Title

Assessing the completeness and correctness of the registration of malignant mesothelioma in Belgium

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Abstract

Objectives : Malignant mesothelioma (MM) is a rare and aggressive cancer mostly caused by asbestos exposure, and for which the diagnosis is difficult.

This study aimed to assess the completeness and correctness of MM registration using 3 independent national databases: the Belgian Cancer Registry (BCR), the population-based mortality statistics (certificates of death, COD), and the Belgian Mesothelioma Registry (BMR).

Methods : The study cohort included all MM reported to the BCR and diagnosed between 2004 and 2012 (n=2,292), all patients reviewed by the pathology commission of the BMR (2004–2012; n=2,019), and COD data for all Belgian citizens (2004–2013).

Available data were compared in terms of registered cases, histological diagnosis, performed immunohistochemical (IHC) tests, and IHC test results.

Results : Comparison of BCR with BMR registrations showed 94.8% concordant cases. The proportion of MM diagnoses originally reported to BCR with unspecified MM morphology was reduced from 25.8% to less than 1%. Results from IHC tests were available for 95.3% of concordant MM cases. Different IHC patterns could be distinguished by MM histology.

MM cases registered at BCR for which COD mentioned an MM as underlying cause of death represented 76.4% of deceased cases.

MM long-term survivors (survival > 3 years; 10.9%) were characterised by distinct clinical and biological characteristics.

Conclusions : A comparison of independent Belgian MM registration databases elucidated under-registration and misclassification and revealed possible reasons for observed discordances. Combining all the available information resulted in enhanced completeness and correctness of MM registration in Belgium and allowed for the identification and characterisation of MM long-term survivors.

Original article

Introduction

Malignant mesothelioma (MM) is a rare and aggressive cancer with a latency period up to several decades [1-2]. MM most commonly originates from the pleura and exposure to asbestos is a well-documented etiological factor. In Europe, the MM incidence rates are expected to peak around 2020 in some countries, and a deceleration or decrease may have already have begun in others [3-4] as a consequence of legislative restrictions implemented in the 1980's on [5-6].

MM mainly manifests through 3 histological subtypes: the epithelioid, sarcomatoid, and biphasic (mixed). The diagnosis of MM remains difficult: the high degree of morphologic heterogeneity can mimic numerous secondary tumours, sometimes resulting in uncertain diagnoses. Depending on clinical circumstances, it is often difficult to obtain adequate and/or sufficient biopsy material for histological analysis to make a firm diagnosis. The insidious onset and appearance of non-specific symptoms, typically only late in the development of the disease, makes MM diagnosis even more challenging [7-9].

The Belgian Cancer Registry (BCR) is a population-based registry reporting all cancer incidences from 2004 onwards. Cancer registration has a firm legal basis in Belgium, as defined in its laws [10-11]. The data flow relies on all information (notifications) provided by oncological care programmes (clinical network) and laboratories for pathological anatomy (pathological network, including the pathology reports), providing substantial information on patient and tumour characteristics. The patient's unique national social security identification number (NSSN) enables linkage with other medical and/or administrative data sources and allows the patient's vital status follow-up [12]. Notably, only MM diagnoses based on a pathological confirmation are registered as such at the BCR, whereas cases not pathologically confirmed are registered as malignant neoplasms of the pleura. Mortality statistics, collected by the Belgian regions, provide information on the number of persons who died due to a specific disease within a given time. In many countries, certificates of death (COD) represent an important element in monitoring disease epidemiology [13]. The BCR receives these data annually from the Belgian regions.

In 2006, the 'Asbestos Fund' (Asbestfonds/Fonds Amiante, AFA; [14]) was established to certify diseases caused by asbestos exposure in Belgium and provide financial compensation to the patients or their relatives. The diagnosis of MM is confirmed by a certifying committee, namely, the Belgian Mesothelioma Panel, composed of expert pathologists. These experts also provide second opinions to other pathologists. The data of all revised

diagnoses are collected in the Belgian Mesothelioma Registry (BMR). The BMR database contains variables that describe patient and applicant data, the date of the meeting of the Mesothelioma Commission, and tumour information (diagnosis, certainty of diagnosis, sample type, immunohistochemical markers [HIC] with test result).

To monitor cancer epidemiology, cancer registration must be complete and correct [15-16]. The aim of this study was to assess and enforce the completeness and correctness of MM registration at the Belgian population level by comparing information from 3 independent databases: the BCR, the COD, and the BMR.

Given a median overall survival of 10.7 months for this disease [17], a secondary goal was to provide additional insights into patient and tumour characteristics of MM long-term survivors, under suspicion for wrong diagnoses or distinct clinical and biological features.

Material and methods

1. *Patient selection*

Data extracted from the BCR database included all cases of MM (n=2,292), coded as C45 under the 10th Revision of the International Classification of Diseases (ICD10; [18]), and malignant neoplasms of the pleura (MNP; ICD10: C38.4, n=52) reported to the BCR, confirmed by pathological examination and diagnosed between 2004 and 2012. This selection was restricted to patients with an official residence in Belgium at the time of diagnosis.

Using their NSSN as a unique patient identifier, this patient selection was compared with the patients registered by the BMR for the same years of diagnosis (n=2,207). Upon removal of double registrations, a final combined study cohort of 2,887 patients was obtained.

Trends in age-standardised incidence (WSR) were quantified by the average annual percentage change (AAPC). A 95% confidence interval (CI) and the p value were calculated from the final regression model.

2. *Comparison of MM diagnoses between BCR and BMR*

For those cases registered by both the BCR and BMR, the registered tumour-related information was compared. More specifically, the diagnosis, histology, and immunohistochemical tests (IHC; including the test result available for 1,989 cases; 84.9%) were analysed.

Inter-rater level agreement between the diagnosis registered at the BCR and reported by the BMR was calculated using the Cohen's kappa (K) statistic (including 95% CI), which account for the possibility of an agreement occurring by chance. Ranging from −1 to +1, 0 represents the amount of agreement expected from random chance, whereas 1 represents perfect agreement between the raters [19-20].

IHC tests and their results were only compared for cases with a concordant diagnosis between the BMR and BCR. To do so, the results were classified into 3 categories: positive, negative, and uncertain/discordant staining result.

3. *Certificates of death*

COD data (2004–2013) was linked to the BCR database through a probabilistic-matching algorithm, based on the niscode (numeric code for Belgian municipalities) of the residence at the time of death, date of birth, date of death, and sex [21]. The analysis included either the underlying cause or all causes of death. If the patient was not registered with an MM diagnosis at the BCR but a C45 was mentioned as cause of death, their death certificate diagnosis was compared with the most recently diagnosed malignancy as known by the BCR.

4. *Identification of long-term survivors*

Long-term survivors were identified as patients who survived at least 3 years after their first diagnosis [22-23]. Differences in the distribution of long-term and nonlong-term survivors with regards to clinical characteristics were assessed by the χ^2-test.

Results

1. *MM incidence in Belgium 2004–2012 as registered at the BCR*

Before the start of this project, the BCR had counted a total of 2,344 cases of MM (n=2,292) and MNP (n=52) between 2004 and 2012, with a four-fold predominance in males (82.1%) and median age of 71 years at time of diagnosis (interquartile range: 63–77 years). Malignant pleural mesothelioma (MPM) represented 92.4% of all MM cases, followed by the peritoneal subtype (6.9%). Over this period, no significant time trend was observed in MM incidence (AAPC=-0.8, CI=[-2.4; 0.8]).

The percentage of MM cases with pathology reports available at the BCR constantly increased from 52.5% in 2004 to 93.4% in 2012 (β=3.4, p=0.03).

2. *Diagnosis and histology comparison between BCR and BMR*

Notably, 1,652 (72.1%) of all MM cases present in the BCR were observed in the BMR database, for which a concordant diagnosis was made in 94.8%. This concordance varied from 92.2% to 97.2% over the time period without a significant trend. Cohen's kappa coefficient was 0.91 (CI=0.73;1.00). For the remaining 86 patients, the BMR expert panel concluded either on a benign disease (n=39) or a secondary tumour (n=42) mimicking MM, or absence of a firm diagnosis (n=5). The remaining 640 (27.9%) MM cases registered at the BCR could not be identified in the BMR database (Table 1); notably, 110 of these diagnoses were made in 2012.

Of the 1,724 MM cases present in the BMR, 1,566 (90.8%) were identified in the BCR database with a concordant MM diagnosis. Eighty-nine cases reported as MM by the BMR were observed in the BCR database but were excluded from the data selection: 40 patients were registered with a diagnosis before 2004 (MM: n=33; other malignancy: n=7), and 13 patients were diagnosed with MM but without residence in Belgium. Regarding the remaining 36 patients diagnosed between 2004 and 2012, 10 were registered at the BCR with a malignant neoplasm of bronchus or lung (ICD10: C34) and 14 with a malignant neoplasm without specification of site (ICD10: C80); within these, no diagnosis of malignant neoplasm of pleura (C38.4) was made.

For those cases with a concordant MM diagnosis (n=1,566), BMR information allowed for a reduction in the proportion of unspecified MM morphologies from 25.8% (n=404) to less than 1% (n=8; Figure 1). For 121 (7.7%) of these cases, the specified morphology differed between BCR and BMR. In cases of discordancy, the diagnosis made by the BMR was prioritised: consequently, the epithelioid, biphasic, and sarcomatoid subtypes represented 75.1%, 13.4%, and 11.5% of concordant MM with known morphology, respectively.

3. Immunohistochemistry

Information regarding IHC was available for 73.4% of BCR cases and 73.0% of BMR cases, respectively.

Results from IHC tests, present in either the BMR and/or BCR, were available for 95.3% (n=1,492) of concordant MM cases: the most frequently performed IHC stainings were anti-calretinin (97.5%), polyclonal anti-carcinoembryonic antigen (CEA-pol; 84.8%), anti-cytokeratins 5/6 (CK5/6; 91.1%), anti-epithelial membrane antigen (EMA; 89.5%), anti-thyroid transcription factor-1 (TTF-1; 78.3%), and anti-Wilms tumour antigen (WT1; 50.5%). At least 2 distinct positive (anti-calretinin, CK5/6, EMA or WT1) and 2 negative markers (CEA-pol and TTF-1) were used for the diagnosis in 1,069 cases (71.7%). Different IHC test patterns were observed in the tissue samples, and this was in line with the MM histological subtypes (Figure 2). Malignant epithelioid mesothelioma was characterised with positive staining for anti-calretinin, CK5/6, cytoplasmic EMA and WT1 in 92.7%, 92.6%, 83.9%, and 90.7%, respectively. Negative staining for TTF-1 and CEA-pol was reported in 99.1% and 96.2% of cases, respectively, regardless of the morphological subtype.

4. Certificates of death

The coupling from the COD data to the BCR database resulted in a linkage of 2,045 out of 2,084 MM patients deceased between 2004 and 2013 (98.1%).

The percentage of MM cases registered at the BCR for which the COD data mentioned a C45 as the underlying cause of death varied from 80.5% to 65.2% (overall: 76.4%), depending on whether these cases were known at

the BMR as MM (Table 2). Further, this percentage differed for patients who died at home (78.2%) compared with those who died in a hospital (80.3%) or nursing home (64.7%), respectively.

For 428 MM cases (20.9%) registered at the BCR and linked with the COD data, C45 was not mentioned as a cause of death. C34, C38.4, and C80 were registered as underlying causes of death for 8.8%, 2.7%, and 1.3% of BCR-MM patients, respectively.

By contrast, some patients, for which the COD data mentioned C45 (n=1,726) or C38.4 (n=220) as the cause of death, were registered at the BCR with a different diagnosis. This was the case for 158 MM (9.2%) and 214 MNP (97.3%), according to the COD data. In both series, most of these cases appeared to be registered at the BCR as C34 (40.5% of MM and 39.7% of MNP, respectively) or C80 (20.3% of MM and 23.4% of MNP, respectively). Six cases (3.8%) reported as C45 deaths were known to BCR with a MNP diagnosis, and 56 cases (26.2%) reported as C38.4 deaths were known to BCR with an MM diagnosis.

5. *Long-term survivors with MM*

Long-term survivors represented 10.9% (n=170) of concordant (BCR-BMR) MM cases. This subpopulation was characterised by a higher percentage of peritoneal MM (8.8% vs. 4.5%, p=0.010), a less pronounced male–female ratio (2.9 vs. 6.2, p<0.001), a higher predominance of the epithelioid subtype (95.9% vs. 72.1%, p<0.001), and a younger age profile (median age at diagnosis: 66 years vs. 71 years, p<0.001; Table 3).

Discussion

Despite flattening incidence trends in some countries, MM remains a persisting health concern in Western society [4].

This study highlights the added value of comparing population-based registries to assess the completeness and correctness of MM registration in Belgium. Such a comparative exercise reveals inconsistencies in diagnoses and identifies cases that could be subject to in-depth review and validation. Further, it increases the availability of information regarding patient characteristics, topography, morphology, incidence date, and performed IHC tests. Taken together, the linkage of data from various sources result in information that is more complete, precise, and reliable.

Not all cases were consistently retrieved across the 3 national databases. The reasons for under- (and over-) registration and discordances in diagnoses as well as morphological subtypes are multiple.

1. *Regarding BMR:*

a) Restrictions for financial compensation apply, and this might explain why some cases were not reported to the AFA in the past and why others might not be reported or recognised in the future. Thus, the objective of the BMR is more administrative than epidemiological;

b) In addition to these restrictions, a fraction of occupation-related mesotheliomas deserving indemnity were not submitted. Some patients might not have been aware of the possible indemnity and the procedures to follow, or the patient's state of health and social environment did not allow them to introduce the demand. This is in line with studies that have observed the following: occupational compensation statistics and mesothelioma registries appear to underestimate the actual numbers of cases [25-26];

c) An MM diagnosis is confirmed by IHC tests that require adequate and sufficient tissue sampling. Small amounts of tissue samples available for diagnosis in combination with tumour heterogeneity might explain some of these discordances. Given the performance status of the patient, invasive diagnostic procedures might not be appropriate, and no firm diagnosis could be made;

d) Before 2006, the Fund of Occupational Diseases (FBZ/FMP; instead of the AFA) collected information on patients with an MM diagnosis, confirmed by the Belgian Mesothelioma Panel. Currently, the FBZ/FMP and AFA are housed together in the Federal Agency of Occupational Risks (FEDRIS);

e) For others, the referring laboratory received (e.g. years later) new tissue samples leading to a distinct diagnosis from the initial one, without providing this material and information to the Mesothelioma Panel.

2. *Regarding COD:*

a) No clear final diagnosis might have been made for patients in a critical clinical condition such as patients who are older and residing in a nursing home. Often, no autopsy is performed in such circumstances;

b) Depending on the circumstances, the death certifying physician might not have been aware of the patient's full medical history. The lack of specificity (3%) found for C38.4 coded deaths is a probative example.

3. *Regarding the BCR:*

a) For some cases not registered by the BMR, an underuse of specific IHC markers by certain pathology laboratories was observed. In that situation, the diagnosis might be questioned and a revision by the BMR expert panel could be envisioned;

b) Sometimes, the definitive diagnosis (e.g. after a case revision by the expert panel of the BMR) is not sent to the BCR (which received only the first APD report). Active retrieval of final diagnoses by source contacting could solve this issue.

A delay of approximatively 2 months was observed between the date of diagnosis, as reported to the BCR by the laboratories for pathology, and the case review/confirmation by the pathologist expert panel. In line with these observations, information registered in the BMR during 2013 for cases already diagnosed and reported to BCR in 2012 were considered in this study. Nevertheless, no information was observed in the BMR database for the 110 MM cases reported to the BCR in 2012.

This study assessed the validity of death certificates as a proxy for mesothelioma incidence, suggesting that mortality data tend to underestimate MM incidence in Belgium by 21%. Similar results were observed in other countries, reporting underestimations of between 13% and 25% [27-29]. Most of the mesothelioma cases that remain unreported in mortality statistics had other causes of death assigned, such as lung cancer or cancer of unknown or unspecified origin. This result has also been observed in a study on Scotland, revealing malignant neoplasm of bronchus or lung (C34), malignant neoplasm of pleura (C38.4), and malignant neoplasm of unspecified site (C80.9) as the cause of death in 4%, 1%, and 1% of MM patients, respectively. Similar observations were made for Belgium in this study: malignant neoplasms of bronchus and lung (C34), malignant neoplasms of pleura (C38.4), and malignant neoplasms of unknown or unspecified site (C80) represented 9%, 3%, and 1% of cases, respectively.

By contrast, the mesothelioma deaths reported in the mortality statistics could be confirmed in 91% of the cases. A similar result was observed by Pinheiro et al., revealing an overall correlation coefficient between mortality and incidence of 0.96 [30].

Overall, the COD data tend to underestimate MM incidence, but mortality statistics can reveal mesothelioma cases that remained unregistered at the BCR. This situation potentially occurs in cases where a patient is in critical clinical condition at time of presentation at the hospital. In that case, the diagnosis of mesothelioma can be considered highly likely based on clinical examination and imaging; however, such a patient may never be discussed at a multidisciplinary oncological consult, and the pathology confirmation of the diagnosis may be

considered less important. As a result, none of the regular data flows to the BCR will recognise the case as a registration. This type of registration bias may lead to an overestimation in survival, which is most suspicious in lethal cancer types such as MM. To attempt to document and eventually recover such 'death certificate only' cases, the BCR recently set up a trace-back exercise, and these results must be awaited.

Besides comparing the different available data sources on mesothelioma cases in Belgium, this study aimed to identify and characterise long-term survivors of the disease. Based on the subgroup of patients with confirmed and concordant MM diagnosis, long-term survivors, defined as patients who survived at least 3 years after being diagnosed with MM, represented 11% of cases. Similar observations were made by the Surveillance of Rare Cancers in Europe (RARECARE) project [31-32]. This subpopulation was characterised by a higher percentage of peritoneal MM, a less pronounced male–female ratio, a younger age profile, and a higher predominance of the epithelioid subtype, as already has been observed [33-34]. Possibly, these cancers are more related with other etiological factors such as genetic predisposition (BAP1 mutation), therapeutic irradiation for other malignancies, chronic inflammation or environmental exposures to other carcinogens (e.g. non-asbestos mineral fibres), or even idiopathic occurrence [35-36]. As this study has now correctly identified long-term MM cases at the Belgian population level, this information serves as an excellent starting point for further analyses, including genomic and expression profiling of the tumour sample and documentation of asbestos exposure or other risk factors to acquire additional in-depth knowledge of MM pathogenesis.

Our observations underline that MM remains a difficult diagnosis. The discordant diagnoses and differences in the use and interpretation of immunohistochemistry tests emphasise the importance of an expert panel of (pulmonary) pathologists in this matter as it exists today in Belgium [8,37]. This need will become even more critical in the current era, as the clinical skills for detecting early cases evolve and the diagnostic challenges for pathologists change in parallel [9,38-40].

As for this study, the cases that remained inconclusive after the confrontation of the data sources will be explored in more detail, and if necessary, a pathology revision will be performed and/or the treating hospital will be contacted. The percentage of diagnoses that changed from an initial MM diagnosis to another diagnosis and vice versa might also be a valuable point to focus on.

In conclusion, the results of this study encourage the consultation of independent national data sources to elucidate possible reasons for under- (and over-) registration and discordances. Given their

different objectives, full integration of existing registries in one central system seems less feasible. However, good handling of related technical and privacy aspects facilitates the coupling and comparison of data sources needed to improve the completeness and correctness of MM registration.. Nevertheless, even more important from a public health point of view is the continuous insistence on primary prevention by removing asbestos from the environment wherever possible, and counselling for the ex-exposed persons.

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References

[1] Lanphear BP and Buncher CR. Latent period for malignant mesothelioma of occupational origin. J Occup Med 1992 Jul; 34(7):718-21.

[2] Bianchi C, Giarelli L, Grandi G, Brollo A, Ramani L and Zuch C. Latency periods in asbestos-related mesothelioma of the pleura. Eur J Cancer Prev 1997 Apr;6(2):162-6.

[3] Pelucchi C, Malvezzi M, La Vecchia C, Levi F, Decarli A and Negri E. The mesothelioma epidemic in Western Europe: an update. Br J Cancer 2004 Mar 8; 90(5):1022-4.

[4] Montanaro F, Bray F, Gennaro V, Merler E, Tyczynski JE, Parkin DM, Strnad M, Jechov'a M et al. Pleural mesothelioma incidence in Europe: evidence of some deceleration in the increasing. Cancer Causes Control 2003 Oct;14(8):791-803. Erratum in Cancer Causes Control 2004 Feb; 15(1):103.

[5] Van den Borre L and Deboosere P. Asbestos in Belgium: an underestimated health risk. The evolution of mesothelioma mortality rates (1969-2009). Int J Occup Environ Health 2014 Apr; 20(2):134-40.

[6] Hodgson JT, McElvenny DM, Darnton AJ, Price MJ and Peto J. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. Br J Cancer 2005; 92:587-593.

[7] Van Meerbeeck JP, Scherpereel A, Surmont VF, Baas P. Malignant pleural mesothelioma: the standard of care and challenges for future management. Crit Rev Oncol Hematol 2001 May; 78(2):92-111.

[8] Scherpereel A, Astoul P, Bass A, Berghmans T et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J 2010; 35:479-495.

[9] Van Zandwijk N, Clarke C, Henderson D, Musk AW, Fong K et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis 2013: 5(6):E254-307.

[10] Wet houdende diverse bepalingen betreffende gezondheid van 13 december 2006, artikel 39. Belgisch Staatsblad. 22 december 2006. / Loi portant dispositions diverses en matière de santé du 13 décembre 2006, article 39. Moniteur Belge, 22 décembre 2006.

[11] Koninklijk Besluit houdende vaststelling van de normen waaraan het zorgprogramma voor oncologische basiszorg en het zorgprogramma voor oncologie moeten voldoen om te worden erkend. Belgisch Staatsblad 21 maart 2003. / Arrêté Royal fixant les normes auxquelles le programme de soins de base en oncologie et le programme de soin d'oncologie doivent répondre pour être agréés. Moniteur Belge, 21 mars 2003.

[12] Cancer Burden in Belgium 2004-2013, Belgian Cancer Registry, Brussels 2015.

[13] Odgerel C-O, Takahashi K, Sorahan T, Driscoll T, Fitzmaurice C, Yoko-o M et al. Estimation of the global burden of mesothelioma deaths from incomplete national mortality data. Occup Environ Med 2017; 0:1-8.

[14] Asbestfonds/Fonds Amiante (AFA) : http://www.fedris.be/afa/afa_fr.html

[15] Barlow L, Westergren K, Holmberg L and Talbäck M. The completeness of the Swedish Cancer Registry – a sample survey for year 1998. Acta Oncol 2009; 48(1):27-33.

[16] McElvenny DM, Darnton AJ, Price MJ and Hodgson JT. Mesothelioma mortality in Great Britain from 1968 to 2001. Occ Med 2005; 55(2):79-87.

[17] Damhuis RA, Khakwani A, De Schutter H, Rich AL, Burgers JA, van Meerbeeck JP. Treatment patterns and survival analysis in 9014 patients with malignant pleural mesothelioma from Belgium, the Netherlands and England. Lung Cancer 2015; 89(2): 212-217.

[18] World Health Organization (1992) International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Geneva: World Health Organization.

[19] Schliep KC, Chen Z, Stanford JB, Xie Y, Mumford SL, Hammoud AO, Johnstone EB, Dorais JK, Varner MW, Louis GMB and Peterson CM. Endometriosis diagnosis and staging by operating surgeon and expert review using multiple diagnostic tools: an interrater agreement study. BJOG 2017; 142(2): 220-229.

[20] McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012; 22(3): 276-282.

[21] Kendrick S and Clarke J. The Scottish record linkage system. Health Bull (Edindurgh) 1993; 51:72-79.

[22] Sugarbaker DJ, Wolf AS, Chirieac LR, Godleski JJ, Tilleman TR, Jaklitsch MT, Bueno R and Richards WG. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg 2011; 40(2):298-303.

[23] Kothmaier H, Quehenberger F, Halbwedl I, Morbini P, Demirag F, Zeren H, Comin CE, Murer B, Cagle PT, Attanoos R, Gibbs AR, Galateau-Salle F and Popper HH. EGFT and PDGFR differentially promote growth in malignant epithelioid mesothelioma of short and long term survivors. Thorax 2008; 63(4):345-51.

[24] Goldberg M, Imbernon E, Rolland P, et al. The French national mesothelioma surveillance program. Occup Environ Med 2006; 63:390–395.

[25] Labrèche F, Case BW, Ostiguy G, Chalaoui J, Camus M and Siemiatycki. Pleural mesothelioma surveillance: validity of cases from a tumour registry. Can Respir J 2012;19(2):109-108.

[26] Kirkham TL, Koehoorn MW, McLeod CB, Demers PA. Surveillance of mesothelioma and workers' compensation in British Columbia, Canada. Occup Environ Med 2011;68:30-5.

[27] Goldacre MJ. Cause-specific mortality: understanding uncertain tips of the disease iceberg. J Epidemiol Community Health 1993; 47: 491-496.

[28] Camidge DR, Stockton DL, Bain M: Factors affecting the mesothelioma detection rate within national and international epidemiological studies: insights from Scottish linked cancer registry-mortality data. Br J Cancer 2006; 95:649-52.

[29] Okello C, Treasure T, Nicholson AG, Peto J and Møller H. Certified causes of death in patients with mesothelioma in South East England. BMC Cancer 2009; 9(28).

[30] Pinheiro GA, Antao VCS, Bang KM and Attfield MD. Malignant mesothelioma surveillance: a comparison of ICD10 mortality data with SEER incidence data in nine areas of the United States. Int J Occup Environ Health 2004; 10(3): 251-255.

[31] Martinez C, Gatta G, Trama A, Capocaccia R, Sánchez-Pérez MJ and Melchor JM. Report with quality considerations on the available data on rare cancers. Available online at the RARECARE website www.rarecare.eu (accessed November 2nd 2017).

[32] Trama A, Marcos-Gragera R, Sánchez-Pérez MJ, van der Zwan JM, Ardanaz E et al. Data quality in rare cancers registration : the report of the RARECARE data quality study. Tumori 2017; 103(1): 22-32.

[33] Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E et al. Survival of pleural malignant mesothelioma in Italy: a population-based study. Int J Cancer 2009; 124: 201-207.

[34] Thomas A, Yuanbin C, Tinghui Y, Ammara G and Prasad V. Distinctive clinical characteristics of malignant mesothelioma in young patients. Oncotarget 2015; 6(18):16766-16773.

[35] Attanoos RL, Churg A, Galateau-Salle F, Gibbs AR and Roggli VL. Malignant mesothelioma and its non-asbestos causes. Arch Pathol Lad Med 2018 Feb 26.

[36] Testa JR, Cheung M, Pei J, Below JE, Tan Y et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2012 ; 43(10) :1022-1025.

[37] Baas P, Fennell D, Kerr KM et al. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5:v31-9.

[38] Chou A, Toon CW, Clarkson A, Sheen A, Sioson L and Gill AJ. The epithelioid, BAP1-negative and p16-positive phenotype predicts prolonged survival in pleural mesothelioma. Histopathology 2017; Sep 10.

[39] Kinoshita Y, Hida T, Hamasaki M, Matsumoto S, Sato A, Tsujimura T, Kawahara K, Hiroshima K, Oda Y and Nabeshima K. A combination of MTAP and BAP1 immunohistochemistry in pleural effusion cytology for the diagnosis of mesothelioma. Lung Cancer 2017; 104:98-105.

[40] Yap TA, Aerts JG, Popat S and Fennell DA. Novel insights into mesothelioma biology and implications for therapy. Nat Rev Cancer 2017; 17(8):475-488.

Highlights

- Comparing population-based registries resulted in 95% of concordant cases
- Completeness and correctness of mesothelioma registration was enhanced
- Reasons for misclassification and under-registration were elucidated
- Distinct immunohistochemical patterns were observed by mesothelioma histology
- Long-term survivors had distinct clinical and biological characteristics

Keywords

malignant mesothelioma; comparing independent databases; completeness and correctness of registration; long-term survivors

		Belgian Mesothelioma Registry (BMR)					N(BCR)
		MM (C45)	Other	No diagnosis	No information	Missing in BMR	
Belgian Cancer Registry (BCR)	MM	1,566	81	5	0	640	2,292
	MNP	0	5	0	0	47	52
	NK/Other	89	141	3	11	0	244
	Missing in BCR	69	130	44	56	0	299
N (BMR)		1,724	357	52	67	687	2,887

Table 1 : Comparison of the diagnoses as reported by the pathology laboratories to the Belgian Cancer Registry (BCR) and made by the expert panel of pathologists from the Mesothelioma Commission (BMR). MM = Malignant mesothelioma; MNP = Malignant neoplasm of pleura, NK = Not known.

		Belgian Mesothelioma Registry (BMR)				Total
		MM	Other	No Diagnosis	Missing in BMR	
Belgian Cancer Registry (BCR) : MM (C45)	COD_UC = C45	1,151 (80.5)	45 (65.2)	5 (45.5)	362 (67.5)	1,563 (76.4)
	COD_ALL = C45	1,192 (83.4)	46 (66.7)	5 (45.5)	374 (69.8)	1,617 (79,1)
	COD ≠ C45	237 (16.6)	23 (34.3)	6 (54.5)	162 (30.2)	428 (20.9)
	Total	1,429	69	11	536	2,045

Table 2 : Distribution of malignant mesothelioma (MM) cases registered at the Belgian Cancer Registry (BCR) for which the certificates of death (COD) could be linked. COD data mentioned a ICD10: C45 as underlying cause of death (COD_UC) or any cause of death (COD_ALL), or no C45 mentioned in the causes of death, compared with the diagnosis made by the pathologists expert panel from the Belgian Mesothelioma Registry (BMR).

Patient and tumour characteristics	Long-term survivors (>=3years)		Overall	P value
	No	Yes		
Overall	1,396	170	1,566	
ICD10				0.010
MM Pleura (C45.0)	1,332 (95.4)	154 (90.6)	1,486 (94.9)	
MM Peritoneum (C45.1)	63 (4.5)	15 (8.8)	78 (5.0)	
MM Other/NS (C45.2-7-9)	1 (0.1)	1 (0.6)	2 (0.1)	
Sex				<0.001
Male	1,203 (86.2)	126 (74.1)	1,329 (84.9)	
Female	193 (13.8)	44 (25.9)	237 (15.1)	
Age group (years)				<0.001
18–59	211 (15.1)	50 (29.4)	261 (16.7)	
60–69	427 (30.6)	61 (35.9)	488 (31.2)	
70–79	559 (40.0)	49 (28.8)	608 (38.8)	
80+	199 (14.3)	10 (5.9)	209 (13.3)	
Median age (IQR)	*71 (63-76)*	*66 (58-72)*	*70 (63-76)*	*<0.001*
Morphology				<0.001
MM epithelioid	1,007 (72.1)	163 (95.9)	1,170 (74.7)	
MM biphasic	207 (14.8)	2 (1.2)	209 (13.3)	
MM sarcomatoid	175 (12.5)	4 (2.4)	179 (11.4)	
MM NOS	7 (0.5)	1 (0.6)	8 (0.5)	

Table 3 : Patient and tumour characteristics of malignant mesothelioma (MM) long-term survivors, defined as patients who survived at least 3 years after being diagnosed, and no long-term survivors. IQR = interquartile range (Q1-Q3), NOS: not other specified.

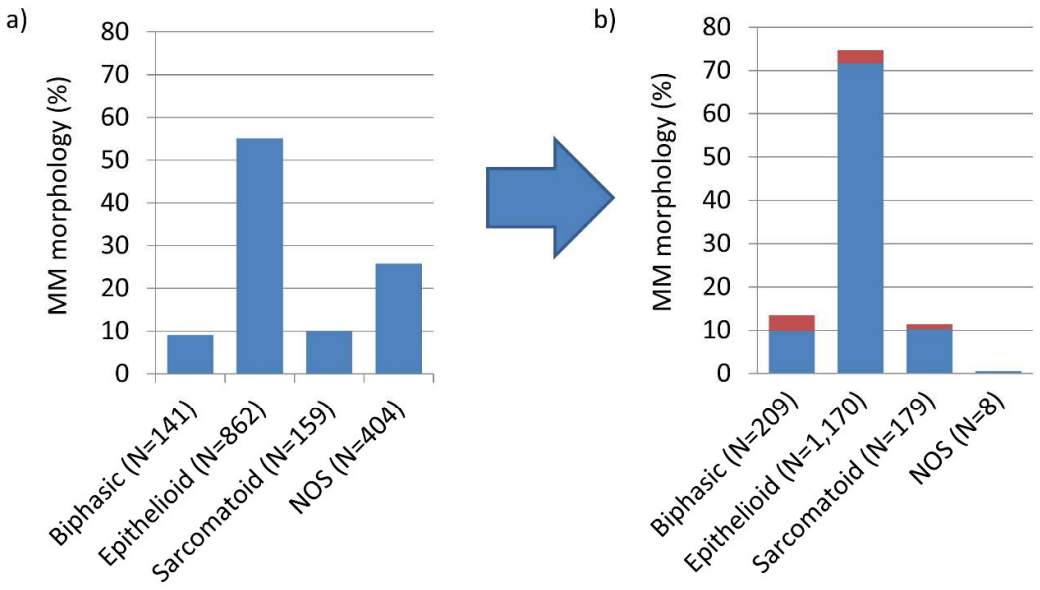

Figure 1

Morphology distribution of malignant mesothelioma (MM) cases at the Belgian Cancer Registry (BCR) before (a) and after considering information from the Belgian Mesothelioma Registry (BMR) (b). Only concordant MM cases in both data sources were considered (n=1,566). In the latter case (b), information from the expert panel of pathologists (BMR) was prioritised over the diagnosis reported to the BCR. The percentage of MM cases for which a discordant morphology was reported between both data sources (BCR and BMR) is highlighted in red (n=121; 7.7%).

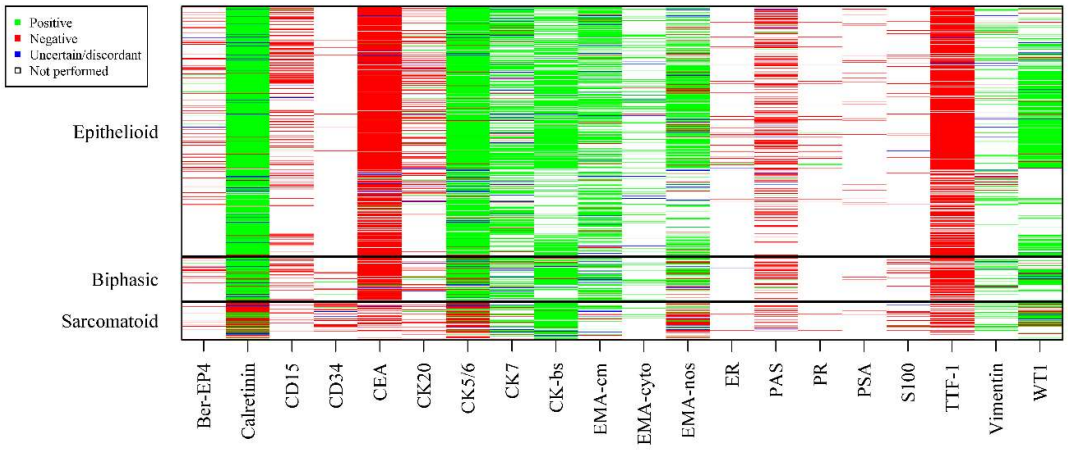

Figure 2

Immunohistochemical (IHC) test results by malignant mesothelioma (MM) morphological subtypes as derived from the Belgian Mesothelioma Registry (BMR) and the BCR (n=1,492). In case of discrepancies regarding morphology and/or IHC tests results, the information provided by the expert panel of pathologists (BMR) were prioritised. Each line corresponds to a patient, and test results were categorised in positive (green), negative (red), and uncertain/discordant (blue). CD: cluster of differentiation; CEA: polyclonal anti-carcinoembryonic antigen; CK: cytokeratin; bs: broad-spectrum; EMA: anti-epithelial membrane antigen; cm: membranous staining pattern; cyto: cytoplasmic staining pattern; nos: not otherwise specified; ER: oestrogen receptor; PAS: periodic acid – Schiff; PR: progesterone receptor: PSA: prostate-specific antigen; TTF-1: thyroid transcription factor-1; WT1: Wilms tumour antigen-1.