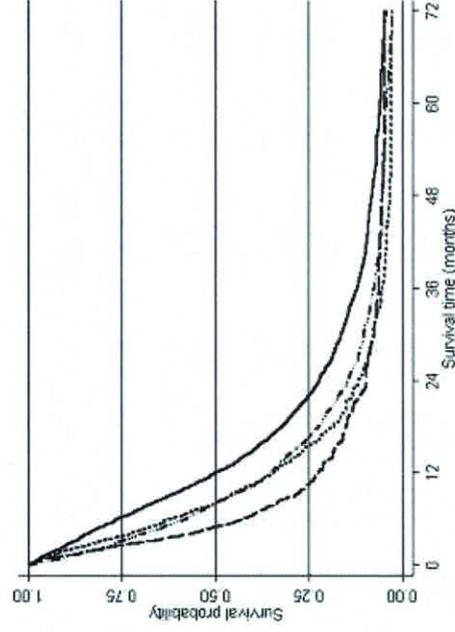
TABLE III – COX PROPORTIONAL HAZARDS REGRESSION, STRATIFIED BY REGIONAL OPERATING CENTRE

Factors	All patients (N = 4100)		Patients with information on treatment (N = 578)	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Women[1]	1		1	
Men	1.1 (1.0–1.2)	0.013	1.2 (0.9–1.4)	0.153
Age				
<55[1]	1		1	
55–64	1.3 (1.1–1.4)	<0.001	1.5 (1.1–1.9)	0.004
65–74	1.4 (1.3–1.5)	<0.001	1.8 (1.4–2.4)	<0.001
75+	1.9 (1.7–2.1)	<0.001	2.7 (1.9–3.8)	<0.001
Calendar period				
1990–1992	1.1 (1.1–1.3)	0.069	1.1 (0.8–1.7)	0.571
1993–1995	1.0 (0.9–1.1)	0.595	1.1 (0.8–1.4)	0.635
1996–1998	1.1 (1.0–1.2)	0.053	1.1 (0.9–1.3)	0.478
1999–2001[1]	1		1	
Morphology				
Epithelioid[1]	1		1	
Mixed	1.4 (1.3–1.6)	<0.001	1.5 (1.2–2.0)	0.002
Fibrous	1.8 (1.6–2.0)	<0.001	1.7 (1.2–2.3)	0.001
Unspecified	1.3 (1.2–1.4)	<0.001	1.3 (1.0–1.8)	0.049
Asbestos exposure				
Yes[1]	1		1	
No	0.9 (0.7–1.1)	0.235	0.8 (0.4–1.5)	0.492
Unknown	1.0 (0.8–1.2)	0.869	0.8 (0.4–1.5)	0.429
Hospital				
With thoracic surgery[1]	1		1	
Without thoracic surgery	1.2 (1.1–1.3)	<0.001	1.1 (0.8–1.4)	0.554
Unspecified	1.3 (1.1–1.6)	<0.001	1.5 (1.2–1.9)	0.002
Treatment				
Treated[1,2]		–	1	
Untreated[3]		–	1.3 (0.9–1.8)	0.148

HR = Hazard ratio, 95% CI = 95% confidence interval.–[1]Reference category.–[2]Ever treated: chemotherapy and/or nonpalliative surgery.–[3]Definitely never treated.

FIGURE 2 – Survival (Kaplan-Meier) by histologic subtype in pleural mesothelioma. Subtypes: epithelioid, solid line (———); mixed, short-dashed line (- - -); fibrous long-dashed line (– – –); unspecified, dashed and dotted line (-·-·-).
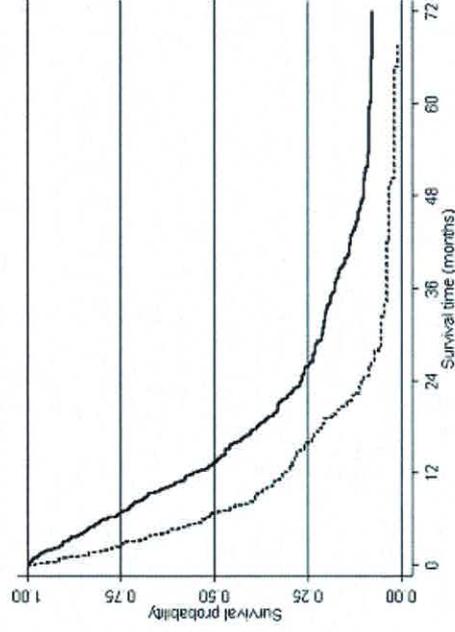
FIGURE 3 – Survival (Kaplan-Meier) by treatment group (see text for explanation). Treatment group: ever treated, solid line (———); never treated, short-dashed line (- - -).

those who had a definite diagnosis, those who were diagnosed in hospitals with a thoracic surgery division, and those who were diagnosed in the most recent calendar periods.

Main multivariate analysis

The simplest and best data-fitting model included gender, age, period, morphology, asbestos exposure and hospital and was stratified according to COR (Table III). As the number of observations was very large, even slight deviations from unity of the hazard ratio (HR) reached statistical significance. The HR showed a clear-cut trend across age-classes, increasing with age. Cases with the epithelioid subtype had better survival, and those with fibrous morphology had the worst prognosis. Marginally but significantly increased HRs were associated with male gender and with being diagnosed in hospitals without a thoracic surgery unit. No trend according to period of diagnosis was observable, even if slight increases in the HRs were present in 1990–1992 and 1996–1998. Asbestos exposure had no significant effect.

Multivariate analysis: Subgroup with data on treatment

Multivariate analyses, restricted to the subgroup of 578 cases that could be definitely classified as ever treated (427) or never treated (151), detected a slight effect of treatment that was not statistically significant. Analyses restricted to persons undergoing surgery (245) or receiving chemo-/radiotherapy (287) gave similar results (data not shown). For proper comparison with the main analysis, the model included, in addition to treatment, gender, age-class, morphology, calendar period of diagnosis, asbestos exposure, and type of hospital as predictive variables and used the COR as the strata-defining variable. To detect possible bias, due to the fact that long-term survivors have *per se* more opportunities to receive treatment, we carried out further analyses restricted to the patients who began their treatment no later than 3 months after diagnosis; the results were comparable with those reported in Table III and are not shown.

Multivariate analysis: other subgroup analyses

As information on smoking habits was available only for cases registered in Liguria, an analysis restricted to this subgroup was conducted. No effect of smoking was detected.

Discussion

The surveillance of mesothelioma is still important despite the stop of industrial asbestos use in most Western countries during the 1990s. Asbestos is in place may continue to create opportunities for exposure. The study of the relationship between asbestos and

TABLE IV – SURVIVAL OF MALIGNANT PLEURAL MESOTHELIOMA CASES IN POPULATION-BASED STUDIES

Study and reference no.	Population	Period	Follow-up	No. cases	Median survival time (months)	% Surviving at (years)			
						1	2	3	5
Janssen-Heijnen et al.[9]	The Netherlands, southeastern	1970–1992	1994	119	N.A.	38%	N.A.	N.A.	N.A.
Neumann et al.[10]	Germany	1987–1999	N.A.	387	13.2[a]	29%[b]	N.A.	5%[b]	N.A.
Desoubeaux et al.[11]	France, Basse-Normandie	1995–1999	2000	66	9.0	N.A.	9%	N.A.	N.A.
Rosso et al.[24]	Pool of Italian Cancer Registries	1990–1994	1999	740	N.A.	34%	N.A.	8%	5%
Magnani et al.[12]	Italy, Piedmont	1990–1998	2000	590	8.5	36%	14%	N.A.	N.A.
Marinaccio et al.[13]	Italy, 5 regions	1997	2001	392	9.2	35%	16%	7%	N.A.
Barbieri et al.[14]	Italy, Brescia province, men	1982–2000	2001	125	7.8	31%	N.A.	N.A.	N.A.
	Italy, Brescia province, women	1982–2000	2001	66	9.7	41%	N.A.	N.A.	N.A.
Gorini et al.[15]	Italy, Tuscany	1988–2000	2002	381	11.0	46%	24%	N.A.	N.A.
Merler et al.[25]	Italy, Veneto	1990–2002	2004	624	10.0	43%	11%	N.A.	N.A.
Kanazawa et al.[16]	Japan, Osaka	1975–1997	N.A.	420	5.0[b]	N.A.	N.A.	N.A.	5%
Chapman et al.[26]	Leeds, UK	2002–2005	2005	146	8.9	N.A.	N.A.	N.A.	N.A.
This study[c]	Italy, 8 regions and 1 province	1990–2001	2005	4100	9.8	42%	18%	10%	5%

N.A.: Not available.–[a]Mean survival time after symptoms onset.–[b]Including cases studied by Magnani et al., Marinaccio et al., Barbieri et al., Gorini et al. and Merler et al.–[c]Including both pleura and peritoneum.–[c]Including microscopically confirmed cases.

MPM is important in order to understand its mechanisms of carcinogenicity. Moreover, survival in MPM patients remains extremely poor and, following the predictions of further increases in incidence, there is interest in identifying treatment options capable of improving prognosis at the population level. In population-based studies, survival times ranged from 5 (median) months to 13.2 (average) months (Table IV). Our study partially overlaps with those by Magnani et al., Marinaccio et al., Barbieri et al., Gorini et al., and Merler et al.[12–15,25] However, even excluding their results, the range of survival time estimates offered by the literature remains unchanged. In the present study, the median survival time was 9.8 months. In some clinical trials, median survival times up to 25 months, depending on the patient subgroup, were reported, but patients enrolled in clinical trials are selected on the basis of strict criteria, mainly in terms of age, performance status and general health conditions.[7,8] Thus they cannot be considered representative of the overall population with MPM.

We identified a small group of long-term survivors (*i.e.*, individuals with survival time ≥48 months) that does not include cases with lesions of uncertain biological behaviour. As shown in Table II, long-term survivors had a higher proportion of women, of relatively young individuals, and of cases with: a definite diagnosis, an epithelioid morphology, a diagnosis between 1999 and 2001, a diagnosis made in hospitals with a thoracic surgery unit, and residence in some regions (mainly Toscana, Emilia-Romagna, Marche). Not all of these factors had significant effects in the multivariate proportional hazards model. Only those that did (Table III) will be discussed.

In previous studies, gender was often indicated as a relevant factor in prognosis, but there is no clear-cut biological explanation for a gender difference that, in our main analysis, was slight and only of border-line significance.

Age was a very important determinant of survival, and death risk increased in older age groups. Younger people are expected to have a better general health status, as well as to tolerate more invasive diagnostic procedures, which may avoid delay in diagnosis. Moreover, symptoms and signs at onset are likely to prompt clinical investigations more quickly.

The morphology of MPM has been usually found to be the most important factor affecting survival, and our results are consistent with this notion. Epithelial-like MPM cases had the longest survival time and fibrous tumour cases the shortest. The behaviour of mixed MPM cases and of cases with unspecified morphology fell in between. This finding was expected, as mixed neoplasms are formed by varying fractions of both cell types, and cases with unspecified morphology include individuals with any possible histotype.

Marginal, although statistically significant, increases in the HRs were present for cases diagnosed in 1990–1992 and in 1996–1998, but no obvious trend in risk of death according to calendar period of diagnosis was observed. Thus, no substantial improvement in prognosis during the study period (1990–2001) is suggested by our data. Whereas treatment effectiveness can be firmly established only through randomised clinical trials (RCTs), only one RCT on chemotherapy in mesothelioma has been so far reported,[6] showing limited improvement in prognosis. In some trials, major improvements in survival after surgery have been reported, but patients were highly selected according to stage of disease and performance status, there was no control group, and there was of course no randomisation.[7,8] In such a framework, population-based observations on secular trends in survival, like our own, can provide useful information.

In previous population-based studies, the association between exposure to asbestos and survival was rarely investigated, as data on exposure are seldom available in general population cancer registries. Desoubeaux et al. found an increased HR for asbestos-exposed cases, while Neumann et al and Marinaccio et al. did not.[10,11,13] In general, we do not expect the biological behaviour of a malignancy to be determined by its etiology, but in the case of mesothelioma some confounding may exist. First, patients recalling a clear-cut history of exposure to asbestos are likely to be diagnosed quickly, while those who do not may experience a significant delay. Observable survival would be affected in the direction of an apparent increase among exposed patients. Secondly, opportunities for obtaining high-quality interviews, which are fundamental to identify exposures due to less-than obvious circumstances, are increased when patients survive longer and remain in better health; this information bias may increase the proportion of patients who are not interviewed or who have poor-quality, uninformative interviews among short-term survivors. Finally, mesothelioma patients without asbestos exposure are rare; for instance, in the study by Desoubeaux et al., there were only 6 unexposed cases.[10] Thus, misclassification of exposure in a handful of patients may seriously bias the effect estimates. Our study was large (122 unexposed cases were available for analysis), and asbestos exposure had no significant effect.

We classified cases according to the type of hospital in which they were diagnosed, whether with or without a thoracic surgery unit. We included the type of hospital in our main multivariate model, in an attempt to control indirectly for the delay in diagno-

MONTANARO ET AL.

sis. Delay in diagnosis may have a major effect on survival estimates when survival is as short as in MPM. It might confound, for instance, the effect of age. We found a slight but significant effect for the type of hospital. As hospitals with a thoracic surgery department are generally large teaching hospitals equipped with the most advanced diagnostic facilities, we believe that this phenomenon reflects the fact that in these settings prompter and more thorough clinical investigations are possible. A true difference in survival might have been present, due to improved prognosis after treatment of some cases. However, this explanation is unlikely, as the same apparent effect of hospital type was observed in our parallel study on peritoneal mesotheliomas, in which thoracic surgery plays no role.[27]

Information on treatment was provided by 4 CORs, and details were limited. Surgical procedures could be classified by distinguishing between those with palliative and those with curative intentions, whereas chemotherapy and radiotherapy were categorized as ever or never done. We showed the model in which all types of treatment were grouped together and compared with the group of untreated patients. No statistically significant effect of treatment was found, and the same occurred when the different treatment options were analysed separately. It may be argued that a suggestion, approaching statistical significance, of better survival in treated cases was indeed present. However, the same problems arise here as in clinical trials: how can treated patients be compared with all other cases? They are likely to differ not only with respect to treatment, but also according to other factors such as age, performance status, and stage of disease at diagnosis. Disease stage and performance status were not known in our study and could not be controlled for. As they are difficult to collect systematically at the population level, population-based studies cannot be expected to lead to firm conclusions on treatment effectiveness. They can, however, help to assess the impact on the overall case mix occurring in the population of treatments whose effectiveness must be previously established in controlled clinical trials. In this sense, our findings cannot prove (or disprove) treatment effectiveness.

Furthermore, our results do not apply to the most recent therapeutic approaches.[5-7] However, studies extending to more recent years will include cases diagnosed after their introduction, and a large basis for assessing how they will affect survival is provided by our results.

A limitation in our data is that no national panel for revising the evidence in support of diagnosis has been set up. The evaluation of such evidence is carried out by CORs, and is generally based on pathological, radiological and clinical reports, but not on the original materials. Thus, some degree of misclassification of diagnosis is possible, even if currently impossible to assess. As major geographical variations in mesothelioma incidence exist in Italy, local experience in the differential diagnosis of mesothelioma may vary accordingly. Similar problems, however, are present in all networks of regional or national cancer registries, such as SEER, and as long as common rules for registration are adopted and complied with, they do not hamper the pooling of data in common databases for survival analysis.[28]

We could obtain precise estimates of survival time, of the proportion of survivors up to 72 months after diagnosis, and of the effects of gender, age, morphology, and exposure to asbestos on survival time, and our observations are in agreement with the results of previous studies. However, information on performance status and disease stage was unavailable. Furthermore, information on treatment could be obtained only for a subset of cases and did not include details on the specific regimens of chemo- or radiotherapy administered. Within these limits, treatment for MPM did not seem to be associated with significant improvements in survival.

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