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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 = 2292), all patients reviewed by the pathology commission of the BMR (2004–2012; n = 2019), 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.

1. 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-

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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.

2. Material and methods

2.1. Patient selection

Data extracted from the BCR database included all cases of MM (n = 2292), 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 = 2207). Upon removal of double registrations, a final combined study cohort of 2887 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.

2.2. 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 1989 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.

2.3. 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.

2.4. 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 non-long-term survivors with regards to clinical characteristics were assessed by the χ^2-test.

3. Results

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

Before the start of this project, the BCR had counted a total of 2344 cases of MM (n = 2292) 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 = .03).

3.2. Diagnosis and histology comparison between BCR and BMR

Notably, 1652 (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 1724 MM cases present in the BMR, 1566 (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