La Medicina del Lavoro

Med Lav 2017; 108, 5: 367-376
DOI: 10.23749/mdl.v108i5.5929

The effects of improving the mesothelioma surveillance network on sensitivity, timeliness in reporting and asbestos exposure assessment

Lucia Mangone[1], Enza Di Felice[1], Cinzia Storchi[1], Antonio Romanelli[2], Serena Broccoli[1], Massimo Vicentini[1], Paolo Giorgi Rossi[1]

[1] Inter-istitutional Epidemiology Unit, Azienda Unità Sanitaria Locale, Reggio Emilia, Italy and Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy
[2] Work Prevention and Safety Service (SPSAL), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy

Key words: Asbestos exposure; mesothelioma registry; sensitivity; surveillance system; timeliness

Parole chiave: Esposizione amianto; registro mesotelioma; sensibilità; sistema di sorveglianza; tempestività

Summary

Background: *In Italy, Mesothelioma Registries (MRs) have been established by law for the epidemiological surveillance of occupational cancers. MRs collect information about asbestos exposure of incident cases, through interviews. In the Emilia-Romagna region, MR was implemented in 1996 and extended its network of health professionals who report suspected mesothelioma in 2001 and 2007.* **Objectives:** *This study evaluated the impact of the extension of the network on MR sensitivity and timeliness.* **Methods:** *Mesothelioma cases were analysed in three subsequent periods: 1996-2001 (before any network extension), 2002-2007 (after first extension) and 2008-2014 (after second extension). Sensitivity was evaluated by the proportion of cases directly reported by the network out of the total number of incident cases; reporting and interview timeliness were assessed by median times between diagnosis and, respectively, reporting and interview. Pleural mesothelioma reporting timeliness was also evaluated by use of quantile regression models, stratified by diagnostic certainty and adjusted by sex and age.* **Results:** *Sensitivity increased from 79.4% (1996-2001), to 89.0% (2002-2007) and to 91.4% (2008-2013). For mesothelioma with diagnostic certainty, we recorded considerably reduced reporting times from the 50th percentile on, whereas for uncertain mesothelioma relevant reductions were observed also in the lower percentiles. A reduced time to interview was observed too, which was more significant for uncertain cases. The proportion of patients directly interviewed increased from 33.5% (1996-2001), to 39.1% (2002-2007), to 49.5% (2008-2014).* **Conclusions:** *The extended network improved the MR sensitivity and allowed shorter reporting and interview times and more frequent patient interviews, thus improving accuracy of exposure definition.*

Riassunto

«L'impatto dell'estensione della rete di sorveglianza del mesotelioma su sensibilità, tempestività e valutazione dell'esposizione ad amianto». **Introduzione:** *In Italia, i registri mesotelioma sono stati istituiti per raccogliere informazioni sull'esposizione ad amianto utili alla sorveglianza epidemiologica dei tumori professionali. In Emilia-Romagna il registro mesotelioma, istituito nel 1996, ha esteso la propria rete di professionisti sanitari, incaricati di*

Pervenuto il 11.11.2016 - Revisione pervenuta il 27.6.2017 - Accettato il 6.10.2017
Corrispondenza: Enza Di Felice, Epidemiology Unit, Azienda Unità Sanitaria Locale Reggio Emilia and Arcispedale Santa Maria Nuova - IRCCS Reggio Emilia, Via Amendola 2, 42122 Reggio Emilia - Tel. 0522335470 - E-mail: difelicee@ausl.re.it

segnalare i casi sospetti, nel 2001 e nel 2007. **Obiettivo:** *Valutare l'impatto dell'estensione della rete sulla sensibilità e la tempestività del sistema di sorveglianza.* **Metodi:** *Sono stati analizzati i casi di mesotelioma nei tre periodi corrispondenti all'implementazione ed estensione della rete (1996-2001, 2002-2007, 2008-2014). La sensibilità è stata valutata attraverso la proporzione di mesoteliomi segnalati dalla rete, mentre la tempestività attraverso i tempi mediani intercorsi tra la diagnosi e la segnalazione o l'intervista, stratificando la casistica per mesotelioma certo e non certo. Per il mesotelioma pleurico, la valutazione della tempestività è stata effettuata utilizzando anche modelli di regressione quantile, stratificati per certezza diagnostica e aggiustati per sesso ed età.* **Risultati:** *La sensibilità nei tre periodi è aumentata dal 79,4% all'89,0%, al 91,4%. Per i mesoteliomi certi c'è stata una forte riduzione nei tempi di segnalazione, soprattutto a partire dal 50esimo percentile, mentre per i mesoteliomi non certi sono state osservate riduzioni rilevanti anche sui percentili bassi. Anche nei tempi all'intervista si è verificata una riduzione, più elevata per i casi non certi. La percentuale di interviste al paziente è aumentata dal 33,5% (1996-2001), al 39,1% (2002-2007), al 49,5% (2008-2014).* **Conclusioni:** *L'estensione della rete ha migliorato la sensibilità del sistema di sorveglianza e ha permesso una riduzione dei tempi di segnalazione e intervista e un aumento di interviste effettuate direttamente al paziente, incrementando in tal modo l'accuratezza nella definizione dell'esposizione.*

Introduction

Malignant Mesothelioma (MM) is a rare cancer: in 2011, Italian incidence rates were 3.8 and 1.5 cases per 100,000 in men and women, respectively (10). Inhalation of asbestos fibres represents the main MM risk factor: in Italian case series, asbestos exposure was detected in 80% of cases (87% in men): occupational exposure was very high in men (83%), much lower in women (33%) (10). Non-occupational exposure was estimated to cause less than 10% of cases (9, 17). Italy is one of the most affected countries in the world because, until the 1992 National Asbestos Ban, many factories had been processing asbestos and more than 3.5 million [metric] tons have been produced or imported (12). Exposed workers were estimated to be 350,000 in 1991 and 76,000 ten years later (17).

In Italy, MM incidence is still increasing, due to its extremely long latency period (on average 44.6 years) (13): mathematical models predict the incidence peak between 2010 and 2025, with about 800-1000 deaths per year in men (14, 22). At present, most recent data related to some Italian regions are recording a decreasing trend (4), while others are still showing an increasing trend (15).

Mesothelioma is also a fatal cancer with a median survival time of 9.8 months for pleural MM cases; less than 10% of patients were alive 3 years after diagnosis (3, 5, 19).

In Italy, Mesothelioma Registries (MRs) mandatorily record epidemiological data about malignant mesothelioma. They work at regional level and converge into a National Registry of Mesothelioma (ReNaM) (10).

The main peculiarity of MRs, compared to general cancer registries, is the ascertainment of asbestos exposure: MRs collect detailed information about past exposure to asbestos, to define any occupational exposures, possibly through the direct voice of the patient (23), which is a relevant point for legal and insurance aspects. Consequently, MRs rely on different criteria for defining cases with higher diagnostic certainty (1). For all these reasons, completeness, timeliness and accuracy of data are strongly required (16), as they are much more critical to MRs than to cancer registries.

Since 1996, Emilia-Romagna Mesothelioma Registry (E-R MR) has been collecting all MM incident cases and information about their exposure to asbestos. To collect all data, E-R MR has connected a large regional health professional network reporting suspected cases. In 2002 and 2008, this network underwent an enlargement process to improve reporting completeness also for extra pleural sites and to reduce times of reporting of new cases.

We aimed at evaluating how the extension of the network reporting impacted on sensitivity and timeliness of the mesothelioma surveillance system.

Methods

Setting

Emilia-Romagna, with its nearly 4.5 million inhabitants in 2016, lies in North-eastern Italy. In this region, many asbestos-related industries operated until the early 1990s. An estimate of Emilia Romagna exposed workers was almost impossible, as asbestos was widely used in many working processes: only for a few processes, cohorts of exposed workers were available, reaching more than 10,000 individuals (2, 8, 21, 26). MM Incidence is one of the highest in Italy: in 2011, 5.2 per 100,000 males and 1.6 per 100,000 females (10).

Data Source

E-R MR was established by a Regional Resolution (DGR n. 862 of 07/03/1995). Its headquarters are located at Reggio Emilia Local Health Authority.

This study included all site MM cases (pleura, pericardium, peritoneum and tunica vaginalis testis) diagnosed from 1996 to 2014 among Emilia-Romagna residents, even if 2014 data were still being completed in May 2015, when analyses were carried out.

The network of health professional reporting cases and its updates

In 1996, a first regional network including pathologists, occupational physicians and mortality registries was set up to report each case of suspected MM to the E-R MR. In 2001, the network was extended to the hospital wards of oncology, pulmonology, thoracic surgery, cancer registries: 40 institutionally defined contacts were established. In 2007, further measures were taken to enlarge the network with a formal Regional Resolution: gynaecology, cardiology, general surgery and urology units were added to increase extra pleural mesothelioma reporting and to improve the timeliness of reporting new case. At present, E-R MR counts on 145 contacts.

On this background, three incidence periods (1996-2001, 2002-2007, 2008-2014) were defined for implementing and enlarging reporting network.

To avoid missing unreported MM and ensure registry completeness, E-R MR team examines all hospital discharge records for pleural malignant tumours (ICD-9-CM codes 163, in primary or secondary diagnosis) and all attributable-mesothelioma deaths, recorded in the regional mortality database (ICD-9-CM codes 163, 158, 164, 186 and ICD-10 codes C45, C38.0, C38.4, C48.1, C48.2, C48.8, C62, D38.2, D48.4).

Diagnostic and exposure classifications

For each case, E-R MR obtained histological and cytological reports and clinical records. After examination of all medical records, cases were classified according to level of diagnosis certainty: certain, probable, possible (including Death Certificate Only -DCO- cases) (Appendix 1).

Furthermore, for each MM case, E-R MR team, together with regional occupational physicians, interviewed patients or their relatives to define their asbestos exposure, through ReNaM questionnaire (20), about work history, hobbies and personal habits (e.g. smoking). The asbestos exposure was assessed and codified into six categories: occupational; familial; environmental; not-occupational; unlikely; unknown (Appendix 1).

Occupational exposures were also divided into three levels: certain, probable or possible.

Analysis

Distribution of all MM cases was calculated by incidence period (1996-2001, 2002-2007, 2008-2014) and age, sex, site, diagnostic classification and asbestos exposure. Age-standardised incidence rates were calculated by sex and year (until 2013), using the standard European population, to evaluate temporal trend. Annual Percent Change (APC) of standardised rates was estimated using the Joinpoint Regression Analysis (7).

Sensitivity of MM surveillance system was evaluated for 1996-2013 period, by percentage of cases reported by the network out of all registered ones,

including MM cases detected through linkage to hospital discharge records or mortality records.

To assess timeliness reached by surveillance system, we measured median times (in days) by certainty level (certain MM or not) comparing diagnosis/reporting to E-R MR dates and diagnosis/interview dates. Date of reporting coincided with the first notification, made by one network member or by a completion source (hospital discharge records or mortality records). We reported also asbestos exposure according to interview responder (patients or their relatives).

Impact of network enlargement on timeliness of reporting and interview was assessed only for pleural MM, which was constantly recorded in the whole period, through quantile regression analysis (6) stratified by certainty level (certain or uncertain MM), adjusting for sex and age.

Assessment was performed also on "direct interview to patients", through a logistic regression adjusted by sex, age and certainty level (certain or uncertain MM).

Incidence period was considered as exposure variable for all models and '2002-2007' period was used as reference class.

Statistical analysis was performed using Stata software, 13.0 version.

Ethics

In Italy, the Mesothelioma Registries are regulated by national law (D.Lgs. n.277/1991, D.P.C.M. n.308/2002, D.Lgs n.81/2008), according to which registration and exposure assessment are National Health Service's duties. Data are treated according to Italian Data Protection legislation (D.Lgs.n.196/2003). During the interview, patients gave their informed consent.

Results

In the period 1996-2014, we recorded 2,134 cases of MM (table 1).

For the complete incidence years (1996-2013), 1,455 male cases and 564 female cases were identified, with crude incidence rates equal to 3.97 and 1.45 per 100,000 respectively. Incidence trend was significantly increasing both in men (APC=3.2) and in women (APC=2.5), as shown in figure 1.

Most cancers affect male population (72.0%), older people (57.6% in people over 70 years) and pleural site (91.1%). Over 85% of tumours were classified as certain MM, most cases occurred in the most recent period.

Asbestos exposure was assessed for 1,756 patients (1,636 cases, through interviews, 120 cases, through clinical records). Out of them, 67.8% were occupational asbestos-exposed, while 8.9% were unlikely to have been exposed. 251 cases showed unknown exposure, as documentation was insufficient (table 1).

A larger network of health professionals led to a better sensitivity: the percentage of MM unreported cases reduced from 27.1% (1996-2001), to 16.3% (2002-2007), and 13.1% (2008-2013).

Over the three time periods, accuracy in diagnostic classification also increased: certain MM increased from 77.6% (1996-2001), to 85.8% (2002-2007) and 88.9% (2008-2014).

A larger network also led to collect more cases in extra pleural sites: 50, 67 and 73 cases in the three analysed periods.

Median time between diagnosis and reporting to the E-R MR decreased from 253 days in the first period to 63 in the last one: the longest time reduction was recorded shifting from the first to the second period. Uncertain MM had longer time of reporting compared to certain MM. Even median time between diagnosis and interview has dropped considerably (from 726 days to 295), especially in recent years. Also, regarding the interview, uncertain MM had longer times (table 2).

Shorter times of reporting led to a higher number of interviews directly involving patient: from 33.5% (1996-2001), to 39.1% (2002-2007) and 49.5% (2008-2014). Compared to their relatives, patients undergoing interviews provided a more accurate definition of asbestos exposure: in particular, certain occupational exposure increased from 36% (342/953) to 61% (414/683), while unknown exposure decreased from 20% (188/953) to 8% (54/683) (test for Chi-squared, p-value<0.001).

Quantile regression coefficients on time of reporting, which represent the difference (in days) in MM reporting between incidence periods, at select-

Table 1 - Distribution of malignant mesothelioma cases. Patient characteristics, tumour site, certainty of diagnosis, and exposure assessment, by period of incidence. Emilia-Romagna region, years 1996-2014

		1996-2001		2002-2007		2008-2014		Total	
Variable		N	%	N	%	N	%	N	%
Sex	Male	349	71.1	483	71.0	705	73.2	1537	72.0
	Female	142	28.9	197	29.0	258	26.8	597	28.0
Age	<40	10	2.0	4	0.6	7	0.7	21	1.0
	40-49	25	5.1	19	2.8	18	1.9	62	2.9
	50-59	74	15.1	83	12.2	66	6.9	223	10.4
	60-69	131	26.7	207	30.4	260	27.0	598	28.0
	70+	251	51.1	367	54.0	612	63.6	1230	57.6
Tumour site	Pleura	441	89.8	613	90.1	890	92.4	1944	91.1
	Peritoneum	40	8.1	60	8.8	65	6.7	165	7.7
	Pericardium	4	0.8	3	0.4	2	0.2	9	0.4
	Testis	6	1.2	4	0.6	6	0.6	16	0.7
Diagnosis	Certain	381	77.6	583	85.7	856	88.9	1820	85.3
	Probable	54	11.0	43	6.3	39	4.0	136	6.4
	Possible	56	11.4	54	7.9	68	7.1	178	8.3
Exposure	Interview done	427	87.0	565	83.1	644	66.9	1636	76.7
	to patients[1]	143	29.1	221	32.5	319	33.1	683	32.0
	to relatives[1]	284	57.8	344	50.6	325	33.7	953	44.7
	Defined[2]	435	88.6	596	87.6	725	75.3	1756	82.3
	Occupational[3]	*255*	*58.6*	*389*	*65.3*	*547*	*75.4*	*1191*	*67.8*
	Certain[4]	*145*	*56.9*	*279*	*71.7*	*410*	*75.0*	*834*	*70.0*
	Probable[4]	*60*	*23.5*	*60*	*15.4*	*79*	*14.4*	*199*	*16.7*
	Possible[4]	*50*	*19.6*	*50*	*12.9*	*58*	*10.6*	*158*	*13.3*
	Familial[3]	*27*	*6.2*	*33*	*5.5*	*38*	*5.2*	*98*	*5.6*
	Environmental[3]	*9*	*2.1*	*17*	*2.9*	*11*	*1.5*	*37*	*2.1*
	Not occupational[3]	*4*	*0.9*	*13*	*2.2*	*5*	*0.7*	*22*	*1.3*
	Unlikely[3]	*67*	*15.4*	*54*	*9.1*	*36*	*5.0*	*157*	*8.9*
	Unknown[3]	*73*	*16.8*	*90*	*15.1*	*88*	*12.1*	*251*	*14.3*
	Not defined	56	11.4	84	12.4	238	24.7	378	17.7
	Refusal/Untraceable	47	9.6	58	8.5	63	6.5	168	7.9
	Not yet contacted	9	1.8	26	3.8	175	18.2	210	9.8
Total		491	100.0	680	100.0	963	100.0	2,134	100.0

[1] percentage out of cases with interview done; [2] for 120 cases the exposure was assessed through other documents; [3] percentage out of cases with defined exposure; [4] percentage out of cases with occupational exposure

ed percentiles (10, 20, 50, 80, 90) showed significant reduced time of reporting for certain pleural MM, especially by comparing the second period with the first (over 100-day reduction in reporting 50% of cases and over 700-day reduction in reporting 80% and 90% of cases). Significantly reduced times were recorded also in comparing the third period and the second one (with a decrease of 27-day, 90-day and 192-day reduction in reporting, respectively, 50%, 80% and 90% of cases) (figure 2a1).

For uncertain pleural MM, significant reductions were observed between the first and second period in all percentiles taken into account (from 64-day reduction in reporting 10% of cases to 650-day reduction in reporting 80-90% of cases). Random fluctuations-compatible reductions were observed between second and third period (figure 2a2).

As concerned certain pleural MM and taking into account time occurring from diagnosis to interview, significant reductions were found especial-

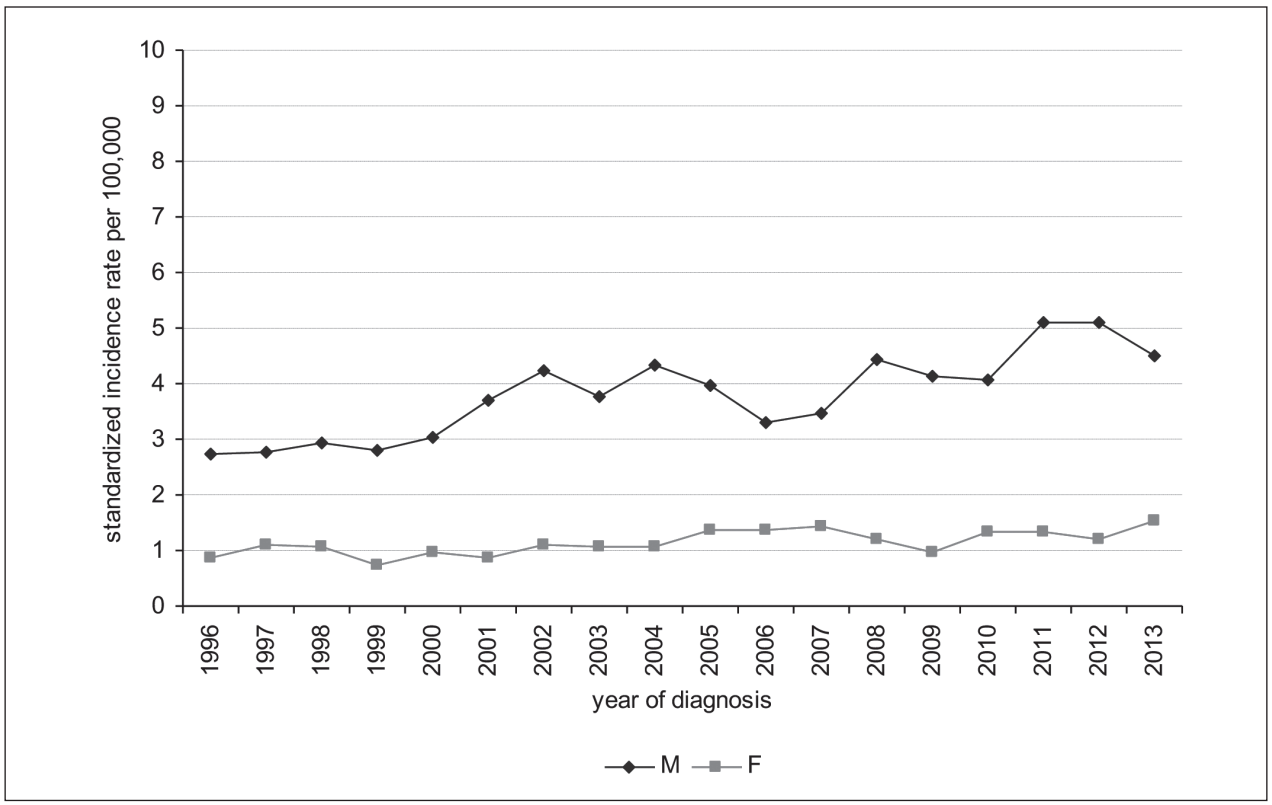

Figure 1 - Standardized mesothelioma incidence rates (European standard population) in Emilia-Romagna region, by year and sex

Table 2 - Median time (in days) between the diagnosis date and reporting date (a) and interview date (b), by period of incidence and diagnostic certainty. Emilia-Romagna region, years 1996-2014

	certain MM		uncertain MM		Total	
Incidence period	n	median time	n	median time	n	median time
(a) time from diagnosis to reporting						
1996-2001	381	177	110	824	491	253
2002-2007	583	81	97	310	680	96
2008-2014	856	55	107	312	963	63
*(b) Time from diagnosis to interview**						
1996-2001	343	585	84	1392.5	427	726
2002-2007	494	356	71	749	565	406
2008-2014	591	284	53	618	644	295

* the median time was calculated including only cases with interview
MM: malignant mesothelioma

ly between the second and third period for higher percentiles (510-day reduction in 80% interviews, 1299-day reduction in 90% interviews), and between the first period and the second one only for the median value (210-day reduction in the latter period) (figure 2b1).

As concerned uncertain pleural MM, decreased time to interview mainly regarded shift from the first

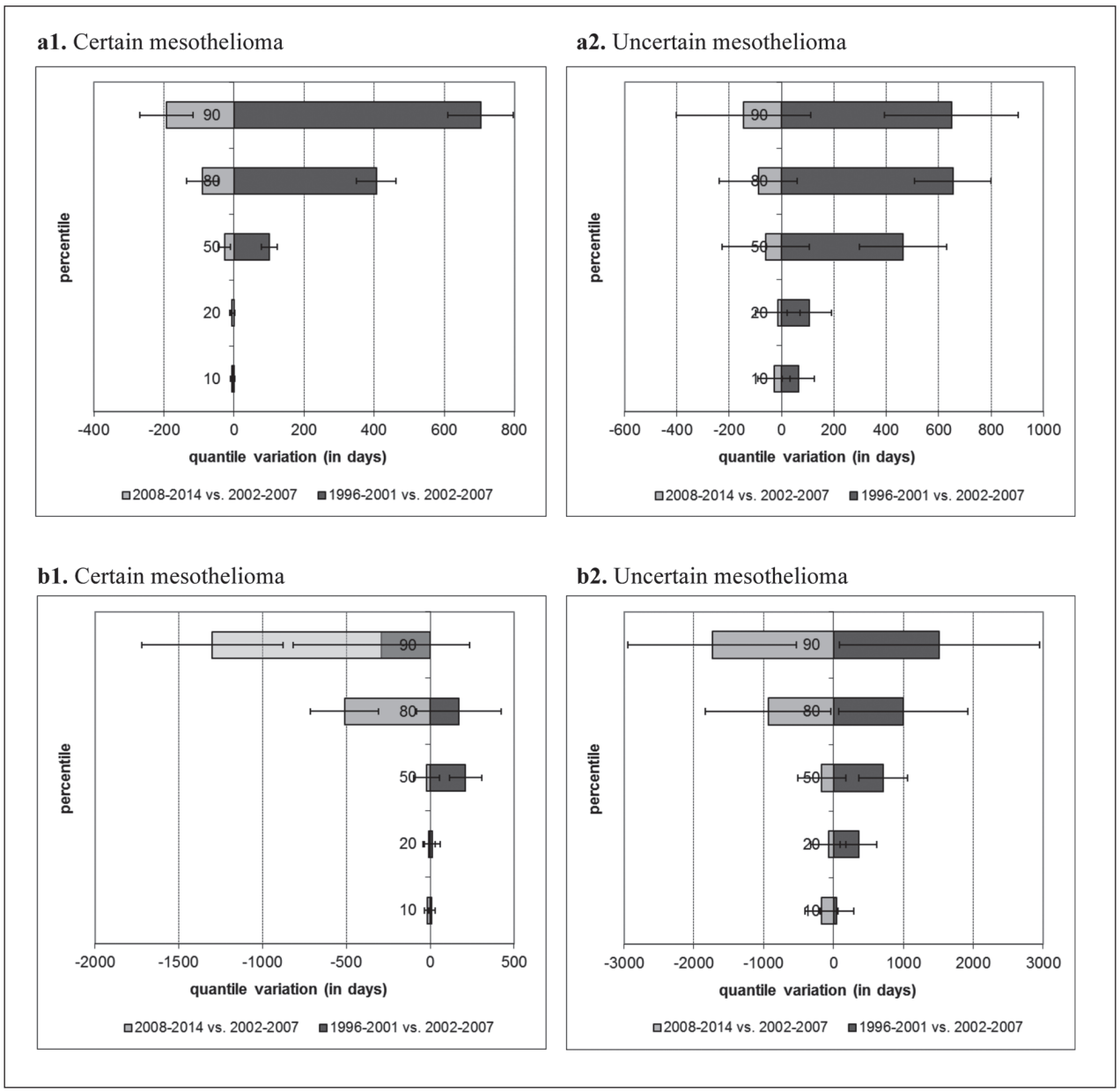

Figure 2. Differences (in days) between diagnosis date and reporting date (a) or interview date (b) by percentile of the distribution in certain and not certain mesothelioma and incidence period. Pleural mesothelioma. Emilia Romagna region, years 1996-2014. Bars represent the change at the 90th, 80th, 50th, 20th, and 10th percentile: dark grey bars represent changes in the 1996-2001 period vs. the 2002-2007 period; light grey bars represent changes observed in the 2008-2014 period vs. the 2002-2007 period. Bars extending toward the right represent longer delays than the reference period (200-2007); bars extending toward the left represent shorted delays than the reference period. Lines at the head of the bars represent 95% confidence intervals. Models are adjusted by age and sex

to the second period: significant differences were observed (357-day reduction at 20th percentile, 709-day reduction at 50th, 998-day reduction at 80th, 1514-day reduction at 90th), while comparing second and third periods, observed decreased times were consistent with random fluctuations (figure 2b2).

Multivariate logistic regression showed a 64% increased likelihood to directly interview the pa-

Table 3. Odds ratio of obtaining a direct interview by period, sex, age and diagnostic certainty . Pleural mesothelioma. Emilia-Romagna region, years 1996-2014.

Variable		Odds Ratio	95% Confidence Interval
Incidence period	1996-2001	0.81	0.60-1.08
	2002-2007	1	
	2008-2014	1.64	1.28-2.10
Sex	Male	1	
	Female	0.74	0.58-0.95
Age (5-years class)		0.81	0.76-0.87
Diagnostic certainty	certain MM	1	
	uncertain MM	0.27	0.18-0.43

tients (Odds Ratio=1.638, 95% Confidence Interval=1.276-2.103) with extended surveillance system from second to third period. Males, younger people and individuals diagnosed with certain MM showed higher likelihood of being directly interviewed (table 3).

Discussion

A better organized and larger health professionals network in E-R mesothelioma surveillance system increased sensitivity in MM reporting and, more importantly, reduced times for reporting and interviewing, thus increasing the chance of collecting information about asbestos exposure directly from patients.

Several studies have highlighted the important role of timeliness and completeness of data, by developing *ad hoc* surveillance systems for specific diseases. Although many of them refer to infectious diseases, some others are related also to cancer and paediatric diseases (24, 27). Timeliness turned out as particularly important in mesothelioma surveillance as it allowed to get updated information for health planning and the most accurate information on asbestos exposure and its modalities (12), thus supporting a more efficient compensation system (11, 12). As far as our second aim was concerned, since mesothelioma is a highly lethal cancer with a very short survival time, only very rapid surveillance allowed directly interviewing patients (23).

Mesothelioma surveillance systems in most Italian regions are mainly based on informal networks, with personal contacts of coordinating centre and the most relevant oncology and lung disease departments (10). Mesothelioma surveillance system in Emilia-Romagna translated into a widespread network of officially appointed health professionals, related to all regional departments where pleural and extra pleural MM may be diagnosed and treated. After its implementation in 1996, this network experienced a two-steps enlargement process, including all oncology and lung disease wards (2001) and other wards which were well-equipped for extra pleural mesothelioma diagnosis (2008).

Consequently, E-R MR produces data on incidence and exposure with an approximately six-months delay: data related to 2014 were available for clinicians and decision makers in June 2015, allowing better management of the patient, while, usually, other MRs get available data with a more than 12-18-month delay (10).

We observed much less time between diagnosis and reporting compared to time between diagnosis and interview, as professionals' network report MM cases, but they are not involved in interviews, thus substantially cancelling improvement efforts made by network. For this reason, work flow needs rearrangement and improvement.

Since the proportion of interviewed cases increased, there was no certainty that median time to interview decreased, even by increasing timeliness, as uncertain MM cases captured by the network were more difficult to be detected, and being timely may be more complex for them. Nevertheless, median time to interview improved. For uncertain MM, we observed a considerable reduction both in the transition from the first to the second period and from the second to the third one.

Strength and limitations

During the study period, many changes in the diagnosis of pleural disease occurred, in particular in the last years: video assisted thoracoscopic surgery became more common in the Emilia-Romagna region, thus allowing histological confirmation of a larger number of cases (25). Improved diagnostic

procedures may have had a positive impact on accuracy and timeliness of reporting, apart from network improvement, by centralizing mesothelioma treatment and improving diagnosis. Nevertheless, surveillance sensitivity and timeliness increased also in uncertain cases. This effect was unlikely to be due to generally improved diagnostic techniques.

Furthermore, although timeliness could also be influenced by other reasons, an increased number of cases directly reported by the network and not by other source could justify the shorter reporting delay found in our study. These findings support possible causal link between network enlargement and improved timeliness.

Network enlargement improved sensitivity of the surveillance system and allowed a reduction in report and interview delay, thus increasing the number of patients directly interviewed and accuracy in the exposure definition.

No potential conflict of interest relevant to this article was reported by the authors

References

1. Allen TC: Accurate diagnosis of mesothelioma. More important than ever. Arch Pathol Lab Med 2013; 137; 601-602
2. Brandi G, Di Girolamo S, Farioli A, et al: Asbestos: a hidden player behind the cholangiocarcinoma increase? Findings from a case-control analysis. Cancer Causes Control 2013; 24: 911-918
3. Gatta G, Ciccolallo L, Kunkler I et al: Survival from rare cancer in adults: a population-based study. Lancet Oncol 2006; 7: 132-140
4. Girardi P, Bressan V, Merler E: Past trends and future prediction of mesothelioma incidence in an industrialized area of Italy, the Veneto Region. Cancer Epidemiol 2014; 38: 496-503
5. Howlader N, Noone AM, Krapcho M, et al: SEER cancer statistics review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/; based on November 2010 SEER data submission, posted to the SEER web site, 2011
6. Koenker R: Quantile Regression. New York: Cambridge University Press, 2005
7. Joinpoint regression Analysis Software downloadable from http://surveillance.cancer.gov/joinpoint/http://www.cdc.gov
8. Luberto F, Amendola P, Belli S, et al: Studio di mortalità degli addetti alla produzione di manufatti in cemento amianto in Emilia-Romagna, Epidemiol Prev 2004; 28: 239-246
9. Marinaccio A, Binazzi A, Bonafede M, et al: Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (ReNaM): epidemiology and public health issues. Occup Environ Med 2015 Jun 4 [Epub ahead of print]
10. Marinaccio A, Binazzi A, Di Marzio D, et al: Il Registro Nazionale Mesoteliomi. Quinto Rapporto. Istituto nazionale Assicurazione Infortuni sul Lavoro. Edizione 2015
11. Marinaccio A, Scarselli A, Merler E, et al: Mesothelioma incidence surveillance systems and claims for workers'compensation. Epidemiological evidence and prospects for an integrated framework. BMCPublic Health 2012; 12: 314
12. Marinaccio A, Binazzi A, Di Marzio D, et al: Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. Int J Cancer 2011 Jun 6 [Epub ahead of print]
13. Marinaccio A, Binazzi A, Cauzillo G, et al: Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register. Eur J Cancer 2007; 43(18): 2722-2728
14. Marinaccio A, Montanaro F, Mastrantonio M, et al: Prediction of mortality from pleural mesothelioma in Italy: a model based on asbestos consumption figures supports results from age-period-cohort models. In J Cancer 2005; 115: 142-147
15. Mensi C, De Matteis S, Dallari B, et al: Incidence of mesothelioma in Lombardy, Italy: exposure to asbestos, time patterns and future projections. Occup Environ Med 2016; 73: 607-613
16. Merler E, Bressan V, Bilato AM et al: Gruppo regionale veneto sui mesoteliomi maligni. I fattori che influenzano in Italia la domanda e il riconoscimento dei mesoteliomi di origine professionale. Epidemiol Prev 2011; 35: 331-338
17. Mirabelli D, Cavone D, Merler E, et al: Non-occupational exposure to asbestos and malignant mesothelioma in the Italian national registry of mesotheliomas. Occup Environ Med 2010; 67: 792-794
18. Mirabelli D, Kauppinen T: Occupational Exposures to Carcinogens in Italy: an Update of CAREX Database. Int J Occup Environ Health 2005; 11: 53-63
19. Montanaro F, Rosato R, Gangemi M et al: Survival of pleural malignant mesothelioma in Italy: a population-based study. Int J Cancer 2009; 124: 201-207
20. Nesti M, Marinaccio A, Gennaro V, et al: ReNaM Working Group. Epidemiologic surveillance for primary

prevention of malignant mesothelioma: the Italian experience. Med Lav 2005; 96: 338-346
21. Pavone VL, Scarnato C, Marinilli P, et al: Mortalità in una coorte di addetti alla costruzione e riparazione di carrozze ferroviarie in un'azienda di Bologna. Med Lav 2012; 103: 112-122
22. Pelucchi C, Malvezzi M, La Vecchia C, et al: The mesothelioma epidemic in western Europe: an update. Br J Cancer 2004; 90: 1022-1024
23. Pinto C, Novello S, Torri V, et al: Second Italian consensus conference on malignant pleural mesothelioma: state of the art and recommendations. Cancer Treat Rev 2013; 39: 328-339
24. Puckett M, Neri A, Rohan E, et al: Evaluating Early Case Capture of Pediatric Cancers in Seven Central Cancer Registries in the United States, 2013. Public Health Rep 2016; 131: 126-136
25. Romanelli A, Storchi C, Sala O, et al: Il mesotelioma maligno in Emilia-Romagna: incidenza ed esposizione ad amianto, aggiornamento al 31 Dicembre 2014 (Regional Report)
26. Zanardi F, Salvarani R, Cooke RM, et al: Carcinoma of the pharynx and tonsils in an occupational cohort of asphalt workers. Epidemiology 2013; 24: 100-103
27. Zanetti R, Schmidtmann I, Sacchetto L, et al: Completeness and timeliness: Cancer registries could/should improve their performance. Eur J Cancer 2015; 51: 1091-1098

Appendix 1
Criteria for diagnosis and exposure definition (ReNaM classification)

The level of certainty diagnosis may be classified into:
- Certain MM: microscopic examination on histological or cytological material, enclosed in paraffin, with a characteristic morphological pattern, also in absence of immunohistochemistry with a characteristic immunophenotypic pattern, of imaging or of clinical diagnosis;
- Probable MM: histological or cytological examination with enclosure in paraffin, but which did not give a clear result indicating mesothelioma (doubtful case) or cytological examination not enclosed in paraffin with a characteristic pattern with explicit indication for mesothelioma and imaging or clinical diagnosis for mesothelioma;
- Possible MM: clinical and radiological data indicative owf mesothelioma and discharge for mesothelioma (with consultation of clinical record) or mesothelioma as a cause of death for Death Certificate Only (DCO) cases.

The asbestos exposure was assessed and codified into six categories:
- Occupational: individuals who have carried out working activities involving asbestos use/exposure;
- Familial: individuals not occupationally exposed, but exposed in their household for cohabitation with at least one worker with certain or probable occupational exposure;
- Environmental: individuals not occupationally exposed, who lived close to an industrial area using asbestos or to asbestos-containing products, or who may have attended asbestos-containing places for not occupational reasons.
- Not occupational: the exposure is linked to activities performed in the household (use of asbestos household goods) or during leisure time (DIY, plumbing repairs, motor vehicle repairs, masonry work, etc.)
- Unlikely: individuals for whom good quality data concerning professional and private history is available. Data allows to exclude asbestos exposure levels exceeding the "natural environmental background level"
- Unknown: the information collected about the individuals are incomplete and insufficient to attribute the exposure level.