

Chapter 1

Trend in the Global Incidence of Mesothelioma: Is There Any Changing Trend After Asbestos Regulation and Ban?



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Abstract Asking “does an asbestos ban lead to a decrease in malignant mesothelioma?” is not a simple question as it may seem. This is largely because the phrase “asbestos ban” refers to a wide range of national situations and processes. It also reflects that countries have varied widely in their speed of reducing asbestos consumption in relation to, or independent of, adopting a ban. Thus, it is analytically complex to address an asbestos ban in relation to mesothelioma incidence, and few such studies have been conducted. The first study to directly address this question compared national-level data of changes in pleural mesothelioma mortality rates versus changes in asbestos use across a range of countries; the authors found correlations between these changes and suggested that there may be an early effect. The second study, which was a birth cohort analysis conducted in Sweden, showed that a later birth cohort (one active in the workforce after the decrease in asbestos use) had a decreased risk of pleural mesothelioma relative to an earlier birth cohort, regardless of gender. These studies implicated a causal effect, wherein an asbestos ban leads to a decrease in mesothelioma incidence. Given the very long latency period for mesothelioma, it can be expected that a much clearer effect will soon become evident in countries that adopted an early ban on asbestos. Furthermore, given the ongoing use of asbestos by many industrializing countries, it is also perti-

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ment to ask: “Did an increase in mesothelioma incidence lead to an asbestos ban in some countries?”.

Keywords Mesothelioma · Incidence · Mortality · Asbestos · Global burden of disease (GBD)

1 Introduction

1.1 Incidence and Mortality

Incidence data are compiled for malignant mesothelioma, along with other cancers, in the monograph series published by the International Agency for Research on Cancer (IARC) [1]. The metrics used to describe incidence include the number of cases and the crude and age-adjusted rates per 100,000 person-years grouped by gender and 5-year periods. Utilizing this dataset, Soeberg and van Zandwijk [2] identified the regions with the world’s highest age-standardized incidence rate (SIR) for mesothelioma (period 2003–2007) as being Bremen (Germany) at 6.0, Genoa (Italy) at 5.6, and Western Australia (Australia) at 4.5 per 100,000 person-years among men. They also noted that the population-level mesothelioma incidence rate rarely exceeded 1.0 per 100,000 (or 10 per million) person-years. A major limitation of this dataset is that data are confined to the catchment areas of the respective cancer registries (mostly regional, some national) and are only updated every 5 years. Nonetheless, actual data reported to and compiled by cancer registries worldwide provide additional insight. For example, although China lacks nationwide statistics on mesothelioma mortality, the SIR for mesothelioma in Beijing City was reportedly 0.3 and 0.2 per 100,000 person-years among men and women, respectively (period 2003–2007) [1].

Here, the *reported* data, such as those for incidence and mortality, should be clearly distinguished from *estimated* values. For example, Zhao et al. [3] reported the following estimates for all mesothelioma in China in 2013: 2041 incident and 1659 death cases; 1.50 per million (M) person-years (crude incidence rate); and 1.22 per M person-years (crude mortality rate). Although these are likely to be underestimates, the report represents an important first step in clarifying the mesothelioma situation in China.

Mesothelioma has one of the poorest survival rates of all cancer types, with a 5-year survival rate <10% and a median survival time <1 year. The incidence, therefore, approximates mortality and can be surrogated by mortality data. Mortality data are generally more available and accessible than incidence data, especially for mesothelioma, so the global situation (or “burden”) of mesothelioma is commonly expressed in terms of mortality (the number of deaths).

1.2 WHO Mortality Database

The WHO Mortality Database is a compilation of mortality data by age, gender, and cause of death, as reported annually by countries (i.e., WHO Member States) from their civil registration systems [4]. In general, the data are most complete for developed countries (though coverage of years are variable), whereas developing countries often have incomplete or missing data [5].

Delgermaa et al. [6] conducted a descriptive analysis of all mesothelioma deaths in the WHO Mortality Database, which recorded 92,253 mesothelioma deaths in 83 countries during 1994–2008. The crude and age-adjusted mortality rates (AAMR) were 6.2 and 4.9 per M person-years, respectively, with an AAMR increase of 5.4% per year during the 15-year period. The trends varied substantially by continent: the AAMR increased significantly in the countries of Europe (3.7% per year, $p < 0.05$) and Asia (3.4% per year, $p < 0.05$) but not the Americas (7.9% per year, not significant [NS]) or Oceania (−0.5% per year, NS). The AAMR increased significantly in countries of the high-income group (5.5% per year, $p < 0.05$) but not the middle- and low income groups (2.2% per year, NS). The mean age at death was 70 years and the male-to-female ratio was 3.6:1. The three countries with the highest number of deaths were the USA, the UK, and Japan, and those with the highest AAMR were the UK (17.8 per M person-years), Australia (16.5 per M person-years), and Italy (10.3 per M person-years).

When viewing global mortality statistics, some limitations must be considered. For one, mesothelioma is technically difficult to diagnose: malignant pleural mesothelioma (MPM) can be misdiagnosed for lung cancer arising in peripheral areas and peritoneal mesothelioma can be difficult to differentiate from ovarian cancer in women. For another, malignant mesothelioma was first classified as category C45 in the tenth edition of the International Classification of Disease (ICD-10, 1994), but the reporting of mesothelioma based on ICD-10 varies widely by country: developing countries usually lack the infrastructure and/or expertise to diagnose mesothelioma; developed countries have only gradually established the expertise to accurately diagnose mesothelioma, and misdiagnosis is still not uncommon compared to other cancer types. This becomes a source of bias, especially regarding data for earlier years and countries with few reporting years.

Two reports utilizing the WHO Mortality Database revealed a clear contrast between the mesothelioma situation in Asia [7] and Europe [8]. Mesothelioma deaths were reported to the WHO by 17 (36%) of 47 countries in Asia and 37 (70%) of 53 countries in Europe (the observed periods were 1994–2008 in Asia and 1994–2012 in Europe). When combined with asbestosis, the continental burdens of asbestos-related deaths (ARDs), relative to the world, were 13 and 60% for Asia and Europe, respectively [7, 8].

1.3 GBD Estimates of Mesothelioma

The Global Burden of Disease (GBD) study, which is a comprehensive regional and global research program that assesses mortality and disability from major diseases, injuries and risk factors [9], is one of the largest scientific collaborations in the world. It is widely and often cited as a reliable source for global public health data and trends.

An earlier GBD study (conducted for the year 2010) estimated that 33,160 cancer deaths were caused by occupational exposure to asbestos but did not report a specific estimate for mesothelioma [10]. In later GBD studies, mesothelioma was estimated as either “all mesothelioma” or “mesothelioma caused by occupational exposure to asbestos.” The GBD study for 2013 substantially upgraded the estimate to 194,000 cancer deaths caused by occupational exposure to asbestos [11], with 33,700 due to all mesothelioma [12] (Table 1.1).

Several reports/studies on national-level trends have suggested that the mesothelioma incidence may have peaked (or is peaking) in several developed countries but did not provide evidence for a substantial decrease of the disease burden in those countries [19–21]. Even in the absence of an actual increase of incidence, the diagnosis and reporting of mesothelioma are improving widely across developed countries and beginning in some industrializing countries. Thus, at least a nominal increase should be observable due to improved reporting alone. The chapter authors, therefore, believe that the GBD estimates indicating a global *decline* of mesothelioma incidence/mortality (Table 1.1) are unlikely to be correct.

The chapter authors further surmise that the GBD estimates for mesothelioma are underestimated and/or biased because: (1) the rates and numbers estimated for China and India (not shown here) are low given their relatively long and heavy use of asbestos, which would substantially decrease the global estimate due to their population size (underestimation); (2) the female-to-male ratio found in most GBD estimates (not shown here) is much higher than common knowledge (bias); and (3) a separate study to project GBD estimates from the year 2016 to the year 2040 forecasted a substantial increase from 30,200 to 50,600 mesothelioma deaths per year [22] (not shown in Table 1.1). However, annual GBD estimates from 2017 to 2019 show a steady decrease (Table 1.1), which contradicts the long-term forecast.

Table 1.1 Estimates of mesothelioma by the global burden of disease (GBD) study

Year of GBD study	All mesothelioma (A)	Mesothelioma due to occupational exposure to asbestos (B)	Other mesotheliomas (C)
2013	33,700 [12]	Data not found	Not applicable
2015	32,400 [13]	23,000 [14]	9,400
2016	30,200 [15]	27,600 [16]	2,600
2017	29,900 [17]	27,000 [18]	2,900

A: GBD Causes of Death Collaboration; B: GBD Risk Factors Collaboration; C: Calculated by chapter authors as A – (minus) B

1.4 Other Global Estimates of Mesothelioma

In 2005, prior to the GBD study, Driscoll et al. [23] estimated the global burden of mesothelioma at 43,000 deaths per year (Table 1.2). This was derived by combining estimates of the proportion of exposed workers and of exposure levels (based on workforce data and the Carcinogen Exposure [CAREX] database) with absolute risk measures for mesothelioma. The study provided a breakdown of the estimated number by WHO regional groupings, but not by countries or continents. This estimate has been referenced by many studies, as well as by position papers of the WHO and other United Nation agencies.

More recently, Odgerel et al. [25] estimated the global burden of mesothelioma at 38,400 deaths per year by extrapolating national-level “quality data” for mortality rates and asbestos usage data (Table 1.2). This estimate is lower than that of Driscoll et al. but substantially higher than recent estimates of the GBD study (Table 1.1). Odgerel et al. applied objective criteria to judge the “quality” of mesothelioma data in the WHO Mortality Database, with “insufficient” data defined as: (1) a crude period mortality rate of 0.5 per M per year or less (i.e., less than half the widely accepted background level); (2) two or fewer reported years of data; or (3) 10 or fewer total reported deaths for the entire period. Of the 230 studied countries, 104 (45%) countries reported data and 126 (55%) did not; for the former, the data quality was sufficient for 59 (57%) countries and insufficient for 45 (43%). Thus, the global status of reports on mesothelioma deaths and their data quality can be conservatively summarized as follows: less than half of all countries have national statistics, of which only half is of sufficient in quality.

2 Asbestos Bans and Mesothelioma

2.1 Global Situation of Asbestos Bans

According to Kazan-Allen [26], since Iceland totally banned asbestos in 1983, a total of 67 countries/regions have adopted a total (compared to a “partial”) on asbestos. Table 1.3 shows that five European countries, particularly those of northern Europe (with the notable exception of Finland, which banned asbestos in 2005), independently banned asbestos in the 1980s, followed by Liechtenstein in 1990 and

Table 1.2 Global estimates of mesothelioma by studies other than the GBD study

Author	Estimated global mesothelioma deaths	Year/period
Driscoll et al. (2005) [23]	43,000 deaths per year	2000
Park et al. (2011) [24]	174,300 deaths for 56 countries with data 38,900 deaths for 33 countries without data	1994–2008
Odgerel et al. (2017) [25]	38,400 deaths per year 9.9 deaths per million population/year	1994–2014

Table 1.3 Countries that adopted total asbestos bans during 1982–2019 [26]

Continent/ group	Up to 1989	1990–1999	2000–2009	2010–2019	Total
Europe	Denmark, Iceland, Norway, Sweden, Switzerland	Poland	<i>EU</i> ^a : Austria, Belgium, Bulgaria, Croatia ^b , Cyprus ^b , Czech Republic ^b , Estonia, Finland, France, Germany, Greece ^b , Hungary ^b , Ireland, Italy, Latvia, Lithuania ^b , Luxembourg, Malta ^b , Netherlands, Portugal ^b , Romania, Slovakia ^b , Slovenia, Spain <i>Non-EU</i> : Gibraltar, Liechtenstein, New Caledonia ^c , UK	Israel, North Macedonia, Monaco, Serbia, Turkey	39
Middle East		Bahrain, Kuwait, Saudi Arabia	Egypt, Jordan, Oman	Iraq, Qatar	8
Asia/ Oceania		Brunei	Australia, Japan, South Korea	New Zealand, Taiwan	6
Americas			Chile, Honduras, Uruguay	Argentina, Brazil ^b , Canada, Colombia	7
Africa		Djibouti	Algeria, Gabon ^b , Mauritius ^b , Seychelles ^b , South Africa	Mozambique	7
Total	5	6	42	14	67

The chapter authors constructed this table based on data by Kazan-Allen [26]

^aPartial adoption of the asbestos ban was adopted in several European countries prior to 2005; where information on total ban is not available, the 2005 EU-wide total asbestos ban year is noted

^bTotal ban compliance not verified or not strictly enforced: Brazil, Croatia, Cyprus, Czech Republic, Greece, Gabon, Hungary, Lithuania, Malta, Mauritius, Portugal, Slovakia, Seychelles

^cNew Caledonia is a French territory situated in Oceania

Poland in 1997. By the end of the first decade of 2000, all EU member states had to comply with EU Directive 1999/77/EC [27] to ban all types of asbestos beginning in January 2005.

A range of countries of non-EU Europe, Asia/Oceania, and the Americas followed suit mostly after the turn of the century, with the notable exceptions of Canada (ban in 2018) and the USA (no ban at present). Russia, Kazakhstan, China, Zimbabwe, and Brazil are still mining asbestos (i.e., “asbestos-producing”), and the majority of industrializing countries in Asia/Oceania, Africa, and the Middle East have not adopted total bans on asbestos. Moreover, even under a “total” ban, certain items and/or situations may be exempted; their status may vary by country, as can the implementation of and compliance with the law (Table 1.3, footnote).

Such variation in the definition of “ban” makes it difficult to assess the possible relationship between an asbestos ban and mesothelioma incidence. Furthermore,

the speed at which countries have tapered off consumption, in relation to, or independent of, adopting a ban, has increased over time [28]. Therefore, for the purpose of data analysis, the status of the ban may be more adequately represented by the speed of reduction of asbestos consumption as a continuous variable than a binomial or categorical variable.

2.2 *Does an Asbestos Ban Lead to a Decrease in Mesothelioma Incidence?*

By applying a straightforward ecological study design, Lin et al. [29] showed that there is a clear correlation between the level of asbestos use and subsequent mesothelioma rates, implicating that countries using more (less) asbestos will subsequently shoulder higher (lower) burdens of mesothelioma. Using the conventional steps of statistics [i.e., moving from assessing a cross-sectional correlation to a delta (Δ ; change over time) correlation], Nishikawa et al. [30] conducted a natural extension of the study of Lin et al. by asking whether a substantial reduction in asbestos use (as often caused by an asbestos ban) affected a reduction in the mesothelioma burden.

Specifically, Nishikawa et al. [30] assessed the interrelationship between mortality from pleural mesothelioma and the adoption of national bans on a global scale. Age-adjusted period mortality rates (MRs) in men for pleural mesothelioma during 1996–2005 were calculated for 31 countries. “Trends” were characterized by calculating the annual percent changes (APCs) of the MRs. The APCs were further grouped by whether they reflected “increase (\uparrow),” “equivocal (\rightarrow),” or “decrease (\downarrow),” and then compared with historical patterns of asbestos use and the national ban status. Trends in mortality showed significant increases (\uparrow) in five countries and marginally significant increases (\uparrow) in two countries and were equivocal (\rightarrow) in 24 countries. Whereas the global median APC was 4.5% per year, non-significant negative APC values were recorded in five countries of northern and western Europe: Austria (APC, -5.9% per year; year of ban, 1990), Finland (-0.3% per year, 1992), France (-1.0% per year, 1996), Iceland (-1.4% per year, 1983), and Norway (-2.7% per year, 1984).

Importantly, the change in asbestos use during 1970–1985 was a significant predictor of APC in male mortality for pleural mesothelioma, with an adjusted R^2 value of 0.47 ($p < 0.0001$). Moreover, a graph plotting the change (Δ) in asbestos use on the x -axis and APC (also “ Δ ”) on the y -axis showed that all of the above countries recorded reductions in asbestos use and thus contributed substantially to the overall correlation. Although the study could not establish the direct effect of a ban, it suggested that an asbestos ban leads to a decrease in mesothelioma incidence.

The authors conservatively noted that the study period was inadequate (i.e., too short) to depict trends in many countries and the observed relationship may have reflected only early effects of the ban on mesothelioma rates. Given the long latency

time required for mesothelioma, the full consequences of such effects would require a longer observation period. Nevertheless, the study took advantage of the earliest opportunity to analyze the relationship based on national-level data from a range of countries.

Jarvholm and Burdorf [31] argued that it is difficult to evaluate the impact of an asbestos ban based on population-level trends in mesothelioma mortality rates and that such an evaluation must consider age-specific mortality rates for consecutive birth cohorts. They thus utilized Swedish data (Sweden having adopted an early national ban) to assess how a ban influenced age-specific mortality rates over time. The authors noted that although Sweden banned asbestos in 1982, the use of asbestos was already substantially reduced in this country by around the mid-1970s. Therefore, the authors compared the incidence of pleural mesothelioma in birth cohorts who started to work before and after the mid-1970s. The age of starting work was assumed to be 15–20 years and, due to an increase in immigration over time, the birth cohort analysis was restricted to persons born in Sweden.

The analysis showed that the later birth cohort (active in the workforce *after* the decrease in asbestos use) had a decreased risk of pleural mesothelioma relative to the earlier birth cohort for both genders: the relative risks (RR) of men and women born 1955–1979 versus men and women born 1940–1949 were 0.16 (95% CI 0.11–0.25) and 0.47 (95% CI 0.23–0.97), respectively. This finding was clearly illustrated by a line graph showing incidence rates (*y*-axis) versus age (*x*-axis): the lines of the earlier birth cohort were almost always positioned higher than those of the later birth cohort when compared for the same age. In contrast, a line graph depicting the trend over time (*x*-axis) in *overall* incidence (*y*-axis) showed only a minimal change. The authors rightly highlighted that the decrease in actual exposure is more important than a ban per se, but concluded that although their findings were for Sweden, similar interventions in other countries will reduce the occurrence of pleural mesothelioma.

2.3 Does a High Mesothelioma Incidence Lead to an Asbestos Ban in Some Countries?

When considering the relationship between an asbestos ban and mesothelioma incidence, one should bear in mind the various effects that can arise from the long latency period (in the order of decades) of mesothelioma. For example, a straightforward comparison between asbestos-banned and no-ban countries will often reveal *higher* mesothelioma incidence in the asbestos-banned countries, relative to the no-ban countries. This trend is evident in the findings of studies on mesothelioma mortality in Asia [7] and Europe [8].

This likely reflects that countries with high mesothelioma incidence *consequently* adopted asbestos bans, the process of which took some time. In turn, after

adopting an asbestos ban, the expected reduction in the incidence of mesothelioma can manifest only after several decades. Meanwhile, current asbestos-using (i.e., no-ban) countries continue to do so, mostly because the health effects of asbestos use (e.g., the increased incidence of mesothelioma) are not observable until several decades later.

The following two contrastive questions, therefore, are not mutually or self-contradictory:

- Q_A : Does an asbestos ban lead to a decrease in mesothelioma incidence?
- Q_B : Does a high mesothelioma incidence lead to an asbestos ban?

Q_A was tested by the studies introduced in Sect. 2.2, although the timing was too early to observe the full effect in a global analysis. However, Q_B remains to be investigated in both a global analysis and by analyzing national-level data.

3 Conclusion: The Need for International Cooperation

A wide consensus holds that mesothelioma is caused specifically by exposure to asbestos. Although researchers continue to study other possible causes and contributing factors, including the role of genetics, mesothelioma is currently unique among cancers in having one confirmed cause. It has been established that contact with asbestos occurs via occupational exposure, non-occupational exposure to building/industrial/natural sources, and household exposure. If these statements are true, and if asbestos exposure can be eliminated via banning asbestos, it will naturally follow that mesothelioma will be eliminated, or at least substantially reduced, by a ban.

Given that around 70 countries have already banned asbestos (the earliest being Iceland in 1983) [26], it is theoretically possible to construct an analytical framework to examine the effect. In reality, however, only a few analytical studies have addressed asbestos bans in relation to mesothelioma incidence, because researchers may have considered it difficult to detect such an association. This, in turn, could reflect that: (1) it may be too early to observe the full effect in view of mesothelioma's long latency period; (2) it is uncertain how an asbestos ban relates to the elimination of exposure; (3) the term "asbestos ban" covers a wide range of national situations and processes; and (4) asbestos usage can be reduced in relation to, or independent of, an asbestos ban. Nevertheless, two studies [30, 31] have suggested that asbestos bans have caused subsequent decreases in mesothelioma incidence.

Today many industrializing countries continue to use asbestos despite the abundant science on ARDs. It is thus important to share the experience and expertise of asbestos-banned countries. It will also be important to answer the yet-unaddressed question of "Did an increase in mesothelioma incidence lead to an asbestos ban in some countries?" High priority should be given to promoting asbestos bans while simultaneously improving mesothelioma diagnosis in the scheme of international cooperation with developing countries.

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