



Epidemiology of mesothelioma in the 21st century in Europe and the United States, 40 years after restricted/banned asbestos use

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Abstract: Research has established a strong association between asbestos exposure and malignant mesothelioma, a deadly form of cancer. Since the early 1980's many countries have restricted or banned the production of asbestos, leading to a decline of occupational asbestos exposure in many industrialized countries. However, some countries continue to use asbestos, and worldwide rates of mesothelioma are still increasing. Because of the long latency between exposure and mesothelioma occurrence and the persistence of environmental exposure, incidence rates (IR) may decrease very slowly for several years ahead. In this review, we examine estimates of asbestos consumption before widespread asbestos regulations and the trends in incidence and mortality rates, as well as changes over time for the United States and Europe. In some countries with earlier asbestos restrictions, mesothelioma incidence has been in a modest decline over time. However, asbestos exposure is still a burden worldwide and legislative action is needed to obtain a full ban. The pattern of mesothelioma is shifting from a mostly male disease to a disease that affects females as well in substantial numbers. Studies on unknown sources of asbestos exposure, of other sources of natural exposure to asbestos and asbestos-like fibers, as well as of individual genetic susceptibility to asbestos fibers are needed.

Keywords: Carcinogen regulation; environmental exposure; incidence trends; mortality

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Introduction

Mesothelioma is a rare, but deadly form of cancer, arising in the mesothelial surfaces (1) in the pleura, peritoneal, and pericardial cavities; the most common form of mesothelioma, accounting for 65–70% of all cases, is malignant pleural mesothelioma followed by peritoneal (30%) and pericardial mesothelioma (1–2%) (2). There are three subtypes, according to the histological morphology: epithelial, sarcomatoid, and biphasic (1).

Mesothelioma has a very poor prognosis with a median survival from the time of presentation of approximately 9–12 months (3). Despite the introduction of modern

therapeutic interventions, only modest changes in survival are observed over time (1). There is a well-established causal relationship between asbestos exposure and malignant mesothelioma, although the latency period can be long. Research suggests that the average latency period is approximately 40 years, although in some cases, it may be as long as 60–70 years (4–9). The association with asbestos exposure is especially strong for the pleural site, where 80% of patients report a history of asbestos exposure (2). Among asbestos highly exposed individuals, the lifetime risk of mesothelioma can vary from 5–10% to 25% (3,4,10). Increased knowledge and better regulations since the early 1980's, with restrictions or bans on production and use of

asbestos in many developed countries has led to abatement of exposure, particularly in the occupational setting. Four subsequent bans on asbestos between 1973 and 1989 in the United States (US) resulted in decreased asbestos consumption and production, followed by a decline of mesothelioma incidence and mortality rates 20 years later (11). However, despite bans, people may still be exposed to asbestos, due to its presence in several structures such as schools or public buildings, and the construction of residential areas in close proximity to former asbestos mines, factories, or soil containing natural asbestos. Thus the disease burden associated with environmental asbestos exposure remains difficult to quantify and is understudied (6,7,12). Furthermore, a ban on the use and production of asbestos has not been implemented globally; countries that have a ban instituted it at different points in time (5), making the estimate of the future mesothelioma risk in the general population uncertain.

The goal of this report is to provide an overview of asbestos use, and mesothelioma incidence and mortality in the US and Europe [defined as the 53 countries in the European region of the World Health Organization (WHO)] (13), within the context of changes in asbestos policies around the world.

Data sources and methods

This report used several publicly available data sources. Asbestos consumption (calculated as production plus imports minus exports) was assessed per capita, in 1980 and 2007, using reports from the United States Geological Survey (USGS) (14,15), with population estimates compiled by the World Bank (16). Negative values of asbestos consumption (reflecting export of storage from previous years) were treated as zero. Overall and age specific mesothelioma incidence rates (IR) [2008–2012] were extracted from the Cancer Incidence in Five Continents Volume XI (CI5 Vol. XI) data made available by the WHO and the International Agency for Research on Cancer (IARC) (17). IR over time were calculated using Surveillance, Epidemiology, and End Results (SEER) data (18) (US) and WHO C15*plus* data (Europe) (17,19), which includes annual incidence of selected cancers for the longest possible period. For this analysis, only registries with continuous information from 1980–2012 were included (SEER-9 Registries for the US; Denmark, France Calvados, France-Doubs, France-Isere, Germany-Saarland, Iceland, Israel, Italy-Parma, Norway, Switzerland-Geneva and UK-Scotland for Europe).

Mortality rates were queried from the IARC WHO Cancer Mortality Database (20). All incident and mortality rates are age-adjusted to the world standard population (21).

Results

Worldwide bans on asbestos and asbestos consumption

Since the 1970's, countries have banned asbestos to varying degrees, with 67 countries worldwide having a total ban, as of July 15, 2019 (22). Although the US banned some forms of asbestos in 1973, and attempted to ban most asbestos-containing products in 1989 through the Toxic Substances Control Act, the ban was overturned in 1991 (23). To this day, the US does not have a full nationwide ban on asbestos. However there are many laws regulating the use of asbestos at the federal, state, and local level (24). In Europe, individual regulations banning asbestos were passed from the 1980's through the early 2000's in many countries (13,22,25,26). Member states of the European Union (EU) banned five of the six types of asbestos in 1991 (amosite, crocidolite, anthophyllite, tremolite, and actinolite) and a ban prohibiting the new use of chrysotile went into effect on January 1, 2005 (27). Details of asbestos bans, by country are shown in *Table 1* (13,22,25,26).

Previous research (5,13) has defined asbestos consumption >1 kg/capita/year as "high", as it corresponded to a 2.4- and 1.6-fold increase in mesothelioma deaths among men and women, respectively. Consumption >2 kg/capita/year was considered "very high". Data from 1980 (14), before asbestos bans were widely implemented, show that asbestos consumption was very high in some parts of Europe, exceeding 5 kg/capita in the former Soviet Union (estimates for Russian Federation and Kazakhstan: 9.6 kg/capita), Cyprus (7.4 kg/capita), Germany (5.6 kg/capita), and former Yugoslavian states (combined estimates for all former Yugoslav nations: 5.2 kg/capita). Asbestos consumption for Belgium and Luxembourg (4.7 kg/capita), Hungary (4.0 kg/capita), Switzerland (3.3 kg/capita), Italy (3.2 kg/capita), Czech Republic and Slovakia combined (3.1 kg/capita), Austria (2.7 kg/capita), Denmark (2.7 kg/capita), Ireland (2.5 kg/capita), Poland (2.3 kg/capita), France (2.3 kg/capita), and Portugal (2.04 kg/capita) all exceeded 2 kg/capita, while it exceeded 1 kg/capita in Spain, Greece, United Kingdom, Netherlands, and Finland. Consumption in the US was also high at 1.6 kg/capita (*Figure 1A*), although it was already in decline from its peak in the early 1970's (28).

Table 1 Asbestos bans and regulations in the United States and Europe

Country	Year	Description
United States	1973	Ban on spray-applied surfacing asbestos-containing material for fireproofing and insulation
	1989	Toxic Substances Control Act bans most asbestos-containing products
	1991	Ban overturned, no current nationwide ban
European Union		
Austria [†]	1990	Ban on chrysotile asbestos
Belgium [†]	1998	Ban on chrysotile asbestos is introduced
Bulgaria	2005	Ban on import, production, and use of all asbestos
Croatia	1993	Ban on crocidolite and amosite
	2006	Asbestos added to list of prohibited substances, in line with EU regulations, but ban is not thought to be well enforced
Cyprus [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Czech Republic [†]	1998	Ban on the import of asbestos
	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Denmark [†]	1980	Ban on uses of asbestos, with exceptions
	1985	Extends ban to include asbestos cement products, further restrictions in 1986–1988
Estonia [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Finland [†]	1992	Phase-out ban on chrysotile
France [†]	1996	Ban on chrysotile
Germany [†]	1993	Ban on chrysotile asbestos (minor exemptions), amosite and crocidolite were banned previously
Greece [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Hungary [†]	1988	Ban on amphibole asbestos, with further bans on non-chrysotile asbestos in 1992, 2001, and 2003
	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Ireland [†]	2000	Ban on chrysotile asbestos
Italy [†]	1992	Ban on all types of asbestos (with some exceptions until 1994)
Latvia [†]	2001	Ban on asbestos (some exemptions)
Lithuania [†]	1998	First law restricting asbestos use
	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Luxembourg [†]	2002	Phase out ban on asbestos
Malta [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Netherlands [†]	1991	First in a series of bans on chrysotile
Poland [†]	1997	Ban on all asbestos
Portugal [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Romania	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Slovakia [†]	2005	Prohibits new use of chrysotile, other forms of asbestos previously banned under EU regulations
Slovenia [†]	1996	Ban on production of asbestos cement products

Table 1 (continued)

Table 1 (continued)

Country	Year	Description
Spain [†]	2002	Phase out ban on asbestos
Sweden [†]	1982	First in a series of bans on various uses of asbestos
	1986	Ban on use of all asbestos products
United Kingdom [†]	1999	Ban on chrysotile asbestos, with minor exceptions
Other European nations		
Albania	–	No ban
Andorra	–	No ban
Armenia	–	No ban
Azerbaijan	–	No ban
Belarus	–	No ban
Bosnia and Herzegovina	–	No ban
Georgia	–	No ban
Iceland	1983	Ban on all types of asbestos (with exceptions); bans updated in 1996
Israel	1980	Series of restrictions on asbestos, which eventually became a de facto ban
Kazakhstan	–	No ban
Kyrgyzstan	–	No ban
Monaco	2016	Total ban on all forms of asbestos
Montenegro	–	No ban
North Macedonia	2014	Total ban on all forms of asbestos
Norway	1984	Ban on all asbestos
Republic of Moldova	–	No ban
Russian Federation	–	No ban
San Marino	–	No ban
Serbia	2011	Ban on all asbestos
Switzerland	1989	Ban on crocidolite, amosite, and chrysotile
Tajikistan	–	No ban
Turkey	2010	National regulation banning use of all types of asbestos
Turkmenistan	–	No ban
Ukraine	2017	Complete ban on asbestos announced, implementation may be delayed
Uzbekistan	–	No ban

[†], members of the European Union as of 2005, subject to the directive mandating all member states ban new uses of chrysotile. Other forms of asbestos were banned in 1991 for EU member states. All member states of the EU, Iceland, Israel, Macedonia, Monaco, Norway, Serbia, Switzerland, and Turkey have banned the use of all types of asbestos, as of July 15, 2019. EU, European Union.

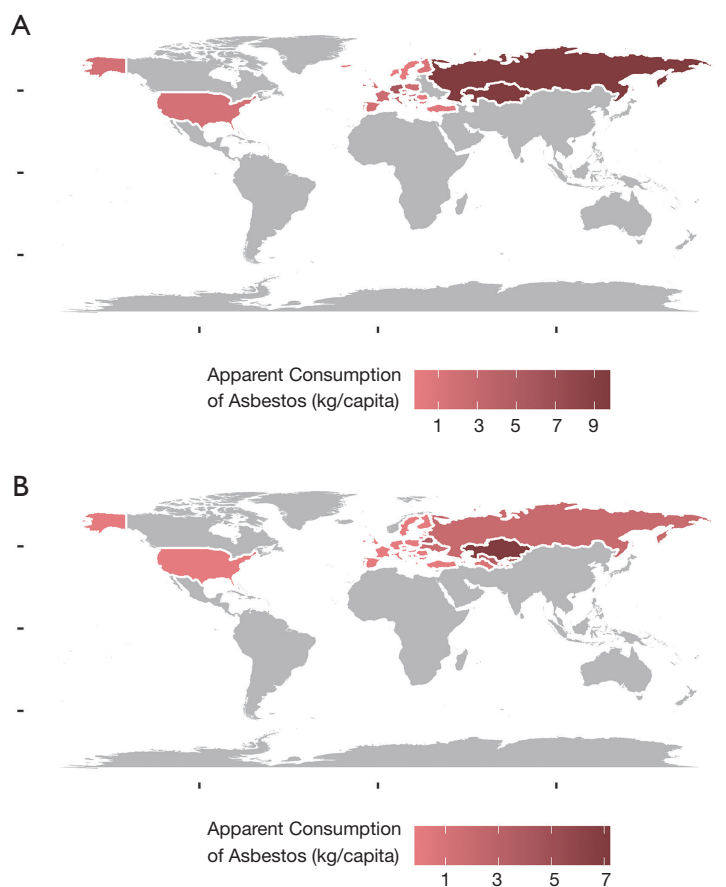


Figure 1 Apparent consumption (kg/capita) of asbestos in (A) 1980 and (B) 2007 in the United States and Europe.

The most recent available data refer to 2007 (15), and indicates that asbestos consumption has declined considerably in most countries in the years since bans were enacted (or attempted) (*Figure 1B*). US consumption was 0.003 kg/capita in 2007, while most of the countries in the EU had decreased to 0 (or nearly 0) kg/capita. Asbestos consumption remained high or very high in Kazakhstan (7.0 kg/capita), Kyrgyzstan (4.0 kg/capita), Belarus (3.5 kg/capita), Uzbekistan (3.2 kg/capita), Russian Federation (2.0 kg/capita), and Ukraine (1.8 kg/capita).

An advance report from the USGS for 2016 (29) indicates that consumption has started to decline in Ukraine (0.4 kg/capita) and Belarus (0.6 kg/capita), although it remains high or very high in the Russian Federation (1.6 kg/capita), Kazakhstan (1.4 kg/capita), Kyrgyzstan (1.1 kg/capita), and Uzbekistan (2.2 kg/capita).

Mesothelioma IR

Research has shown that IR of mesothelioma are lower in women than in men, and this difference has been attributed to historical differences in occupational asbestos exposure (30,31). From 2008 to 2012, the world standardized IR (WSIR), per 100,000 persons in the US was 0.9 for males and 0.3 for females. Overall in Europe, the WSIR per 100,000 was 1.7 for males and 0.4 for females. Data is limited for nations of the former Soviet Union, Russian Federation and former Yugoslavia, but for those with data, reported WSIR for males and females were 0.5 and 0.3 (Russian Federation), 1.5 and 0.3 (Croatia), and 1.5 and 0.5 (Slovenia) per 100,000 persons. In some of the other countries with very high asbestos consumption, WSIR remain high, particularly for males versus females: 2.0 and 0.4 (Belgium), 2.0 and 0.3 (Switzerland), 1.9 and 0.3

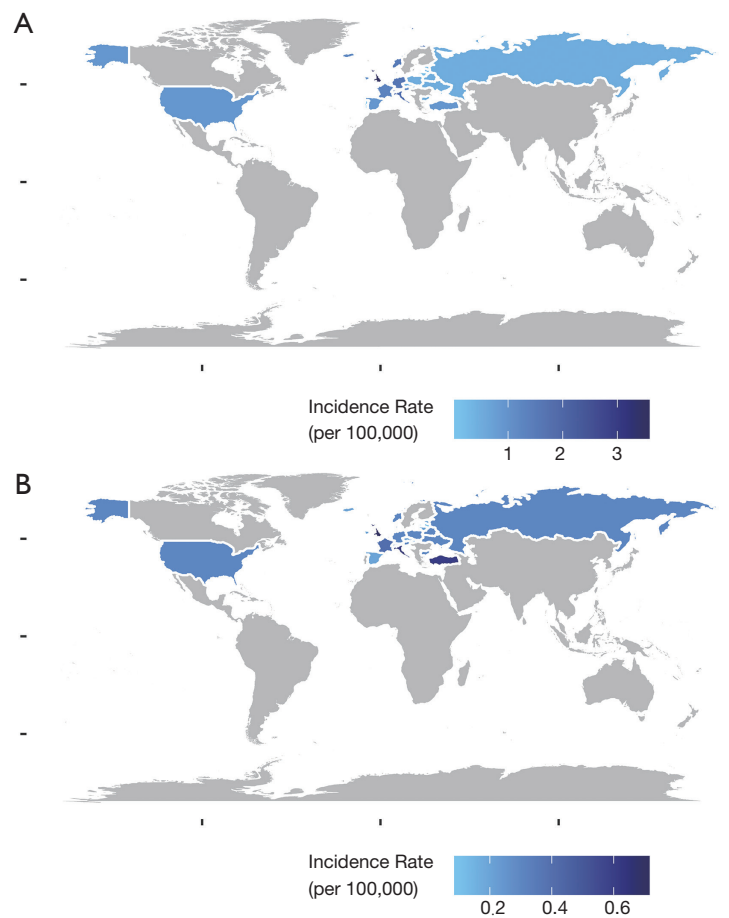


Figure 2 World standardized incidence rates of mesothelioma in the United States and Europe for (A) men and (B) women, 2008–2012.

(Denmark), 1.8 and 0.6 (Italy), and 1.6 and 0.3 (Germany) per 100,000 persons. WSIR are also very high in the Netherlands (2.8 in males and 0.4 in females), and United Kingdom (3.4 and 0.6) (Figure 2). As women generally are less likely to be occupationally exposed, the high WSIR in females observed in certain countries, such as Italy, United Kingdom, and Turkey may indicate other sources of exposure that are difficult to detect, such as higher levels of environmental exposure. The classification of environmental, non-occupational exposure to asbestos is very heterogeneous in the literature and often includes (I) areas with naturally occurring asbestos, (II) neighborhood exposure based on residence in close proximity to industrial/mining sources of asbestos, and (III) household exposure for family members of occupationally exposed people, of which the latter two are more specific exposure risk factors

for females (6). Furthermore, a caveat when comparing data collected in different countries is that there may be differences in patterns of reporting for mesothelioma, misclassification in diagnosis, or lack of the medical resources required to accurately diagnose the disease.

Age related patterns

Mesothelioma is extremely rare in younger subjects, with a sharp uptick in IR starting between 50–60 years of age (4). Prior to age 50, the annual WSIR in the US for males is ≤ 0.3 per 100,000 persons, while for females it is ≤ 0.2 . In Europe, the rates are ≤ 0.6 per 100,000 for males and ≤ 0.4 per 100,000 for females for the same age group. In the US, the IR for males aged 50–54 years is 0.6 per 100,000, while for females it is 0.4 per 100,000. The rate

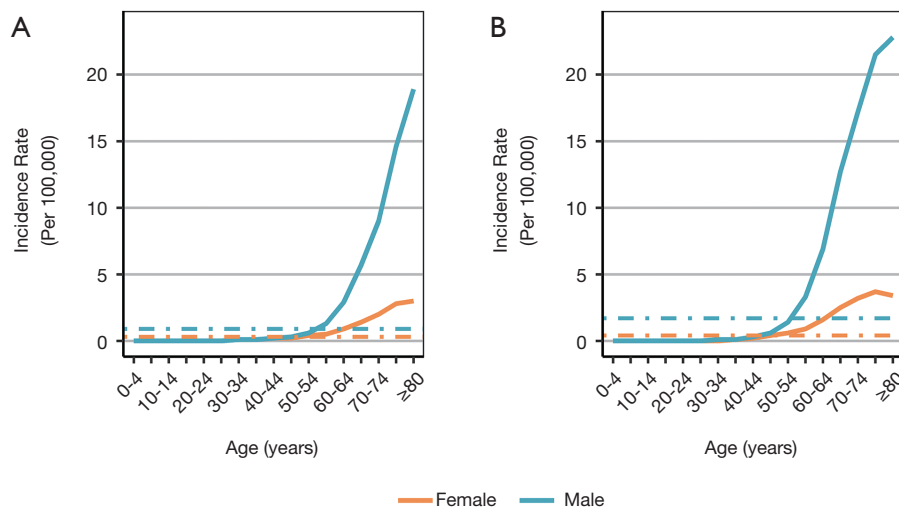


Figure 3 Age specific annual incidence rates [2008–2012], for (A) United States and (B) Europe, by gender.

starts climbing faster in Europe, with an IR of 1.4 per 100,000 for males, and 0.6 per 100,000 for females at age 50–54 years. As people age, this gap across the US and Europe continues to widen, particularly for males. For those ≥ 80 years, the IRs for males in the US and Europe are 18.9 and 22.8 per 100,000, respectively; for females, it is 3.0 and 3.4 per 100,000 (*Figure 3*).

Time trends

Given the long latency period of mesothelioma (approximately 40 years, on average) (4), we may now just be beginning to see the effects of asbestos bans. In the US there is no official ban in place, however attempts were made to ban asbestos as far back as 1973, and as a result general consumption was lower in 1980 in the US as compared to Europe. Over time, the IR has started to decline in the US from 1980–2016, mostly driven by a decline in the IR for males, while females have mostly held steady (*Figure 4A*). In Europe, rates of mesothelioma were rising sharply in the early 2000's, and may just now be beginning to level off (*Figure 4B*). This may be partly due to the later introduction of asbestos bans in parts of Europe, and the higher consumption observed at least 40 years ago in many geographic areas. As overall rates have slowly fallen in the US, and risen in Europe, with steady rates for females, females now make up a larger portion of those with mesothelioma in the US than in Europe (*Figure 4C*).

Mesothelioma mortality

Survival rates for mesothelioma are low, with estimated median survival of 9–12 months (3). Research has shown that females have significantly better overall survival (32–34), and speculated reasons include less amount and duration of exposure (35), more favorable clinical characteristics (36,37), and protective effects of estrogen (38,39). For countries in which IR and mortality rates were available, the ratio of the mortality rate to the IR was calculated. In almost all cases, this ratio exceeds 0.5, and in many cases exceeds 0.75, indicating high mortality rates among those with mesothelioma. Generally, the ratio was lower for females (*Table 2*), reflecting the better survival reported by individual studies for females with all forms of mesothelioma.

Comment

Although the US recognized the dangers of asbestos exposure early and in 1973 produced the first asbestos regulation followed by a complete ban in 1989, the country currently has no nationwide ban. Many countries in Europe independently implemented partial or total asbestos bans in the 1980's and 1990's, while member states of the EU banned most types of asbestos in 1991, with a complete ban on all remaining types of asbestos in effect starting in 2005. However, many non-EU states implemented bans

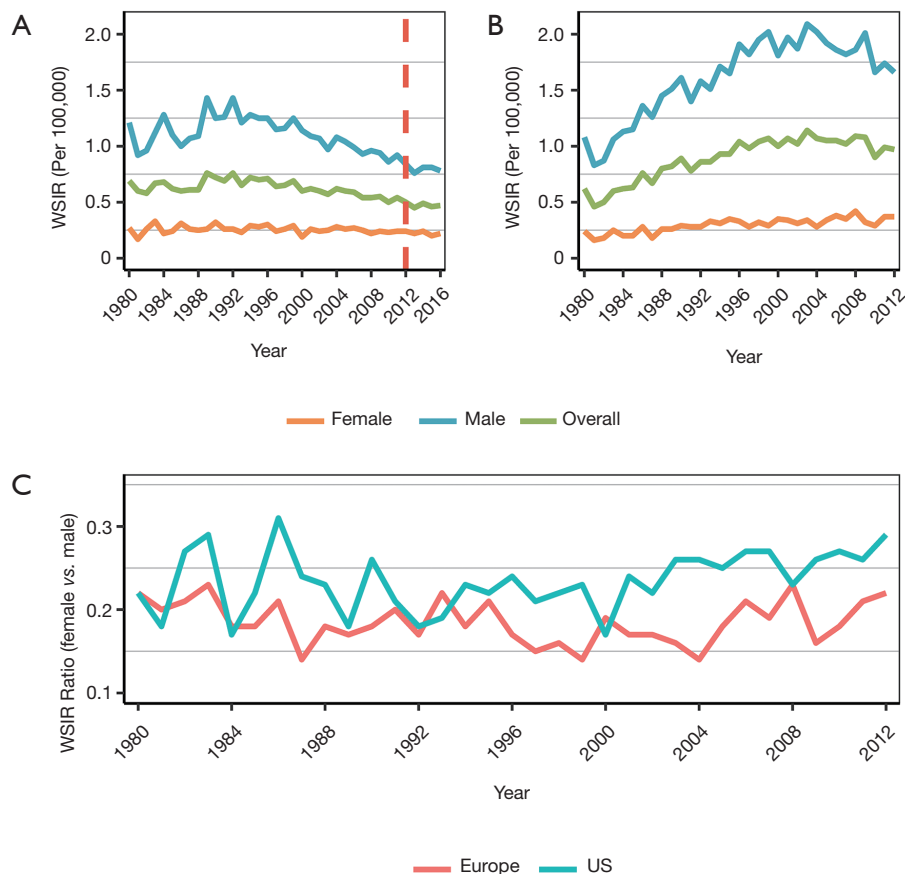


Figure 4 World standardized incidence rates (per 100,000) over time, overall and by gender in the (A) United States, and (B) Europe. (C) Ratio of world standardized incidence rates for females vs. males, over time in the United States and Europe.

later, while some still have no ban in place. The difference in the timeframe for asbestos ban legislation in the US and Europe, combined with a latency period of decades between exposure and mesothelioma partly explains why a slight decrease in mesothelioma standardized IR is seen in the US, consistent with previous research (11), while the incidence has just started to level off in Europe. There is speculation that the observed decrease in mesothelioma incidence is slower than projected (40), and that other factors, including individual genetic susceptibility, could play a role (41).

However, observational data from cancer registries prove that legislation on asbestos use and production is an effective way to decrease occupational exposure to asbestos, and therefore, mesothelioma rates in the general population, especially in males. Current legislation is insufficient to address neighborhood asbestos exposure based on residence in close proximity to industrial/mining sources of asbestos and household asbestos exposure for family members of

occupationally exposed people, as well as other sources of environmental exposure. To further decrease risk from environmental asbestos exposure, legislation for building in regions with naturally occurring asbestos should be explored. These results stress the need for a global forum to urge countries that currently don't have an asbestos ban to start implementing appropriate legislation.

One interesting observation is that any change in IR is mainly caused by a decrease in mesothelioma occurrence among males, while the IR of mesothelioma for females remains more stable. This may reflect the fact that asbestos exposure has shifted from occupational, mostly present in males, to environmental exposure, and indicates that current asbestos regulations do not sufficiently consider all sources of environmental exposure. The male/female (M/F) ratio has been used as a relatively reliable surrogate to distinguish environmental from occupational exposure (6,7), with a M/F ratio approaching one as a sign

Table 2 Ratio of annual world standardized mortality rates to incidence rates [2008–2012], by country, for males and females

Country	Mortality rate to incidence rate ratio [2008–2012] [†]	
	Male	Female
United States	0.89	0.67
Austria	0.82	1.00
Belgium	0.80	0.75
Bulgaria	0.20	0.00
Croatia	0.87	1.00
Cyprus	0.62	0.33
Czech Republic	0.75	0.50
Denmark	0.68	1.00
Estonia	1.00	0.50
France	0.85	0.75
Germany	0.69	0.67
Iceland [†]	0.42	1.00
Ireland	0.90	0.50
Israel	0.86	0.50
Italy	0.83	0.67
Latvia	1.00	1.00
Lithuania	1.00	1.00
Malta	0.74	1.00 [‡]
Netherlands	0.89	0.75
Norway	0.80	0.67
Poland	0.80	0.67
Portugal	0.60	–
Slovakia	0.29	0.50
Slovenia [†]	0.60	0.80
Spain	0.67	1.00
Switzerland	0.90	0.67
United Kingdom	0.88	0.83

[†], combined incidence rates are available from 2008–2012. Combined mortality rates are queried from all years available from 2008–2012 for each country. For some countries, not all years from 2008–2012 were available. [‡], due to data from difference sources, some mortality rates exceed incidence rates for the same time frame. Those ratios are recorded as 1. Russian Federation, Turkey, Ukraine, and Belarus reported incidence rates, but no mortality information. Armenia, Finland, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Luxembourg, Republic of Moldova, Romania, Serbia, and Sweden, reported mortality rates, but not incidence information. Albania, Andorra, Azerbaijan, Bosnia and Herzegovina, Greece, Macedonia, Monaco, Montenegro, San Marino, Tajikistan, Turkmenistan, and Uzbekistan reported no mesothelioma information.

that environmental exposure plays a more important role. The identification of current sources of environmental exposure to asbestos and the associated health effects in the general population remains an important area of future research, including the identification of geographic areas where asbestos is naturally present in the environment (42). The difference in incidence with gender is of special importance because females with malignant mesothelioma have a significantly better survival than males, although the precise reasons for this observation are still uncertain (32,33). Given the positive effects of legislation on occupational exposure to asbestos, the next step will be to shift the focus of research and legislation to environmental sources of asbestos exposure, in order to target all potential avenues of asbestos exposure. Because mesothelioma is a rare but deadly disease, and combined with the changing landscape of asbestos exposure, mesothelioma registries capturing mesothelioma cases in real-time are of utmost importance to investigate the many unanswered scientific questions. Countries with mesothelioma registries are able to research and respond to the current scientific and legislative needs associated with mesothelioma incidence and mortality.

In conclusion, we report here the status of mesothelioma epidemiology in the recent years, and observe that asbestos exposure is still a burden worldwide, and legislative action is needed to obtain a complete ban. The pattern of mesothelioma is shifting from a mostly male disease to a disease that affects females as well in substantial numbers. Studies on unknown sources of asbestos exposure, of other sources of natural exposure to asbestos and asbestos-like fibers, as well as of individual genetic susceptibility to asbestos fibers are needed.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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