Review Article

Hotspots of malignant pleural mesothelioma in Western Europe

Valerie Nuyts[1], Tim Nawrot[1,2], Benoit Nemery[1,3], Kristiaan Nackaerts[3]

[1]Department of Public Health and Primary Care, Centre for Environment and Health, KU Leuven, Leuven, Belgium; [2]Centre for Environmental Sciences, University of Hasselt, Hasselt, Belgium; [3]Department of Respiratory Diseases, University Hospitals Leuven, KU Leuven, Leuven, Belgium

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Correspondence to: Kristiaan Nackaerts, MD, PhD. Department of Respiratory Diseases University Hospitals Leuven, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Email: Kristiaan.nackaerts@uzleuven.be.

Abstract: Malignant pleural mesothelioma, a highly invasive tumour, has been epidemiologically linked to an occupational or environmental exposure to asbestos. Although asbestos has been widely used in diverse industrial applications and in construction, some industrial sectors have been affected much more than others. The objective of this review was to describe the existence of clusters of malignant pleural mesothelioma in Western European countries, based on epidemiological studies published between 2000 and 2015. MEDLINE (PubMed) and Embase were searched for relevant studies on spatial clustering of mesothelioma in Western European countries. Eventually, 16 different studies published between 2000 and 2015 were selected for a comprehensive analysis. Relevant studies on spatial clustering of mesothelioma were found for Belgium, the Netherlands, the United Kingdom, Germany, France, Spain, Italy and Denmark. Clustering of pleural mesothelioma was found mainly around shipyards (16 studies) and asbestos cement industries (10 studies). Although malignant pleural mesothelioma may be found throughout Western Europe, the present study indicates specific areas with higher past and also probable future incidence.

Keywords: Asbestos; mesothelioma; Europe; spatial clustering

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Malignant pleural mesothelioma (MPM) has a latency time that ranges from 20 to 50 years but most patients die within 9 to 12 months after diagnosis. The dominant cause of MPM is inhalation of asbestos fibres. Worldwide, there was a peak in asbestos consumption around 1980, with approximately 4.8 million tons of asbestos per year. Hereafter, consumption started to decrease to a stable level around 2 million tons of asbestos per year in 1997 (1). The main reason for this consumption drop was the limitation in asbestos use in Western Europe and North America. Robust ecological correlations have been demonstrated between a country's incidence of MPM and the per capita amount of imported (or consumed) asbestos in that country, 40 years earlier (2). Asbestos has been used in many industrial applications and in construction. Epidemiological studies have demonstrated links between increased risks of MPM and specific occupations and exposures, such as shipyards and asbestos-cement manufacturing. This has led to a higher prevalence of MPM in certain geographical areas, e.g., close to harbours with shipbuilding or close to plants manufacturing asbestos-cement. An emblematic example of such a hotspot is the city of Casale Monferrato (Italy), where an asbestos-cement company was recently convicted for having caused MPM among its workers and inhabitants.

The epidemiology of asbestos-related diseases in European countries has been intensively studied with regard to its time course. The geographic distribution of MPM has also been studied within countries but, to our knowledge, no studies have investigated the occurrence of mesothelioma hotspots at a European level.

We have compiled the existing evidence of geographical clusters of MPM in Europe, as obtained from recent

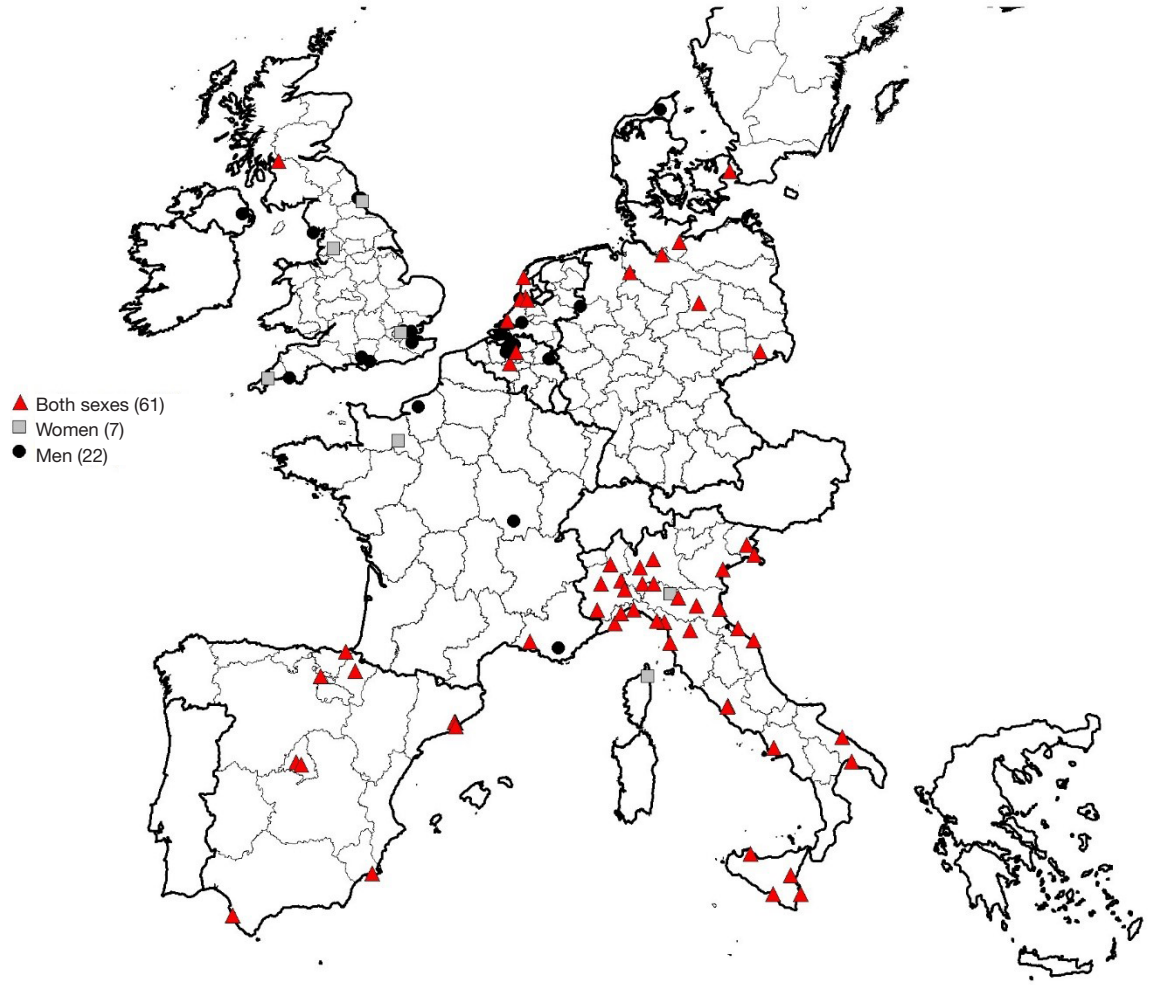

Figure 1 Spatial distribution of identified hotspots of malignant mesothelioma in Western Europe, based on studies published between 2000 and 2015. Cartography by H. Vandenhoeck (Dpt Informatics and Communication Technology, KU Leuven). Note: absence of hotspots does not necessarily mean that there were no other clusters of mesothelioma.

publications.

We used MEDLINE (PubMed) and Embase to find relevant studies on spatial clustering of MPM in the 21st century in Western Europe (1 January 2000 to 31 December 2015). We focused on publications of MPM, excluding studies dealing only with peritoneal and/or pericardial mesothelioma. Our search included studies for France, Belgium, The Netherlands, Germany, the United Kingdom, Ireland, Luxembourg, Italy, Spain, Portugal, Switzerland, Austria, Denmark, Finland, Sweden, Norway and Poland. The keywords used for our search were (spatial OR clusters OR geographic OR geographic distribution OR mapping OR municipality OR municipal) AND mesothelioma AND the country that was considered.

We created a map describing hotspots of MPM in Europe, as provided in the selected publications. Standardized mortality ratios and relative risks were transformed to incidence rates per 100,000 people by multiplying these values by the age-standardized incidence rates per country (*Table S1*) (3).

Sixteen different studies published between 2000 and 2015 were selected for an in depth analysis (4-19). We also found one study on spatial MPM clustering for Europe in general (20). All data of these publications were used to visualize MPM hotspots in Western Europe (*Figure 1*). The symbols of the MPM hotspots in this figure are located at the midpoints of the municipalities or regions, as described in the publications. The specific sources of asbestos

exposure for these MPM hotspots were described in most of the publications. In publications where no specific asbestos sources of exposures were described, we did not conduct further searches.

Montanaro *et al.* used the EUROCIM database to summarize geographical variations for MPM incidence within Europe (20). They observed a high geographical variation in the truncated age-standardized rates (ASR) per 100,000 for mesothelioma between different European countries, with the highest ASR for men occurring in Scotland (8.8/100,000), England (8/100,000) and The Netherlands (7.4/100,000). For other European countries, ASRs of 0.6 to 4.24/100,000 were observed. The ranking was similar for women but with lower ASR values compared to men. The authors also studied regional cancer registries, with highest the ASRs for men being observed in the regions of Trieste (17.2/100,000), Genoa (14.4/100,000) and Rotterdam (13.1/100,000).

We found relevant studies on country-specific spatial distribution of MPM for Italy (n=6), the United Kingdom (n=3), Spain (n=2), Belgium (n=1), the Netherlands (n=1), Germany (n=1), France (n=1), and Denmark (n=1). The hotspots identified in these different publications were visualized in *Figure 1*.

There is consistency in these epidemiological studies on spatial hotspots of MPM. Most clusters occurred close to shipyards (16 studies) and known asbestos-cement industries (10 studies). It is reasonable to conclude that MPM clusters near the seaside were due to harbours with shipyards (or with petrochemical plants or refineries). It is likely that a high incidence of MPM found among, e.g., dockyard workers or in seafarers of a specific country is also accompanied by a geographical concentration of mesothelioma patients in conurbations close to these harbour regions. However, other MPM clusters were also explained, depending on the study, by the vicinity of railway construction companies (3 studies), asbestos textile manufacturing companies (3 studies), iron and steel industries (4 studies), petrochemical industry (6 studies), asbestos-using industries (4 studies), industrialized areas (2 studies), hazardous dumping sites (1 study), a military defence station (1 study), an electrical power plant (1 study) and furniture industries (1 study). One hotspot attributed to natural asbestos exposure was observed in Biancavilla (Italy) (4 studies) as a result of the presence of a stone quarry contaminated by fluoro-edenite fibres (16).

We did not attempt to pool or meta-analyse data from different sources, mainly because the denominators (expected numbers of deaths) were calculated per country and not for the entire area covered by the studies, and also because the statistical methods (and power) to identify clusters differed between studies. This means that the existence and "magnitude" of clusters depend both on the number of cases of mesothelioma in the area of interest and on the background incidence of malignant mesothelioma in a country (or comparison area). In other words, a high incidence area in one country might not appear as a cluster in another country. Consequently, the present map only shows areas identified as "high incidence" areas within their country and not all clusters should be considered as having the same degree of intensity in quantitative terms.

Also, if no hotspots are shown, this does not necessarily mean that there were no clusters of mesothelioma, but simply that the existence of such clusters was not investigated (or published in accessible journals). The possibility of underestimation of mesothelioma cases must be kept in mind, because not all patients with MPM have been registered in mesothelioma databases. For example, in France, MPM incidence data were only recorded for 26 out of 96 districts by the French National Mesothelioma Surveillance (9). This will lead to an underestimation of mesothelioma incidence in this particular population. Moreover, mesotheliomas are also found outside high incidence areas, because asbestos use has been widespread in industry and buildings throughout Europe, and because previously exposed residents or workers may have moved from hotspots to other areas.

Although there were some limitations for studying the spatial distribution of MPM in Western Europe, there was also much consistency between all these studies. Most MPM clusters occurred near asbestos cement industries and shipyards. We believe that this spatial distribution will continue to be observed in the future. Therefore, even in European countries with persistent environmental asbestos exposure risks (mainly because of not yet completely cleared community asbestos exposures), continuous vigilance for the epidemiological spread of MPM hotspots is required in the next decades.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Detailed description of 14 European studies, published between 2000 and 2015, that investigated the geographical distribution of malignant mesothelioma

Country	Study	Year of publication	Study year(s)	Study population with age-standardized incidence rates*	Spatial mesothelioma hotspots	Mortality or incidence ratio OR relative risk	Mortality or Incidence-rate (per 100,000)	Other values (counted cases)
Belgium	Van den Bume et al. (6)	2014	1999–2009	Men: 2.0 per 100,000; women: 0.4 per 100,000 [2011]	For men	SMR		
					- Sint-Niklaas	3.4	6.80	
					- Mechelen	2.5	5.00	
					- Dendermonde	1.8	3.60	
					- Halle-Vilvoorde	1.4	2.80	
					- Antwerp	1.34	2.68	
					For women			
					- Mechelen	2.8	1.12	
					- Halle-Vilvoorde	2.5	1.00	
The Netherlands	Burdorf et al. (5)	2005	1999–2002	Men: 2.85 per 100,000; women: 0.33 per 100,000 [2006–2011]	For men	SIR		
					- Groot-Rijnmond	2.04	5.81	
					- Zaanstreek	1.92	5.47	
					- Other Zeeland	1.85	5.27	
					- Limond	1.69	4.82	
					- Zuidoost Zuid- Holland	1.48	4.22	
					- Haarlem	1.44	4.11	
					- Zuid-Limburg	1.36	3.88	
					- Groot-Amsterdam	1.36	3.88	
					- Twente	1.23	3.51	
					- Kop van Noord- Holland	1.23	3.51	
					For women			
					- Zaanstreek	2.62	0.92	
					- Twente	2.17	0.76	
					- Haarlem	2.03	0.71	
					- Kop van Noord- Holland	2.00	0.70	
					- Groot-Amsterdam	1.63	0.57	
					- Groot-Rijnmond	1.35	0.47	
United Kingdom	McElvenny et al. (6)	2005	1981–2000	Great Britain, Men: 3.5 per 100,000, women: 0.6 per 100,00 [2000–2011]	For men	SMR		
					- West Dunbartonshire	6.37	22.3	
					- Barrow in Furness	5.93	20.7	
					- Plymouth	3.96	13.8	
					- Portsmouth	3.88	13.6	
					- South Tyneside	3.57	12.5	
					- North Tyneside	3.40	11.9	
					- Southampton	3.25	11.4	
					For women			
					- Barking and Dagenham	6.49	3.9	
					- Sunderland	5.75	3.4	
					- Blackburn and Darwen	4.84	2.9	
					- West Dunbartonshire	4.51	2.7	
	HSE (7)	2005	1981–2005	Great Britain, Men: 3.5 per 100,000, women: 0.6 per 100,000 [2000–2011]	For men	SMR		
					- West Dunbartonshire	5.37	18.8	
					- Barrow-in-Furness	5.40	18.9	
					- Plymouth	3.41	11.9	
					- North Tyneside	3.36	11.8	
					- Portsmouth	3.35	11.7	
					- South Tyneside	3.17	11.1	
	Mak et al. (8)	2008	1981–2002	South-East England	For men and women	M: 6.5–7; F: 1.5–2		
					- South Essex			
					- Kent and Medway			
					- North East London			
Germany	Schonfeld et al. (9)	2014	2000–2010	Germany	West Germany	M >5, F >1.5		
					- Bremen			
					- Hamburg			
					- The Northern port cities			
					East Germany	M >2, F >0.75		
					- Sachsen			
					- Sachsen-Anhalt			
France	Goldberg et al. (10)	2010	1974–2005	France	For men	3.55–5.08		
					- Seine-Maritime			
					- Sabine-et-Loire			
					- Var			
					- Bouches-du-Rhône			
					For women	1.32–1.62		
					- Orne			
					- Bouches-du-Rhône			
					- Haute-Corse			
Spain	López Abente et al. (11)	2005	1999–1998	Spain, Men: 0.6 per 100,000, women: 0.2 per 100,000 [1975–2010]	For pleural cancer	SMR		
					- Municipality	5.10	3.06	
					- Ripollet	6.83	4.10	
					- Cerdanyola Del Valles	10.05	6.03	
					- Minveria De Etxo	3.72	2.23	
					- Cedíz	3.63	2.18	
					- Pozuelo De Alarcon	3.30	1.98	
					- Cartagena	3.19	1.91	
					- Pamplona	3.18	1.91	
	García-Gómez et al. (12)	2015	2007–2011	Spain	Asbestos-related cancers			
					- Catalonia			37 cases
					- Madrid			33 cases
					- Basque Country			27 cases
Italy	Mastrantonio et al. (13)	2002	1988–1997	Italy	Highest regions			
					- Liguria		4.77	
					- Piedmont		2.68	
					- Friuli Venezia Giulia		2.44	
					- Lombardy		2.07	
					Highest provinces			
					- Alessandria		6.59	
					- Gorizia		6.21	
					- Taranto		3.37	
					- Livorno		3.31	
	Marinaccio et al. (14)	2012	1993–2004	Italy	Highest regions			
					Men:			
					- Piedmont		5.56	
					- Valle d'Aosta		4.71	
					- Lombardy		3.84	
					- Friuly-Venezia Giulia		6.28	
					- Liguria		14.13	
					- Emilia-Romagna		4.35	
					Women:			
					- Piedmont		3.18	
					- Valle d'Aosta		1.41	
					- Lombardy		1.87	
					- Liguria		2.23	
					- Emilia Romagna		1.16	
					Clusters			
					North-West			
					- Casale Monferrato	4.0–124.4 per 100,000, not specified per cluster		
					- Broni			
					- La Spezia			
					- Savona			
					- Genova			
					- Grugliasco, Turin			
					- Nole, Turin			
					- Cuneo			
					North-East			
					- Trieste			
					- Monfalcone			
					- Venice			
					Central Italy			
					- Livorno			
					South-Italy			
					- Castellammare di Stabia, Napoli			
					- Taranto			
					Sicily			
					- Augusta, Syracuse			
					- Biancavilla			
	Fazzo et al. (15)	2012	1995–2002	Italy, Men: 3.55 per 100,000, women: 1.35 per 100,000 [2008]	Highest regions			
					- Piedmont		3.3	
					- Lombardy		2.5	
					- Liguria		6.0	
					- Friuli Venezia Giulia		3.5	
					Clusters in men			
					North-West Italy	RR		
					- Casale Monferrato	11.6	41.18	
					- Sarri'Chiavar, Genova	3.2	11.36	
					- La Spezia	4.1	4.56	
					- Broni	7.1	25.21	
					- Deiva Marina, La Spezia	3.3	11.72	
					- Collegno, Turin	2.4	8.52	
					North-East Italy			
					- San Pier d'Isonzo, Gorizia	7.4	26.27	
					- Muggia, Trieste	4.3	15.27	
					Central Italy			
					- Livorno	4.6	16.33	
					- Fosdinovo, Massa- Carrara	4.8	17.04	
					- Falconara Marittima, Ancona	2.5	8.87	
					- Calleo, Piacenza	4.6	16.33	
					- Granarolo dell' Emilia, Bologna	1.8	6.39	
					- Fivizzano, Massa- Carrara	6.9	24.14	
					South Italy			
					- Taranto	6.9	24.50	
					- Pimonte	3.2	1.36	
					- Bari	2.5	8.88	
					- Napoli	1.6	5.68	
					Sicily			
					- Vittabate, Palermo	2.3	8.17	
					- Priolo Gargallo, Syracuse	3.8	13.49	
					Clusters in women			
					North-West Italy			
					- Casale, Monferrato	21.9	29.57	
					- Broni	9.3	12.56	
					- Frugarello, Alessandria	2.6	3.51	
					- Sarnico, Bergamo	11.9	16.07	
					- Genova	1.6	2.16	
					North-East Italy			
					- Monfalco	6.2	8.37	
					South Italy			
					- Ercolano, Napoli	2.3	3.11	
	Fazzo et al. (16)	2012	2003–2009	Italy, Men: 3.55 per 100,000, women: 1.35 per 100,000 [2008]	Highest regions			
					- Friuli Venezia Giulia		3.0	
					- Liguria		5.4	
					- Lombardy		2.4	
					- Piedmont		3.0	
					Clusters in men			
					North-East Italy	RR		
					- Trieste	4.8	17.04	
					- Monfalcone	6.9	24.495	
					North-West Italy			
					- Casale Monferrato	13.4	47.57	
					- Broni	3.3	11.71	
					- Liguria	4.8	17.04	
					- Genova	4.7	16.68	
					Central Italy			
					- Livorno	5.1	20.24	
					- Ravenna	3.3	11.71	
					- Bologna	2.1	7.46	
					- Carrara, Massa-Carrara	3.9	13.85	
					- Colleselvetti, Livorno	8.4	29.82	
					South Italy			
					- Bari	8.2	29.11	
					- Taranto	2.7	9.59	
					Sicily			
					- Priolo Gargallo, Syracuse	6.9	24.49	
					- Syracuse	3.8	13.49	
					Clusters in Women			
					North-West Italy			
					- Casale Monferrato	28.7	38.73	
					- Broni	17.1	23.09	
					- Collegno, Turin	4.4	5.94	
					Central Italy			
					- Alseno, Piacenza	9.6	12.96	
					- Collecchio, Parma	11.3	15.26	
					South Italy			
					- Bari	4.0	5.40	
					- Taranto	4.3	5.81	
					Sicily			
					- Biancavilla	25.9	34.97	
	Gallo et al. (17)	2013	1974–2006	Italy	Pleural cancer			
					North-West Italy			
					- Liguria		F: 14	
					- Casale Monferrato		M: 7.04, F: 3.43	
					- Broni		M: 2.82, F: 1.59	
					- La Spezia		M: 8.59, F: 1.12	
					- Genova		M: 6.19, F: 1.67	
					- Savona		M: 4.09, F: 0.95	
					North-East Italy			
					- Gorizia		M: 8.12, F: 0.95	
					- Trieste		M: 7.05, F: 0.9	
					- Venice		M: 2.67, F: 0.82	
					Central Italy			
					- Livorno		M: 3.86, F: 095	
					- Ancona		M: 2.03, F: 0.4	
					South Italy			
					- Taranto	All RR >1, not specified per cluster	M: 3.44, F: 0.7	
					- Pimonte		F: 1.32	
					Sicily			
					- Syracuse		M: 1.98, F: 0.64	
					Mesothelioma			
					North-West Italy			
					- Turin		M: 2.44, F: 1.15	
					- Milano		M: 2.12, F: 0.93	
	Corfiati et al. (18)	2015	1993–2008	Italy, Men: 3.55 per 100,000, women: 1.35 per 100,000 [2008]	Clusters			
					North-West Italy			
					- Casale Monferrato		All incidence rates > 3.55	
					- Cavagnolo, Turin			
					- Cirié, Turin			
					- Collegno, Turin			
					- Dalmine, Bergamo			
					- Genova			
					- Legnano, Milano			
					- Sarnico, Bergamo			
					- Savona			
					- Broni			
					- La Spezia			
					North-East Italy			
					- Ravenna			
					- Reggio dell'Emilia			
					- Trieste			
					- Venice			
					Centre of Italy			
					- Fiorenzuola d'Arda, Piancenza			
					- Padua, Bologna			
					- Carrara, Massa-Carrara			
					- Ancona			
					- Civitavecchia, Rome			
					- Livorno			
					- Pesaro			
					- Piombino, Livorno			
					- Prato			
					South Italy			
					- Bari			
					- Castellammare di Stabia, Napoli			
					- Napoli			
					- Taranto			
					Sicily			
					- Biancavilla			
					- Gela			
					- Palermo			
					- Syracuse			
Denmark	Skammarriz et al. (19)	2013	1943–2009	Denmark	For men			
					- Northern Jutland		1.38	
					- Copenhagen		1.33	
					For women			
					- Copenhagen		1.24	