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研究課題名（和文）Trends in global mesothelioma mortality using a birth-cohort analysis

研究課題名（英文）Trends in global mesothelioma mortality using a birth-cohort analysis

研究代表者

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研究成果の概要（和文）：本研究では中皮腫の世界的疾病負担を推定するため、入手可能かつ推定可能な国別データを用いて記述的分析を行なった。
その結果、中皮腫死亡者数は毎年増加傾向を示し、直近2年間でデータが得られる55か国の中皮腫死亡者は14,601人/年、百万人当たりでは9.89人/年（95%信頼区間は5.45-15.25人/年）と推定された。これらの数値から得られた中皮腫の世界的疾病負担（中皮腫死亡者数/年）は、非調整推定値で68,800人/年(石綿使用量による調整推定値は49,900人/年、大陸別による調整推定値は 53,400人/年)となった。これらは先行研究による推定値よりも高めではあるが、合理的な数値であった。

研究成果の概要（英文）：Goal:The current study descriptively analysed national mortality data with regard to their availability and referability for extrapolation, and extrapolated the referable data to estimate the global burden of mesothelioma deaths.

Result:The global numbers and rates of mesothelioma deaths increased each year. The 55 referable countries recorded 14,601 mesothelioma deaths per year over the two most recent years with available data, yielding a two-year mortality rate of 9.89 (95% CI, 5.45-15.25) deaths per million per year. By extrapolating these numbers, the unadjusted annual global burden of mesothelioma deaths was estimated as 68,800, which ranged between 49,900 and 53,400 after adjusting for selected attributes. Our estimates were reasonably close to the previously reported values, albeit on the higher end.

研究分野：　Epidemiology

キーワード：　mesothelioma　epidemiology　asbestos　burden of disease

1. 研究開始当初の背景

Malignant mesothelioma (mesothelioma, hereafter) is an aggressive form of cancer that is caused by exposure to asbestos and shows increasing incidence worldwide.[1,2] The world has heard repeated calls for the need to eliminate asbestos-related diseases (ARDs), including mesothelioma, and to stop using asbestos.[3-5] ARDs are beginning to be recognized as a global health issue,[5] thereby warranting the assessment of the global burden of mesothelioma. The number of mesothelioma deaths is an indicator of its disease burden because most patients die within two years[6] and the number of incident cases is seldom known.

The mortality database[7] maintained by the World Health Organization (WHO) compiles the number of deaths by disease category, calendar year, gender, and, age brackets, as reported by their member states (MS) and territories/insular regions ("territories," hereafter). Mesothelioma was first included in this database in 1994 coded as C45 under the 10th Revision of the International Classification of Diseases.[8] We previously reported a descriptive analysis of mesothelioma deaths recorded in the database between 1994 and 2008.[9] Although only a fraction of countries had reported data for a limited number of years, more data have since become available.

Several attempts have been made to estimate the global burden of mesothelioma. Driscoll et al (2005) estimated the annual number at 43 000 deaths.[10] This figure has been widely quoted to guide preventive activities, such as in the WHO document on the elimination of ARDs.[3] The 2014 WHO document on chrysotile asbestos[4] quoted 59 000 annual deaths.[11] Recently, the Global Burden of Disease 2013 Mortality and Causes of Death Collaborators reported an estimate of 33 700 annual deaths.[12] The difference between these estimates is nearly two-fold; moreover, it is unlikely that actual numbers decreased recently. However, these estimates are not amenable to verification, as it is difficult to access the analysed data and examine the utilized methods in detail. The manner and extent to which the estimations applied existing mortality statistics are also unclear.

2. 研究の目的

The objectives of this study are to: i) descriptively analyses national mortality data in terms of availability and referability for extrapolation; and ii) utilize these findings and extrapolate the referable data to estimate the global burden of mesothelioma deaths.

3. 研究の方法

We analysed data from 192 (99.0%) of 194 WHO-MS (Cook Islands and Niue were precluded for their lack of population data), 35 territories and two non-MS (Kosovo and Liechtenstein, identified separately[13,14]). We refer to these entities collectively as "countries" (N=229) hereafter. The analysed countries had a total population of 6.95 billion, which reasonably represented the global population.

In November 2014, we extracted data from the WHO Mortality Database regarding mesothelioma (C45) deaths from 1994 to 2012 in the MS and territories that reported these data. Data for Switzerland (an MS) were absent from the database but were identified from the literature.[15] We calculated crude mortality rates ("mortality rates (MR)" hereafter) by dividing the number of mesothelioma deaths (combined for gender and all mesothelioma types) by the total population of the MS, territory or group, in the same year or period. Thus, the MR of a group of countries was the average MR of the constituent countries weighted by population. We distinguished between annual MR (i.e., MR for one calendar year) and period MR (i.e., MR for two or more consecutive or intermittent calendar years). Population data were obtained from the WHO,[8] the United States Census Bureau,[16] and the United Nations,[17] and were prioritized for use in that order.

We grouped all studied countries (N=229) into "reporting" and "non-reporting" countries based on data availability, and then sub-classified the reporting countries based on the following criteria for non-referability: i) whole-period MR of 0.5 death per million per year or less, which is half the widely accepted background level of mesothelioma at 1.0 case per million per year[6,18,19] (i.e., the country suffered from underreporting and/or under-diagnosis; "underreporting," hereafter); ii) two or fewer reporting years (i.e., the country reported but lacked experience in terms of time); and/or iii) ten or fewer total reported deaths (i.e., the country reported but lacked experience in terms of the number of cases). Thus, if a country satisfied one or more of the three conditions, then it was considered

"non-referable" for extrapolation; otherwise, it was considered "referable" for extrapolation.

To estimate the global burden, we extrapolated the period MR of the referable countries to the combined group of non-referable and non-reporting countries. This was done both directly (i.e., direct extrapolation) and at the stratified level of attributes (i.e., attribute-adjusted extrapolation). We employed three attributes that we judged to have potential explanatory power for MR, and thus enable extrapolation within the attribute's subgroups. These attributes were the historical level of asbestos use, the continental region, and the employment % in the industrial sector.

For asbestos-adjusted extrapolation, we extracted data on raw asbestos use from the United States Geological Survey (USGS)[20,21] and its updated data file (Virta RL, USGS, personal communication, March 6, 2013). We adopted the USGS definition of use (production + import - export), and obtained data by country, across various interval of years. We interpolated use values for calendar years lacking data and treated negative values as zero. Asbestos use in countries that made a political transition was treated as previously described.[22] Per capita asbestos use was calculated by dividing the volume of asbestos use by the population size (obtained as described above), and complemented for the period of 1925-50 based on the work of Lahmeyer.[23] Cumulative asbestos use for the period 1925-85 was considered to contribute to mesothelioma deaths of the study period. Countries were stratified into four subgroups ("no use," "low," "middle" and "high") based on their levels of per capita and cumulative asbestos use.

For continent-adjusted extrapolation and general description of regions, we defined Oceania, Africa, Asia, Europe and the Americas according to the United Nations.[24] For employment-adjusted extrapolation, we extracted the percentage data of employment for "industry" (the other two categories were "agriculture" and "services") by country according to the World Bank.[25] No data were available for 48 countries. Employment data were extracted for the period 1980-2012; no data were available for earlier periods. We grouped all listed countries into three equal-sized subgroups designated as "low," "middle," and "high." Countries not listed in the above database were placed in the "no data" subgroup. The latter subgroup did not include any country that reported mesothelioma deaths, so the value of 1 death per million population per year (i.e., the widely accepted background level for mesothelioma[6,18,19]) was used for extrapolation.

We conducted Pearson partial correlation analyses to investigate the relationship between period MR and the number of reporting years and total reported deaths. We conducted linear regression analyses to investigate the time-trend of annual MR, and further to identify the best-fit model for the period MR calculated as the moving average of the annual MR for a combination of calendar years with available data. Weighting was applied for the size of the at-risk population. To determine the actual period MR optimal for extrapolation, the best-fit model was identified by comparing the R2, mean-squared error, and p-values. To calculate the 95% confidence interval (CI) of the MR for a group of countries, we first calculated the 95% CI of the mean of the number of deaths based on the commonly used formula.[26] Microsoft Excel (Microsoft Corporation, Redmond, USA) and SAS Version 9.4 (SAS Institute, Inc., Cary, USA) were used to compile and analyse data.

4．研究成果

Ninety-nine countries reported mesothelioma deaths (88 MS and 11 territories); they varied widely by region, ranging from three in Oceania to 39 in the Americas, and also by calendar year, ranging from three in 1994 to 70 in 2008 and 2009. Similarly, the number of reporting years varied widely, ranging from one (11 countries) to 19 (the Czech Republic and Denmark), with a mean and median of 9.2 and 10 years, respectively, and a total of 914 years. Of the MS, 106 did not report mesothelioma deaths to the WHO.

A statistically significant correlation was found for the relationship between period MR and total number of deaths (partial correlation coefficient, 0.68; $p<0.001$), but not between period MR and number of reporting years (partial correlation coefficient, 0.05; $p=0.702$) adjusted for population size. The period MR for the 99 reporting countries varied 103-fold, ranging from 0.04 (in Saudi Arabia and Egypt) to 44.56 (in the British Virgin Islands) with a mean and median of 6.19 and 2.91 deaths per million per year, respectively.

Of the 99 reporting countries, 20 (20.2%) recorded a period MR of 0.5 or fewer deaths per million per year, 21 (21.7%) reported data

for two years or less, and 32 (32.3%) reported a total of 10 or fewer mesothelioma deaths; these numbers were not mutually exclusive, and overlapped. By satisfying one or more of the pre-determined criteria, 45 (45.5%) countries were considered "non-referable," and the remaining 54 countries (54.5%) "referable," for extrapolation. The 45 non-referable countries were combined with the 129 countries (106 MS + 24 territories - Switzerland) that did not report mesothelioma to the WHO to form the group of 174 countries for which the number of mesothelioma deaths were estimated.

The 54 referable countries represented all regions, but were skewed by region, with two in Oceania, one in Africa, seven in Asia, 31 in Europe, and 13 in the Americas. The total number of reporting years for the referable countries was also skewed by region, with 24, 15, 80, 431 and 167 years for Oceania, Africa, Asia, Europe, and the Americas, respectively. We thus had referable data for a total of 717 years (i.e., 78.4% of 914 reported years). The period MR for the 54 referable countries was 8.453 deaths per million per year. Switzerland, which is a MS but did not report relevant information to the WHO, separately recorded 649 deaths during 1994-2005 (12 reporting years) 15 for a period MR of 7.51 deaths per million per year. Switzerland was combined with the group of 54 referable countries to form a group of 55 referable countries with a period MR of 8.449 deaths per million per year.

Annual MR of the 55 referable countries increased steadily from 1994 to 2012 ($\beta 1=0.35$, $p<0.0001$ and adjusted $R2=0.89$, $p<0.0001$ for the model). The period MR of 8.45 deaths per million per year was equivalent to the annual MR averaged over the entire study period which corresponded to a calendar year of about 2005 on the regression line. Fewer data were available for the beginning and end of the study period.

Because the two-year moving average model showed the best fit for trend, the two-year MR of the two most recent years with available data for the 55 referable countries, was used for extrapolation. This corresponded to the 2008 to 2012 calendar years for all countries. The 55 referable countries recorded an average of 14 601 deaths per year during these years for a two-year MR of 9.89 (95% CI, 5.45-15.25) deaths per million population per year. These numbers were used for extrapolation.

The reported number of 14 601 annual deaths in the referable countries (N=55) was added to the estimated annual number of deaths for the estimated group (N=174), to produce totals of 68 800 deaths obtained via direct extrapolation (without adjustment), 53 400 deaths obtained via asbestos-adjusted extrapolation, 49 900 deaths obtained via continent-adjusted extrapolation, and 51 800 deaths obtained via employment-adjusted extrapolation.

Our extrapolation method required an assumption of comparability between the referable and estimated countries in terms of MR. "No adjustment" extrapolation assumed direct comparability, whereas "adjustment by attributes" extrapolation assumed comparability after stratification. More specifically, adjusting for continent, employment and asbestos assumed comparability based on continental affiliation, industrial profile and historical asbestos use, respectively. The most relevant extrapolation method was likely the one adjusted by historical asbestos use, because mesothelioma is almost exclusively attributable to past asbestos exposure, and the extent of asbestos use has repeatedly predicted subsequent rates of ARDs at national levels.[27-29]

There are obvious limitations in the present study. First, many countries did not report mesothelioma deaths to the WHO, including those that recorded asbestos usage. The non-reporting of mesothelioma in a country that used asbestos at substantial levels with sufficient elapsed time cannot be interpreted as an indication of no cases. Second, we used arbitrary criteria to define countries as underreporting or reporting but lacking experience, and this may have introduced bias in either direction. However, the less than ideal capacity to diagnose and report mesothelioma cases in some of the referable countries should have contributed to under-estimation. Third, the exact timing of asbestos use differed between the high-use countries of economically developed status and those of developing status, e.g., Asia where asbestos use started relatively late. Thus the extrapolated numbers for these developing countries may overestimate their current number of mesothelioma deaths and better reflect the reality in the years to come. Fourth, the age structure and life expectancy are variable in the referable and estimated countries which could not be accounted for by our extrapolation method.

The strength of our method was the reproducibility of its findings due to the use of commonly accessible data and a straightforward algorithm. The present estimates are thus amenable to update, refinement and verification. The lack of such features in earlier studies prohibited reassessment of the estimated values. In contrast, this study may be verified against actual numbers and cross-verified with existing methods. The estimation of the global mesothelioma burden will naturally improve as more countries report referable data and fewer countries require extrapolation. The WHO Mortality Database will accumulate more data over time, but the data will continue to vary in their quality and availability given the between-country difference in their medico-social infrastructures and current stages in the mesothelioma epidemic. Because these national differences are likely to persist for some time, efforts to estimate the global mesothelioma burden will continue to be challenging. The priority for a worldwide asbestos ban notwithstanding, improving the quantification of the global mesothelioma burden is needed for additional preventive action.

PS: The graph and figures were not shown due to the requirement of adherence to the template provided.

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５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

Paper “Can National Mortality Data be Extrapolated to Estimate the Global Burden of Mesothelioma Deaths?” is under review of journal “Environmental Health Perspectives” since 25 March, 2016.

〔雑誌論文〕（計　　件）

〔学会発表〕（計　　件）

〔図書〕（計　　件）

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