

Review Article

Elimination of asbestos use and asbestos-related diseases: An unfinished story

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Asbestos is a proven human carcinogen. Asbestos-related diseases (ARDs) typically comprise lung cancer, malignant mesothelioma, asbestosis, pleural plaques, thickening and effusion. International organizations, notably the World Health Organization and the International Labour Organization, have repeatedly declared the need to eliminate ARDs, and have called on countries to stop using asbestos. However, the relevant national-level indicators (e.g., incidence/mortality rates and *per capita* asbestos use, as well as their interrelationships) indicate that ARDs are increasing and asbestos use is continuing in the world. Lessons learned by industrialized countries in terms of policy and science have led to a growing number of countries adopting bans. In contrast, industrializing countries are faced with a myriad of forces prompting them to continue using asbestos. Full-scale international cooperation will thus be needed, with industrialized countries sharing their experiences and technologies to enable industrializing countries to make smooth transitions to banned states and achieve the goal of eliminating ARDs. (*Cancer Sci* 2012; 103: 1751–1755)

Asbestos is a proven human carcinogen. The World Health Organization (WHO) asserts that “asbestos is one of the most important occupational carcinogens causing about half of the deaths from occupational cancer”.⁽¹⁾ Asbestos is also often exemplified as a chemical pollutant and environmental carcinogen. Cancers for which avoidable exposure is a factor, particularly exposure to chemicals at the workplace and in the environment, warrant special attention.^(1–3) Accordingly, the WHO and the International Labour Organization (ILO) have together called on countries to eliminate asbestos-related diseases (ARDs)^(2,4) and to address their root cause, the use of asbestos.⁽¹⁾ Many industrialized countries, including Japan, have banned asbestos use.^(5,6) ARDs are reported to have passed their peak in some industrialized countries,^(7–10) but we argue herein that, from a global perspective, neither the asbestos use nor ARD is a finished story.

What is Asbestos?

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers of the serpentine and amphibole series. These include the serpentine mineral, chrysotile (white asbestos) and the five amphibole minerals, crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, tremolite and actinolite.⁽¹¹⁾ The composition of chrysotile is close to the ideal unit cell formula $(Mg_3Si_2O_5(OH)_4)_n$; it is a hydrated magnesium silicate, with possible substitution by other elements in the crystal structure.⁽¹²⁾ In scale, asbestiform

minerals have large fiber lengths (such as 5–10 μm) and small fiber diameters (usually under 1 μm).⁽¹³⁾ Commonly, only fibers over 5 μm in length with an aspect ratio >3:1 and a diameter of <3 μm are counted, meaning that the fiber count should be regarded only as an index of the actual numbers of fibers present in a sample.⁽¹⁴⁾

Asbestos use began 4500 years ago. During the 20th century it became known as the “magic mineral” due to its wide industrial applications, which include asbestos-cement products (flat and corrugated panels as well as pipes); automotive applications (brakes, clutch components and engine gaskets); insulation for boilers, steam pipes and electrical wiring; spray-on asbestos products for protecting steel girders in buildings; and reinforcing, heat-resistant fillers for plastics.⁽¹⁵⁾ The demand for asbestos peaked around 1977, when some 25 countries produced a combined total of 4.8 million metric tons per year, and some 85 countries overall manufactured asbestos products.⁽¹⁵⁾ Global use has decreased since then, but remained fairly stable at 2.1 million metric tons per year during 2003–2007.⁽¹⁶⁾ The majority of this volume was consumed by industrializing countries, notably Asian and Commonwealth of Independent States (CIS) countries.^(16–18) Chrysotile represents 95% of the asbestos used worldwide since 1900,⁽¹⁹⁾ and virtually all of the asbestos used today. Currently, 90% of asbestos is used to manufacture asbestos-cement building materials,⁽¹⁾ and asbestos remains a popular raw material for construction industries in the developing world.^(20,21)

We previously demonstrated that countries increase their asbestos use proportionally to their economic development, as measured by *per capita* Gross Domestic Product (GDP).⁽²²⁾ However, after a country reaches a certain level of economic development, the trend reverses, following a trajectory with a turning point at around 10 000–15 000 Geary-Khamis Dollars *per capita* GDP (a hypothetical monetary unit used to enable comparisons across countries and over time).^(23,24) At present, industrializing countries are exactly following the early trajectory curve once followed by industrialized countries, and there are strong economic incentives behind the dependence of industrializing countries on asbestos. Around 125 million people are estimated to be occupationally exposed to asbestos each year.⁽¹⁾ Many industrialized countries have adopted total bans on asbestos, but only after suffering serious disease burdens.

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What are Asbestos-related Diseases?

Asbestos-related diseases typically comprise lung cancer, malignant mesothelioma, asbestosis (fibrosis of the lungs), pleural plaques, thickening and effusions.⁽¹⁾ Most ARDs are thus pulmonary, except for the peritoneal type of mesothelioma. In 2009, however, the International Agency for Research on Cancer (IARC) concluded that several non-pulmonary forms of cancer can be caused by exposure to asbestos; cancers of the larynx and ovary were linked with sufficient evidence, and those of the colorectum, pharynx and stomach were linked with limited evidence.^(11,25) Asbestos exposure may also be associated with risks of systemic autoimmune disease,⁽²⁶⁾ and a possible link between asbestos exposure and cardiovascular disease was recently proposed.⁽²⁷⁾ A common feature of ARDs in general and asbestos-related cancers in particular is the long latency period between the first exposure and disease onset. The clinical diagnosis of ARDs thus requires a detailed patient interview and occupational data on asbestos exposure and its appropriate latency. Histopathological confirmation is required for suspected asbestos-related cancers and for resolution of differential diagnoses.⁽²⁸⁾ In Japan, the administrative definition of ARDs includes five entities: (i) mesothelioma; (ii) lung cancer; (iii) asbestosis; (iv) diffuse pleural thickening; and (v) benign pleural effusion under the Workmen's Compensation Law (Ministry of Health, Labor and Welfare),⁽²⁹⁾ and four entities (points i–iv above with highly impaired lung function added to iii and iv) under the Asbestos Health Damage Relief Law (Ministry of Environment).⁽³⁰⁾

Malignant mesothelioma stands out among the ARDs because, (i) there is a direct causal relationship with asbestos exposure,⁽³¹⁾ with an etiological fraction of 80% or more,^(28,32) (ii) prognosis is poor, with a median survival time of 9–12 months after diagnosis,⁽³¹⁾ and (iii) although it is still a rare cancer, its incidence is increasing in many countries.^(33–36) The latency time from first exposure is usually between 30 and 50 years, and is presumed to be the longest among occupational cancers. To describe the global baseline, we recently analyzed all mesothelioma deaths recorded in the WHO mortality database.⁽³⁶⁾ Eighty-three countries reported 92 253 mesothelioma deaths during the observed period of 1994–2008, yielding crude and age-adjusted mortality rates of 6.2 and 4.9 per million individuals, respectively. The mean age at death was 70 years, and the male-to-female ratio was 3.6:1. The age-adjusted mortality rate increased by 5.4% per year, more than doubling during the observed period.⁽³⁶⁾

The WHO has officially declared that all commercial types of asbestos (chrysotile, crocidolite, amosite, anthophyllite, tremolite and actinolite) cause cancer in humans.⁽¹⁾ This position reflects that of the IARC,⁽³⁷⁾ which has repeatedly stated since 1973 that there is sufficient evidence to support the carcinogenicity of all asbestos types. Although the potency differences among fibers of various types and dimensions have been debated with respect to lung cancer and mesothelioma, the fundamental conclusion is that all forms of asbestos are carcinogenic to humans.⁽²⁵⁾

The Ecological Perspective

We have published a series of articles examining national indicators for the levels of asbestos use and ARD rates.^(17,38,39) The first article⁽³⁸⁾ assessed the geographical correlation (i.e., the ecological relationship) between the mesothelioma rate and asbestos use in ten Western countries and Japan. The data point for mesothelioma deaths in Japan in 1995 fell outside the otherwise linear relationship found for Western countries, prompting us to propose that the historical pattern of asbestos use in Japan had lagged behind that of Western countries, and

thus the cumulative exposure effect had not yet reached the level experienced by Western countries at this point.⁽³⁸⁾ In a follow-up study,⁽³⁹⁾ we refined our statistical analysis and incorporated mortality data from all available countries regarding pleural and peritoneal mesothelioma and asbestosis. We found that historical asbestos use explained 74% of the variation for mesothelioma and 79% of that for asbestosis (both $P < 0.0001$). An increment of 1 kg *per capita* asbestos use corresponded to a 2.4-fold increase in mesothelioma and a 2.7-fold in asbestosis.⁽³⁹⁾ Notably, the abovementioned Japanese data was no longer an outlier in our updated analysis.

Given that historical levels of asbestos use appeared to predict the rates of ARDs, we next asked whether and how the adoption of an asbestos ban would subsequently impact a country's disease rates.⁽⁴⁰⁾ We considered an asbestos ban as a national intervention and related it to the rate of pleural mesothelioma. We found that the adoption of an asbestos ban doubled the pace of reduction in asbestos use, and observed that changes in asbestos use during 1970–1985 correlated with changes in the age-adjusted mortality rates of pleural mesothelioma during 1996–2005 ($R^2 = 0.47$, $P < 0.0001$).⁽⁴⁰⁾ The implication was that bans reduced the use of asbestos, which in turn decreased the subsequent rates of pleural mesothelioma. However, we also noted that the bans were preceded by turning points in asbestos use, and our observation period for disease rates probably did not extend far enough to encompass the full effects of the asbestos bans.⁽⁴⁰⁾

We further applied the known correlation to estimate the number of ARD cases.⁽¹⁷⁾ Because age-adjusted rates cannot be used to estimate the number of cases, we first examined the relationship between the 15-year cumulative number of reported mesothelioma cases during 1994–2008 and cumulative asbestos use during 1920–1970 among countries with data on both mesothelioma and asbestos use. The resulting relationship was then used to estimate the cumulative number of unreported mesothelioma cases (i.e., the hidden burden of disease) for countries that do not report statistics for mesothelioma. A total of 39 000 unreported cases were estimated for 33 countries over the 15-year period, led by Russia (21 308 estimated missing cases), Kazakhstan (6500), China (5107), India (2158) and Thailand (545).⁽¹⁷⁾

Ecological relationships are often criticized for their “ecological fallacy”, i.e., the error in drawing individual-level causal inferences from relationships observed using aggregate data. In the case of ARDs, however, there is wide consensus that the evidence for causality is sufficient. Our primary motive for evaluating the ecological relationships of ARD has been to describe the relationships of national-level factors and suggest policy implications. Furthermore, national indicators *per se* often provide good insight. For example, Asia (as defined by the United Nations) accounts for 64% of the world's current asbestos use but only 13% of recent asbestos-related deaths in the WHO mortality data.⁽¹⁸⁾ This probably reflects the fact that Asia used smaller amounts of asbestos in previous decades, but suggests that it is likely to become a global center of ARDs in the future.⁽⁴¹⁾ We must also keep in mind that a lack of data should not be interpreted as indicating that a country does not have any problem with asbestos-related issues. For example, although no asbestos-related statistical data are available for the US-affiliated Pacific islands, abatement and disposal of asbestos is known to take place.⁽⁴²⁾

The Japan Asbestos Episode

On 29 June 2005, the media reported that 51 deaths due to ARDs had occurred among former and current employees of a major machinery company that had historically manufactured asbestos-containing products (ACPs).⁽⁴³⁾ The number of

involved “asbestos victims” grew to include not only former employees but also residents who had lived near the company. Gradually, similar stories came to light throughout the country in relation to asbestos-heavy and -using industries. Non-government organizations (NGOs) played active roles in identifying victims, tracing perpetrators and pressuring the government to act more strongly. The media intensely covered related issues for more than a year, impacting Japanese society at large⁽⁴⁴⁾ with the recognition of a social problem that became known as “the Kubota Shock”.

In 1971, the Ordinance on Prevention of Hazards due to Specified Chemical Substances implemented work-environment measurement of asbestos in Japanese asbestos-handling workplaces,⁽⁴⁵⁾ and a 1975 amendment prohibited the spraying of asbestos and mandated specific medical examinations for workers.⁽⁴⁶⁾ The use of crocidolite and amosite was prohibited in 1995 via amendment of the Enforcement Order (EO) of the Industrial Safety and Health Law (ISHL). The ILO Asbestos Convention of 1986⁽⁴⁷⁾ prohibited the use of the two amphibole fibers, but Japan did not ratify the ILO Asbestos Convention until 2005,⁽⁴⁸⁾ after the Kubota shock. Asbestos was used at substantial levels in Japan until the mid-1990s, and has been used at much lower levels since the turn of the century. Although many industrialized countries had adopted total or *de facto* bans of asbestos by this point, Japan maintained a “controlled-use”⁽⁴⁹⁾ policy until the painful lesson was finally learned, and lawmakers acknowledged that “the risks of exposure to asbestos cannot be controlled by technology or regulation”.⁽⁵⁰⁾

The Japanese government amended the EO of the ISHL to prohibit the manufacture of 10 designated products containing asbestos in 2004 (pre-Kubota Shock). However, this can be characterized as a “prohibition in principle”, in that it listed only prohibited items (i.e., it was a negative list). The importation of raw asbestos into Japan has ceased since 2005,⁽⁵¹⁾ presumably as a combined effect of the legal amendment and the Kubota Shock. On 1 September 2006 (the year after the Kubota Shock) the government adopted a total ban on asbestos⁽⁵²⁾ and published a list of exempted items (i.e., a positive list) that included joint sheets and gaskets for special purposes. The exempted items were thereafter progressively removed from the list, and were completely eliminated on 1 March 2012.^(6,46) From a policy perspective, therefore, the Kubota Shock of 2005 became the final tipping point leading to the complete banning of asbestos in Japan in the strictest sense.

The Unfinished Sequel

The WHO estimates that worldwide more than 107 000 people die each year from ARDs resulting from occupational exposure.⁽⁵³⁾ Asbestos-related lung cancers comprise the bulk of ARDs, but it is extremely difficult to estimate the precise fraction because it is hard to attribute causes to lung cancer, and the relevant criteria (mostly for compensation purposes) differ across countries. A convenient method for estimation is to apply the known ratio of mesothelioma to asbestos-related lung cancer. However, the values reported for occupationally exposed populations vary widely from 1:1 to 1:10,^(54,55) and it is debatable whether such ratios can be extrapolated to general populations. Thus, asbestos-related lung cancer presents a great challenge and an opportunity for future research.

The future estimation of mesothelioma was first pursued by Peto *et al.*,⁽³⁴⁾ whose work has been widely reproduced to form a subgenre in the medical literature.⁽⁵⁶⁾ The Peto⁽³⁴⁾ study used a birth-cohort model to predict the future number of male mesothelioma deaths in the UK, and the term “epidemic” was used to describe the future trend of mesothelioma

in several European countries.⁽³³⁾ These articles had a significant impact in showing that even a rare form of cancer could increase rapidly. In Japan, future predictions of male pleural mesothelioma deaths were first reported at a 2002 conference^(57,58) and published thereafter. Murayama *et al.*⁽³⁵⁾ estimated more than 20 times increase relative to the baseline level whereas Takahashi⁽⁵⁶⁾ estimated six to seven times increase relative to the baseline level. Unfortunately, neither study accounted for the historical patterns of asbestos use. These predictions should therefore be refined by the incorporation of updated incidence/mortality and population data, and the model should be validated with respect to accumulating real-world values.

Most future projections have been conducted for industrialized countries, and suggest that ARDs will continue to increase for many years to come.^(33,35,59,60) A few exceptions show indications of flattening or possible peak-outs,⁽¹⁰⁾ but these come from countries that substantially reduced asbestos use earlier than other countries.⁽⁴⁰⁾ Many industrialized countries, including Japan, are supposed to have taken stringent regulatory measures to prevent ARDs while using asbestos. Currently, however, no epidemiological data can be found to support the notion that these policies have effectively prevented ARDs. Furthermore, it is improbable that the industrializing countries currently using asbestos have implemented the relevant measures more effectively than the industrialized countries.⁽⁶¹⁾

The Predicaments of Industrializing Countries

Industrializing countries continue to use asbestos today, and some countries are even increasing their use. The lessons learned by industrialized countries have thus far been ignored and even contradicted by industrializing countries. Several interrelated factors may help explain this:

- 1 The industrial properties of asbestos, particularly its durability, cheapness and accessibility, are primary advantages that work as strong economic incentives.
- 2 Asbestos-related diseases have long latency periods, such as 30–50 years for mesothelioma. Thus, countries that started depending on asbestos <30–50 years ago have seen little, if any, indication of the related diseases. In fact, economic development in many industrializing countries has accelerated since the 1990s, with parallel increases in their asbestos dependence. Thus, the ARD latency time has not yet reached saturation in these countries.
- 3 Mesothelioma is still rare and ARDs are difficult to diagnose. Confirmatory diagnosis for mesothelioma and the attribution of lung cancer to asbestos exposure (i.e., the diagnosis of an asbestos-induced lung cancer) requires levels of clinical, pathological and social resources that are not yet available in industrializing countries.
- 4 Companies and countries with incentives to sell asbestos and ACPs have shifted their focus to industrializing countries⁽²⁰⁾ due to bans in many industrialized countries and growing demands from the construction sectors of industrializing countries.
- 5 External and internal sources create pressures on the governments and markets of industrializing countries.⁽⁵⁰⁾ These may include propaganda along the lines, for example, that whereas amphiboles are not, chrysotile is safe to use, which is a misreading (intentional or otherwise) of the position of international organizations and scientific consensus. Threats have been made against scientists who express opposition. The “pro-asbestos” lobbies of exporting parties use consultants and liaise with domestic parties possessing vested interests. Furthermore, certain labor

unions have claimed that asbestos use will help maintain employment, while some politicians have stated that asbestos helps the poor.

The above factors often converge in a manner unique to each industrializing country, causing government officials to claim, for example, that they are using asbestos, but do not have any ARDs.

The Case for Full-scale International Cooperation

The goal of eliminating ARDs is justifiable, and we believe that it should target both present and future ARD burdens. The key to countering the future burden is undoubtedly to stop the use of all asbestos,^(1,53) but we must also promote industrial hygiene during the transition period without compromising the cause for a total ban. The recognition, diagnosis, treatment and compensation of ARDs should be improved, particularly in countries that report no or few ARDs despite having a known history of asbestos use. To this end, we call on the international community to promote worldwide cooperation involving countries with a wide range of experiences in asbestos, i.e., from “asbestos-dependent” countries to “banned” and “in transition” countries. This would have the advantage of bringing together complementing technologies and experiences to match the varied needs of the beneficiaries.⁽⁶²⁾

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In 2007, the 60th World Health Assembly endorsed a global plan of action (GPA) on workers’ health 2008–2017, and made reference to a global campaign for the elimination of ARDs.⁽⁶³⁾ Priority 1.3 of GPA 2009–2012 was to “Develop and disseminate evidence-based tools and raise awareness for the elimination of ARDs”, which later developed into Priority 1.2 of GPA 2012–2017, under the “Regional and national programs on occupational cancer, silica and ARDs”.⁽⁶⁴⁾ The Asian initiative to eliminate ARDs (the Asian Asbestos Initiative, or AAI), which was embarked upon by the authors and colleagues in 2008,^(65,66) achieved widespread recognition and became a formal component of the GPA. The fourth international seminar (AAI-4) was successfully organized by our Korean colleagues in 2011,⁽⁶⁷⁾ and AAI-5 is planned as a joint Korea-Japan endeavor in 2012. The AAI aspires to provide a model that will pave the way for the ultimate elimination of ARDs worldwide.

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