Review of the effectiveness of predictive models for mesothelioma to identify lessons for asbestos-related policy

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Abstract

Predictions of future cases of asbestos-related disease have been undertaken at a national level to inform government policy and planning for future health needs. In general, we can separate the methods used to predict future cases of mesothelioma into models that use a) direct or b) indirect estimates of asbestos exposure. Direct estimates are those that have been derived mostly for occupationally exposed cohorts, where airborne fibre levels were measured over time. Indirect estimates tend to be information about total or fibre-specific asbestos imports or use from a range of time points. Most predictions undertaken at the national level have predicted future cases for males only and assume that indirect estimates of asbestos consumption reflect occupational asbestos exposure. These models tend to fit the observed data reasonably well but have undergone several refinements in order to improve their fit. Fewer attempts have been made to predict cases of mesothelioma resulting from *non*-occupational asbestos exposure, and most have not subsequently revisited their prediction to ascertain its accuracy so the robustness of these methods is unclear. Because of the change in asbestos use in recent decades, more attention should be paid to understanding the risks and burden of future cases arising from non-occupational exposure. A range of current data exist that should be sufficient to incorporate into models to predict future cases of mesothelioma arising from non-occupational asbestos exposure. Models could be tested for their accuracy by comparing them against the most recent 10 years of observed cases or against cases in women, whose most common source of exposure is non-occupational.

Predictions of the future burden of disease are undertaken for a variety of policy and planning reasons. Knowledge about the future number of cases of a particular disease can assist health planners to allocate resources for primary prevention, screening and diagnosis, treatment, and palliative care. Estimates of the future burden of disease can also be used to evaluate prevention programs. For example, the number of observed cases after the introduction of a prevention program could be evaluated against the number of expected cases, assuming that the disease trends before the program was introduced continued into the future. In the same vein, a prediction that estimated a heavy future burden of a particular disease could alert public health specialists to instigate a prevention program in order to avoid that prediction scenario (Bray and Moller 2006).

The simplest type of cancer prediction extrapolates past trends of cancer incidence or mortality to some date in to the future, but more information is required in order to estimate more complex scenarios. Ideally, information about the effect of a risk factor on the cancer of interest would be known by sex and age group for the past, present and future. In addition, the prevalence of exposure to that risk factor in the population would also be known. This information would then be used to develop a statistical model that describes the relationship between the risk factor and the cancer rate. However, in reality, cancer is not associated with only one risk factor, and usually the prevalence of exposure in the population is unknown and risk factor data are not available at the level

required (e.g. by age group and sex and calendar time). The exception is lung cancer and smoking, where the effect of smoking on lung cancer is well known, as is the prevalence of exposure to smoking, often by age group, sex and calendar time. As such, predictions of lung cancer epidemics associated with smoking have been regularly estimated (Winkler et al. 2011; Yamaguchi et al. 1992; Pierce et al. 1991) and have been shown to be reliable. For example, among Finnish males the observed incidence of lung cancer was shown to fit well with earlier predictions of lung cancer incidence estimated from hypothetical changes to smoking habits (Bray and Moller 2006; Moller et al. 2002).

Predictions of asbestos-related diseases

At a national level, predictions of future cases of asbestos-related disease have been undertaken to attempt to predict which year the peak number of cases may occur, after which the disease may then decline (Peto et al. 1995; Segura et al. 2003), and to inform government policy and planning for future health needs. Among occupational cohorts, predictions of future cases have been estimated to highlight the burden of disease in that cohort (de Klerk et al. 1989). They have also been undertaken to predict the future number of compensation claims resulting from people with mesothelioma caused by exposure to Johns Manville asbestos products (Stallard et al. 2005).

Historically, asbestos exposure occurred among workers who worked with the raw asbestos, mining and milling it or processing it in textile or asbestos cement factories (Landrigan 1991). Subsequently, other workers, such as carpenters and plumbers, insulators, shipbuilders and railway workers, were exposed from their use of the manufactured asbestos product. Latterly, workers who maintain buildings or remove asbestos from buildings have the highest asbestos exposure potential (Frost et al. 2008). Non-occupational exposure occurred among family members of asbestos workers, who brought their clothes home for laundering or among those who lived nearby to an asbestos factory or who worked in a building that contained asbestos (Robinson 2012).

Increasingly we need to turn our attention to the risks associated with, and the future burden of, asbestos-related diseases resulting from exposure to non-occupational sources of asbestos. Australia was an avid producer and consumer of asbestos. It was mined in Western Australia and New South Wales, and Australia also imported raw asbestos fibre and manufactured asbestos products, and manufactured its own asbestos cement products and asbestos goods.

More than 60 percent of production and 90 percent of consumption of raw asbestos was by the asbestos cement manufacturing industry (Hughes 1978). Asbestos cement products, specifically fibro sheeting, were used largely as a building material for industrial and commercial premises, and as cladding for the outside of residential housing or as water and drainage piping, roofing shingles, guttering, and fencing throughout Australia. Asbestos was also used as an insulation material (e.g. Mr Fluffy homes in Canberra). The post-World War II housing boom until the 1960s saw 25 percent of all new homes built in Australia (52 percent in NSW) clad in asbestos cement, and up to 70 percent contained some form of asbestos (National Occupational Health and Safety Commission 2004). Because of this Australia has a large amount of *in situ* asbestos in variable condition, throughout the built environment. Less is known about the risk of disease associated with exposure to *in situ* asbestos, largely in the form of asbestos cement. However, cases of mesothelioma have developed among do-it yourself home renovators (Olsen et al. 2011), and there are numerous reports of cases resulting from low dose asbestos exposure (Bourdes et al. 2000; Magnani et al. 2001).

Similarly, there is no known asbestos exposure threshold below which risk of disease does not occur (Iwatsubo et al. 1998). What is known is that the number of people exposed to *in situ* asbestos in Australia is probably very large, but the amount they have been exposed to, in most circumstances, is likely to be very low. Predictions of the future burden of asbestos-related disease that may emerge from low dose asbestos exposure might provide some insight about how best to manage the remaining *in situ* asbestos in Australia. For example, the future disease burden can be modelled against a range of prevention scenarios to inform policymakers about which prevention strategies would have the greatest impact (e.g. result in the fewest cases of mesothelioma). A particular comparison could be the future burden of mesotheliomas resulting from low dose asbestos exposure if *in situ* asbestos were removed as a priority from all government, commercial and domestic residences in Australia; or from only government and commercial premises; or if removal was not prioritised but *in situ* asbestos was contained. Furthermore, understanding the size of the possible future burden of asbestos-related disease can inform future health planning, budget allocation for screening and diagnosis, treatment, and palliative care.

In the subsequent sections, a definition of asbestos and asbestos-related diseases is presented, and a discussion of the multi-stage model of carcinogenesis that has been used as the basis for many of the prediction methods. A discussion of different methods used to predict future cases of asbestos-related diseases follows.

Asbestos

Asbestos is the commercial name of a number of naturally occurring minerals that have crystallised to form long thin fibres and fibre bundles. There are two family types of asbestos: amphibole and serpentine. There are at least five varieties of amphiboles: crocidolite (blue asbestos), amosite (brown asbestos), actinolite, tremolite, and anthophyllite. Crocidolite fibres generally have the finest diameter. Amosite fibres are slightly thicker, and the less commercially used varieties of actinolite, tremolite, and anthophyllite are coarser (Roggli and Coin 1992). Chrysotile (white asbestos) is from the serpentine group of minerals and has been the most common commercially used form of asbestos.

Asbestos-related diseases

The inhalation of asbestos fibres is associated with both benign and malignant diseases. Asbestosis (diffuse interstitial pulmonary fibrosis) is a fibrosis of the lungs, and patients with well-established asbestosis present with symptoms of shortness of breath and a dry cough. It is a progressive but not necessarily fatal disease (Doll and Peto 1985). Asbestosis generally develops after heavier exposure, although the minimum amount of asbestos exposure needed to cause asbestosis is unclear. Other benign conditions associated with asbestos exposure include discrete plaques and pleural calcification, diffuse pleural thickening and thickening of the interlobar fissure (Reid et al. 2005).

Cancers associated with asbestos exposure include malignant mesothelioma, which presents as a diffuse involvement of a mesothelial surface, most commonly in the pleura and less frequently in the peritoneum, pericardium and testes. It is universally fatal, with a median survival period of between nine and twelve months (Musk et al. 2011). All four major histological types of lung cancer (adenomatous, squamous, undifferentiated large-cell, and small-cell carcinoma) are related to asbestos exposure. Other cancers

caused by asbestos include cancers of the larynx, and there is inconsistent evidence for cancers of the colon and rectum, stomach and pharynx (Straif et al. 2009). Ovarian cancer has been associated with asbestos exposure (Straif et al. 2009), although there is some doubt that this may be peritoneal mesotheliomas misdiagnosed (Reid et al. 2011).

Malignant mesothelioma has a long latency period (the period of time that has passed since first asbestos exposure to the onset of the disease or death), rarely developing within 15 years since first exposure (Antman and Aisner 1987), yet increasing with time since first exposure for up to 45 years for pleural, and longer for peritoneal, mesothelioma (Reid et al. 2014). Mesothelioma mortality rates have been found to be proportional to the 3rd or 4th power of time since first exposed to asbestos (Peto et al. 1982).

Multi-stage model of carcinogenesis

Multi-stage models of carcinogenesis attempt to describe the biological processes involved in cancer development in mathematical and conceptual terms. The simplest model was proposed by Armitage and Doll in 1954 to explain the observation that age-specific cancer incidence curves increased linearly with age (Armitage and Doll 2004). Plotting the logarithm of incidence against the logarithm of age resulted in a straight line with a slope between four and five (Breslow and Day 1987). For many cancers this model represented the background age specific rate, and *k* (power of time since first exposure) was equal to five or six (Breslow and Day 1987). The basic premise of the Armitage/Doll model was the assumption that cancer develops from a single normal cell that has undergone a series of transitions. The occurrence of the last transformation leads to cancer in that cell. The number of cells at risk at the start is assumed to be large, but the probability of the critical number of transformations occurring in any individual cell is considered to be small (Breslow and Day 1987). If this model were true, most cancers would develop after the cell has undergone five or six transformations towards malignancy (Kaldor and Day 1996).

For mesothelioma, mortality rises rapidly with increasing time since first exposure and is independent of age (Peto et al. 1982). These observations are best explained by a dose-response model (the mesothelioma mortality rate model), where the increase in subsequent mesothelioma risk is proportional to the cumulative dose inhaled, to a power of time since first exposure lying between three and four, and to a latency period of ten years before mortality begins to increases (Peto et al. 1982). Later work has further refined this model and includes parameters that allow for the clearance of fibres from the lungs (Berry 1999). The mesothelioma rate model is expressed as:

$$\text{Mesothelioma rate} = ce^{-\lambda t}(t - w)^k$$

where ce is cumulative exposure, t is time since first exposure, w is the lag period, k is the power of time since first exposure, and λ is the rate of clearance of asbestos fibres from the lung.

Literature search procedure

To identify the literature predicting future cases of asbestos-related disease, the following search terms were searched singly and together: asbestos, prediction, projection, forecasting, mesothelioma, mesothelioma mortality, asbestosis, exposure,

environmental exposure, age-period-cohort models, risk models, mesothelioma mortality rate. The search was conducted through online databases including the Public Library of Medicine, Web of Science, and the Curtin University library catalogue. Bibliographies of papers were also examined. The search was not time delimited, but this review focuses more heavily on more recent prediction methods, most of which derive from the earliest methods used. Prediction methods used for occupational cohorts that have individual estimates of asbestos exposure were not the focus of this review, but the total exclusion of that method would have made explanation of other methods used difficult. Therefore one paper outlining a prediction method which formed the basis for many subsequent predictions has been included (Berry 1991).

Many of the prediction methods outlined below attempt to use the mesothelioma mortality rate model in their methods. The extent to which they can do this depends largely on the availability and quality of data about asbestos exposure. In general, we can separate the methods used to predict future cases of mesothelioma into models that use direct or indirect estimates of asbestos exposure (Stallard et al. 2005). Direct estimates of asbestos exposure are those that have been derived mostly for occupationally exposed cohorts where airborne fibre levels were measured over time, e.g. the Wittenoom workers where each worker had an exposure based on their job and the length of time in that job (Armstrong et al. 1988). Indirect estimates of asbestos exposure tend to be information about total or fibre-specific asbestos imports, or use from a range of time points. In the epidemiology literature, prediction methods that incorporate information about direct and indirect asbestos exposure are called predictions, while those that do not incorporate any information about asbestos exposure are referred to as projections.

Models based on direct estimates of asbestos exposure

Prediction methods that use direct estimates of asbestos exposure have been used to predict future cases of malignant mesothelioma among cohorts with known estimates of quantitative asbestos exposure, mostly occupational exposure. For example, among Wittenoom crocidolite miners and millers (de Klerk et al. 1989) (Berry 1991; Berry 1999; Berry et al. 2012), or among the women who lived at Wittenoom who were non-occupationally exposed to asbestos (Reid et al. 2009), albeit at quite high levels. Similarly, this model was used to predict cases of mesothelioma among Italian railway workers with known estimates of asbestos exposure (Gasparrini et al. 2008).

The method involves calculating the mortality rate for the cohort to establish the excess deaths from all causes of death, lung cancer and mesothelioma in the cohort compared with the unexposed population. Then maximum likelihood estimates for the mesothelioma rate parameters ce, k and λ are derived from the cohort data, although because of correlation between k and λ, λ is often fixed at 6.7 percent and 15 percent per annum, and only k estimated (Reid et al. 2009). All of this information provides the probability of dying in a year, averaged over each age. This is then applied to the number of surviving workers in a particular year to estimate the number who survive to the end of the next year, using a lifetable-type approach. For example, applying the probability of dying in a year to workers who are still alive at the end of 2015 estimates the number of workers who will be alive at the end of 2016. Subtracting the number of survivors in 2016 from those in 2015 gives the number of deaths for 2016. The number of mesothelioma deaths each year can be calculated by multiplying the mesothelioma death rate with the number of surviving workers in each year (Berry 1991).

Several studies have compared their earlier predictions against observed data and have found a good fit. For example, Berry et al. used five different mesothelioma models, based on different lag times (0, 5 and 10 years) and rates of elimination of asbestos fibres (6.7 percent and 15 percent per annum). They predicted between 250 and 680 cases of mesothelioma among former Wittenoom workers between 1987 and 2020 (Berry 1991). Subsequent revisiting of this prediction showed that the model that incorporated an elimination rate of 15 percent and a lag period of five years had a good fit with the observed data (Berry et al. 2004).

Prediction methods that incorporate individual level data on asbestos exposure should be seen as the 'gold standard' for prediction methods. They are more accurate than other methods because they are based on exact information about demographic characteristics, period of exposure, and cumulative exposure (Gasparrini et al. 2008). But because of the high level of data required they are only capable of being used to predict future disease in a small range of situations, e.g. among workers in specific occupations or industries. Most mesothelioma predictions have been undertaken where direct measures of asbestos are not available, e.g. at the national or regional level where direct exposure estimation would be impossible.

Models based on indirect measures of asbestos exposure

Age-cohort models and age-period-cohort models

Age-cohort (AC) models and age-period-cohort (APC) models have been the method used most often to predict future cases of mesothelioma where direct measures of asbestos exposure are unknown. Most commonly they have been used to predict future cases among whole populations, e.g. for Britain (Peto et al. 1995) or for the Netherlands (Segura et al. 2003). They have also been used to estimate future disease compensation claims among former Johns Manville asbestos cement workers and those exposed to Johns Manville asbestos products (Stallard et al. 2005).

AC/APC models analyse the effects of age at diagnosis or death, birth cohort, and period of diagnosis or death on the past mesothelioma rates (Marinaccio et al. 2005). The information on mesothelioma cases usually comes from a mesothelioma or cancer registry or from a mortality registry. The mesothelioma rates (cases of mesothelioma/population at risk) are organised into age at diagnosis or death groups (usually 5 year age groups e.g. 20–24, 25–29, … 75–79), period of diagnosis or death groups (again, usually 5 year period groups e.g. 1970–74, 1975–79, … 2010–14), and 10 year birth cohort groups. Then, in general, a log linear Poisson regression model is fitted to the age-specific mesothelioma rates to estimate the effects of age and birth cohort and period of death on the mesothelioma rates, and to estimate the relative risk of mesothelioma for each birth cohort. To predict future cases of mesothelioma, the relative risk for the latest period (e.g. 2010–14) is applied for single or grouped years of age to the projected age-specific population.

The earliest predictions of mesothelioma cases at a national or country level were undertaken using models in which mesothelioma risk was related independently to age at death or diagnosis with mesothelioma and date of birth. These models predicted proportional hazards across the different birth cohorts. Asbestos exposure was assumed to be proportional to asbestos imports and was accounted for indirectly by measuring time in birth cohorts (M. Clements et al. 2007). Several predictions for national countries were undertaken using this method and for some of these, subsequent studies revisited the earlier prediction and examined the fit of the prediction against the number

of cases that actually occurred. For Great Britain, between 2700 and 3300 male mesothelioma deaths were predicted to peak in the year 2020 (Peto et al. 1995). Subsequent work showed that this model fit the data reasonably well until 1991, but showed a departure from the fit with later cohorts, predicting more cases of mesothelioma than actually occurred among those later birth cohorts. Similarly, predictions of mesotheliomas in Europe (Peto et al. 1999) and the Netherlands (Peto et al. 1999), when subsequently revisited, overestimated the number of cases (Pelucchi et al. 2004; Segura et al. 2003). This was largely because the mesothelioma rate did not increase as fast with increasing age in the younger cohorts as it did in the older cohorts. More recent birth cohorts would only have been exposed to asbestos early in their working life so it is unclear whether the risk of mesothelioma would continue to increase with age up to 80 years or whether it will flatten out at younger ages for these cohorts (Clements et al. 2007). These methods did not take into account any period effects on the mesothelioma rate. For example, they couldn't account for the lower asbestos exposure experienced by the younger cohorts, after asbestos bans and exposure standards were introduced in the 1970s (Gasparrini et al. 2008). The AC method assumed that the rate increased at the same rate by age for all cohorts and so was unreliable (Hodgson et al. 2005).

In light of these limitations subsequent work undertook predictions at a national level using APC models that included *a priori* assumptions about period effects (Gasparrini et al. 2008). For example, based on the large reduction in the use of asbestos in the Netherlands from 1984, Segura et al. (2003) assumed that the risk of mesothelioma among those born between 1958-62 was 50 percent less than that of those born between 1953–57. Similarly, birth cohorts born after 1962 were assumed to have zero risk of mesothelioma. To this same model a period effect was incorporated, to account for the introduction of the *International Classification of Diseases – Volume 10* (ICD-10), which greatly improved the recording of mesothelioma on death certificates. Compared with the earlier prediction of approximately 1000 deaths in the peak year of 2020 (Peto et al. 1999), this enhanced model predicted a peak year of 2017 and 501 deaths (Segura et al. 2003). However, the accuracy of this later method for predicting future mesotheliomas has not been assessed against observed data.

Other work has incorporated Bayesian statistical methods into APC models to make inferences from past knowledge to improve the fit of these models to identify the relative contribution of age, period and cohort on the risk of mesothelioma (Girardi et al. 2014; Pitarque et al. 2008). However, subsequent work comparing the observed cases against predictions found that the Bayesian enhanced APC model used by Pitarque et al. (2008) underestimated observed mesotheliomas by 41 percent or 261 deaths (López-Abente et al. 2013).

The APC model has also been used to project future cases of mesothelioma using a method that does not require knowledge about asbestos exposure (Martínez Miranda et al. 2015). The statistical model is estimated with Poisson regression without an offset, so is somewhat simpler to model than the more sophisticated APC models that use the log-linear method. The authors suggest that their method can be used to benchmark more sophisticated prediction models. Compared with other predictions for Great Britain, this method projected a peak in 2018 of 2095 (95% CI 1978–2210) cases. This compares favourably with Peto's 2700 peak cases in 2020 (Peto et al. 1995), Hodgson's 1846 cases peaking in 2013 (Hodgson et al. 2005) and Tan's 2040 deaths peaking in 2016 (Tan et al. 2010). The latter two prediction methods (see below) involved complicated constructions of exposure.

Other factors that may have influenced mesothelioma rates but that were generally not accounted for in APC models include improvements in the diagnosis and reporting of mesothelioma over time, where earlier cases may have been missed. A further limitation of these methods is that the analyses were based on the age-cohort distribution of the general population, whereas the mesothelioma cases will mostly come from specific occupational populations (Gasparrini et al. 2008) such as carpenters and asbestos textile workers. Also, many of these models predicted future cases among men only, because asbestos consumption records are an indicator of the use of asbestos exposure that men would incur in certain jobs, whereas women are more likely to obtain their asbestos exposure from sources other than work, e.g. from the general environment or take-home asbestos. These models tend to predict cases from high exposure scenarios only and do not take into account risks from lower exposure. In addition, clearance of asbestos fibres from the lung was increasingly found to be important for the risk of mesothelioma, and this had not been accounted for (Berry 1999).

Other models

Hodgson et al. (2005) attempted to improve the accuracy of mesothelioma predictions in Great Britain and used a model that related current mesothelioma mortality to past asbestos exposure, and also accounted for the clearance of asbestos fibres from the lungs and for the completeness of mesothelioma diagnosis over time. Similar to the earlier models, indirect asbestos exposure was dependent on calendar year, but unlike earlier AC models, it varied with age. This overcame the limitation of earlier models that assumed that the mesothelioma rate increased by age for all cohorts (Hodgson et al. 2005). When compared against observed cases of mesothelioma, the enhanced model fit the data better than the earlier, simpler models and predicted fewer mesotheliomas, around 1950-2450 deaths, peaking between 2011 and 2015 (Hodgson et al. 2005). Confidence intervals for the model parameters and predictions could not be estimated in this enhanced model, so there remained a level of uncertainty in the predicted numbers (Clements et al. 2007; Hodgson et al. 2005; Tan et al. 2010). Further refinement to the model integrated a Bayesian statistical analysis that allowed for data on asbestos imports and levels of asbestos use, and a background rate of mesothelioma, to be included in the model and the calculation of credible and prediction intervals, thus providing a measure of uncertainty. Compared with observed cases between 1968 and 2006, this refined method fit the observed data well and predicted fewer mesotheliomas than the earlier methods, peaking at 2038 male deaths (prediction interval 1929–2156) in 2016 (Tan et al. 2010). To date the predicted cases from this method have not been compared against observed data.
A similar model to that proposed by Hodgson was used to predict future cases of mesothelioma in New South Wales (Clements et al. 2007). This method differed to the former through the use of natural splines as the parameters for change in asbestos exposure by time and age, and assumed that birth cohorts born after 1970 had negligible risk for mesothelioma.

Other authors have used risk function models that are very similar to the models used to predict mortality in the occupational cohort studies discussed above, but with indirect measures of asbestos exposure. Banai et al. (2000) predicted future cases of mesothelioma for the population of French men, who generally had much lower exposure than those other cohorts. This model incorporated a risk of death at a given age as well as a risk function for the mesothelioma mortality rate, and data from past French asbestos imports was used to model overall past asbestos exposure. Their results were very comparable to earlier work that had used the age-cohort method to predict

future mesothelioma cases (Ilg et al. 1998). Using a risk function model based on that used by Banai et al (2000), but adapted for Japanese circumstances, Myojin et al (2012) predicted future cases of mesothelioma in Japan, and only for those who worked in construction and manufacturing rather than the whole population of men. It is unclear how this method fits against observed cases.

Predictions of other asbestos-related diseases

Future cases of asbestosis and lung cancer have been predicted far less frequently than malignant mesothelioma, although the method used to predict these other asbestos-related diseases was similar to those outlined above for mesothelioma. For lung cancer there is an added complication that while most mesotheliomas are accepted as being caused by asbestos exposure, the proportion of asbestos-related lung cancers is less clear, and not clinically distinguishable from those due to other causes – therefore it must be estimated (Darnton et al. 2006). One such estimation provided a ratio of the number of asbestos-related lung cancers per mesothelioma death, where mesothelioma death was used as a proxy for asbestos exposure and based on data from 55 asbestos exposed cohort studies. The ratios varied by fibre type, and ranged from 0.7 (95% CI 0.5–1.0) for crocidolite, 6.1 (3.6–10.5) for chrysotile, 4.0 (2.8–5.9) for amosite, and 1.9 (1.4–2.6) for mixed fibres (McCormack et al. 2012).

Following on from this work, three prediction methods were used to estimate future lung cancers related to asbestos exposure in the Netherlands (Van der Bij et al. 2016). The first method estimated lung cancers from predicted mesotheliomas using the ratio, based on exposure to mixed fibre types, of 1.5 asbestos-related lung cancers per mesothelioma death, as suggested by McCormack et al (2012). The second method applied, from an earlier study, the fraction of lung cancer cases attributable to asbestos exposure (PAR population attributable risk) to the predicted number of lung cancers derived for the period 2011–30 and the projected male demographic distribution between 2011 and 2030. This predicted number of lung cancers was derived from lung cancers observed between 2008–10. The third method used exposure information and asbestos-related lung cancer risk as a function of that exposure to estimate the future lung asbestos-related lung cancers in a lifetable analysis. The three methods varied widely in their future predictions, from a high of 17,500 for method one, to 12,150 for method two, and 6800 for method three. They were unwilling to state which method they thought was the most accurate, instead commenting that the robustness of any method relies heavily on the quality of the information put into it and that the most comprehensive method is not necessarily better than a simple one (Van der Bij et al. 2016).

Work from the United States predicted future deaths from asbestosis among US residents, using past deaths from asbestosis and asbestos consumption[1] per capita as an indirect estimate of asbestos exposure (dos Santos Antao et al. 2009). They found that the model that best fit deaths from asbestosis between 1968 and 2004 used asbestos consumption per capita 48 years prior (1920–56), and used this model to predict future deaths from asbestosis (dos Santos Antao et al. 2009). However, predicted cases have not been revisited to compare against observed cases to determine the accuracy of their model.

Future cases of lung cancer have been estimated among cohorts of workers exposed to asbestos (Berry 1991; de Klerk et al. 1989; Gasparrini et al. 2008), using methods

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[1] Asbestos production, plus imports, minus exports, minus changes to government and industry stocks

similar to those reported above that used direct estimates of asbestos exposure, but where a rate for lung cancer mortality was derived instead of a rate for mesothelioma. None of these predictions have been revisited to compare against observed data.

Predictions of mesothelioma from non-occupational exposure

Most of the prediction methods discussed above considered mostly men, and occupational and high-dose exposure only. Increasingly, cases of mesothelioma have been occurring among people with low-dose non-occupational asbestos exposure, but to date little attention has been paid to the future burden of mesothelioma from low-dose exposure. There are still considerable gaps in our understanding of the risks associated with non-occupational asbestos exposure, and the prevalence of that exposure within the population.

In terms of knowledge, we are uncertain about the dose-response relationship for asbestos-related disease in persons with low dose exposure, particularly the risks associated with domestic or residential exposure. Where information on low dose exposure risk exists, it tends to be from cohorts of people that would have had considerably higher asbestos exposure than that emanating from the built environment. For example, the women from the blue asbestos mining and milling town of Wittenoom were not exposed to asbestos occupationally, but their environment was highly contaminated from mine tailings being distributed around the town (Reid et al. 2008a; 2008b).

At the same time we are uncertain about the amount of asbestos product that remains in the built environment and the condition of that asbestos product, although we do have estimates of the amount of asbestos used and removed over time in Australia (Finity 2016). However, we are uncertain as to its location and uncertain about the amount (level) of exposure that comes from that source of asbestos – although earlier work from the UK and US reported very low levels of asbestos inside buildings that contained asbestos in varying conditions (Burdett et al. 1988; Crump and Farrar 1989). We are also uncertain about who or how many in the population have been exposed to asbestos from this source.

Three studies have been identified that predicted future burden of mesothelioma among those exposed non-occupationally. Azuma et al. (2009) used a model based on the mesothelioma mortality rate model and indirect measures of asbestos exposure to predict future cases resulting from environmental exposure in Japan. This study defined environmental exposure in its narrowest sense, being only that exposure that was not occupational, domestic or from indoor asbestos exposure (e.g. being exposed to asbestos in a room where sprayed asbestos was used). Their model included a parameter for the annual average concentration of asbestos in years, and another for continuous asbestos exposure. The annual average concentration of airborne asbestos in years was estimated from a range of sources in the literature, including trend data for commercial areas beginning in 1981, and exposure measurements from 1968 and 1970. In addition, national field surveys assessing levels of airborne asbestos concentrations were conducted in 1985 and 2005. Estimates were supported from data on the consumption of sprayed asbestos as well as trends in the number of ferruginous bodies detected in the lungs of the general population. Their model fitted well against observed cases of mesothelioma resulting from exclusive environmental asbestos exposure. However, the robustness of this method is unclear, sensitivity analyses comparing a range of exposure scenarios were not conducted, and the predicted cases have not been examined against observed data.

Furlan and Mortarino (2012) predicted future cases of mesothelioma among residents of the Local Health Area (LHA) of Casale, which contains the city of Casale Monferrato, where Italy's largest asbestos cement factory was located. Other work had shown an increased risk of mesothelioma among residents of the LHA (Magnani et al. 1995). Their method was based on one used for epidemic diseases and predicted a total number of deaths and a date for the end of the 'epidemic'. Information on the number of individuals who incurred the same exposure (e.g. the number of people who lived in the LHA at the same time) was needed, rather than individual level asbestos exposure. They predicted future cases in three areas: (1) among residents of the city of Casale Monferrato; (2) in residents of Casale Monferrato and bordering towns; and (3) in the Casale Local Health Area. Their model predicted fewer cases with increasing distance from the asbestos cement factory. Confidence intervals were built for each area, and uncertainty about the number of future cases and the end period of the 'epidemic' in the larger area (LHA) was greatest. One strength of this method was that it could predict future disease among all residents of these areas and not only those who worked for the factory. However, the data requirements were large for this method, and the modelling included several assumptions that had large impacts on the outcomes and uncertainty of the results.

For Australia, Finity (2016) predicted the future burden of mesothelioma by wave of asbestos exposure. Waves 1 and 2 were defined as cases where exposure was from asbestos mining, manufacture and heavy industrial use and asbestos product use, particularly in the building industry. Also included in Waves 1 and 2 were those cases where exposure was from living near an asbestos cement factory or from asbestos brought home on workers' clothes. Wave 3 cases were defined as those where exposure was from asbestos in the built environment, e.g. from disturbing or renovating a home that contained asbestos, background cases, and occupational exposure post-2003 (the year Australia banned all types of asbestos). Finity (2016) used a mesothelioma risk model that predicted the future burden for each exposure wave. To account for asbestos exposure over time, an asbestos volume index was derived based on 100 percent weight for the amount of national asbestos consumption plus a 30 percent weight for the amount of asbestos removed nationally, and reflecting the changing use of asbestos types over time and safe handling procedures. The exposure index was based on the volume of asbestos consumed rather than the number of people exposed. Also included in the model were parameters for age at first exposure and duration of exposure. Exposure duration of 2 years was allocated to Wave 3, assuming a shorter exposure period for a home renovation. The Australian mortality rate and projected population to 2100 were taken from Australian life tables. The model was back-fitted against observed cases from 1988-2014 for each wave separately and together, and showed a good fit for all exposure waves. Similarly, the projected peak of cases across all exposure sources combined closely matched two other predictions that used an APC model with natural cubic splines (Clements et al. 2007; Soeberg et al. 2016). However, Finity (2016) allocated a duration of exposure of 2 years for Wave 3 cases, which may be appropriate for those who obtained their exposure from DIY home renovation, but is likely to underestimate the duration of exposure among those who lived in a house containing ACM for many years.

These three studies highlight the wide range of data used to undertake a prediction of future cases of non-occupationally exposed mesothelioma. To date none of these methods have been assessed against future observed cases, so how accurate they are at predicting future cases is uncertain.

Discussion

As discussed above, most predictions of asbestos-related disease have been undertaken on men and largely based on high-dose occupational exposure. However, as the pattern of use of asbestos has changed in recent decades, so have the risks of exposure in relation to who is exposed and to how much. Therefore we need to improve our understanding about the risks associated with, and the future burden of, diseases resulting from exposure to non-occupational sources of asbestos. Specifically, we need to determine if the models used to predict occupational cases of mesothelioma can be used to accurately predict non-occupational cases, and if existing information about current non-occupational exposure is sufficient to include in those models.

As the risk of mesothelioma is proportional to the dose of exposure, information about total asbestos exposure (indirect exposure), rather than individual level exposure information, should be sufficient to include in a prediction model of future cases of non-occupational exposure. Indeed, Clements et al. (2007b) argue that where exposure data is poor, indirect methods are now state of the art for population level predictions. Estimates of national asbestos consumption have been used to provide information about the period and duration to which workers might have been exposed to asbestos in their occupation. However, this is less informative about the period and duration of exposure for people exposed subsequently to *in situ* asbestos, and should be tested in a range of prediction scenarios to assess its reliability for inclusion in non-occupational exposure prediction models. Alternatively a national survey could be conducted to estimate the proportion of the population that have been or currently are exposed to asbestos from their built environment – but seeking information about self-reported exposure is difficult, unreliable and costly. Also it is not clear by how much the estimate of predicted cases would change if detailed exposure information were available, or whether the hypothesized increase in precision justifies the cost of collecting new non-occupational asbestos exposure data.

Other data do exist that may be used to inform future predictions. The Australian Mesothelioma Registry (AMR) may be a source of information to derive mesothelioma rates based on domestic/residential exposure. They have collected occupational and environmental asbestos exposure on new cases in Australia since 1980 (Leigh and Driscoll 2003). However, collecting exposure information on cases diagnosed since 2010 has been very problematic for the AMR, and they are currently achieving this on only 17 percent of new cases, although these cases have been examined and classed as representative of all newly diagnosed mesothelioma cases (Finity 2016). Moreover, because of the long latency of these diseases, exposure among past cases may not reflect what is occurring today. Because of the reduction in the level of exposure over time, it may not be useful as a base to project forward to predict future cases, although they do inform historical exposures.

Current data on the potential exposure levels from DIY home renovations, the prevalence of exposure to DIY home renovation, and the risk of mesothelioma from DIY exposure, could be used to inform prediction models estimating the future burden from DIY home renovations. Asbestos fibres released during a range of DIY home renovation tasks that involve the removal or disturbance of asbestos cement sheeting have been recently quantified. In situations where there was minimal breakage of cement sheets and where power tools were not used, the exposure was low. However, tasks that involved breaking sheets or using power tools resulted in personal exposures above 0.02f/ml (Benke 2016). Information about the current prevalence of exposure to asbestos from DIY exposure comes from a study conducted in 2008 in New South

Wales, where 44 percent of participants reported renovating their home; 53 percent of those reported being a DIY home renovator and 61 percent of those self-reported having had asbestos exposure (Park et al. 2013). The risk of mesothelioma from DIY exposure was examined using data from the Western Australian Mesothelioma Register. To the end of 2008, 87 cases of mesothelioma (55 in men) were reported where DIY home renovation was the main source of exposure. Over time, the proportion of cases with this source of exposure had been increasing; from 2005–2008, 8.4 percent of male and 36 percent of female cases reported DIY exposure (Olsen et al. 2011).

This review identified that many of the prediction methods assessed the fit of the model by back-fitting their model against past observed cases. Most of the studies reviewed here have not revisited their model at a date in the future to assess how it performed against new cases. A new way of assessing the fit of a prediction model would be to create it as usual from past incident mesothelioma cases or deaths, but exclude the most recent 10 years of incident cases or deaths. Then the accuracy of the model could be tested to see how well it fitted the most recent 10 years of data. A limitation with this method is that the most recent ten years of incident cases would, in most situations, contain the greatest number of cases, due to the long latency period of these diseases. But predicting disease at a national level may permit sufficient cases for this method to be tested. Furthermore, several models could be derived, each based on different existing data about current and past asbestos exposure. Each model could then be tested against the most recent 10 years of incident cases and compared, to inform on the impact of the exposure data on the estimate. From this comparison we will learn whether more asbestos exposure data needs to be collected, given the inherent difficulties and cost associated with collecting such data, or whether the existing data is sufficient for incorporating into future predictions.

Another gap identified in this review was that many of the predictions excluded women from their estimates, in general because of their small number of cases. However, women are more likely to have obtained their asbestos exposure non-occupationally, so estimating the future burden of disease based on past rates in women may inform future burden for the whole non-occupationally exposed population. In the same vein, prediction models could be tested for their accuracy by comparing their predicted cases against observed cases in women.

Conclusion

Future cases of asbestos-related disease have been predicted for a range of populations across many countries. The most robust methods incorporate direct measures of asbestos exposure, but this information is available only for defined occupational cohort studies, e.g. the Wittenoom crocidolite asbestos miners and millers. Other methods that use indirect measures of asbestos exposure, e.g. methods that assume asbestos exposure is proportional to asbestos imports or use, have predicted future cases of mesothelioma among workers with reasonable accuracy. Fewer studies have predicted cases of mesothelioma among populations with non-occupational asbestos exposure, and the robustness of these methods is less clear. Sufficient data about asbestos exposure may exist at a national level to permit an accurate prediction of future burden, but models using different estimates of exposure should be tested to examine the impact on the estimates of asbestos-related disease that may emerge from non-occupational asbestos exposure in the Australian population.

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Table 1. Summary of methods used to predict future cases of asbestos-related disease included in the review

Study	Disease predicted	Population studied	Prediction period	Prediction method	Asbestos exposure	Model sensitivity tested w observed data (past mesothelioma/other cases)	Model revisited to check accuracy of prediction
Occupational cohorts							
Berry 1991	Mesothelioma, lung cancer and asbestosis	Wittenoom workers	1987–2020	Mesothelioma risk model	Direct – cumulative exposure and time since first exposure	Yes	Yes – model that included 15% clearance of asbestos fibres from the lung was repeatedly a good fit
National predictions – occupational exposure							
Peto 1995	Mesothelioma mortality	Males in Great Britain	1990–2040	Age-cohort model	Indirect - asbestos consumption	Yes	Yes - model fit the data up to 1991, but did not fit younger cohorts
Peto 1999	Mesothelioma mortality	Males, Western Europe	1995–2029	Age-cohort model	none	Yes	Yes – was found to overestimate cases
Banaei et al. 2000	Mesothelioma mortality	French males	1997–2050	Risk function model that incorporated risk of death from mesothelioma as a function of past exposure	Indirect – asbestos imports	Yes	No – but this method predicted similar numbers to an earlier APC model
Segura et al. 2002	Mesothelioma mortality	Males/females in the Netherlands	2000–28	Age-cohort and age-period-cohort models	Indirect – asbestos consumption	Yes	No - This method predicted 44% fewer cases than earlier methods
Marinaccio et al. 2005	Mesothelioma mortality	Males in Italy	2012–24	Age-period-cohort model & asbestos consumption model	Indirect -asbestos consumption	Yes	No
Hodgson et al. 2005	Mesothelioma mortality	Males in Great Britain	2002–50	Poisson regression model	Indirect; asbestos consumption	Yes	Yes, however this model has been subsequently enhanced

Study	Disease predicted	Population studied	Prediction period	Prediction method	Asbestos exposure	Model sensitivity tested w observed data (past mesothelioma/other cases)	Model revisited to check accuracy of prediction
Clements et al. 2007	Mesothelioma incidence	Males in New South Wales, Australia	2004–60	Age-cohort model and age/calendar year model similar to Hodgson et al.	Indirect; asbestos consumption	Yes	No
Pitarque et al. 2008	Mesothelioma mortality	Spanish males	2002–17	Bayesian age-period-cohort model	Indirect; asbestos consumption	Yes	Later work showed a 41% underestimate of cases from this method
Tan et al. 2010	Mesothelioma mortality	Males in Great Britain	2007–50	Bayesian enhanced poisson regression model	Indirect; age-specific exposure and overall population exposure	Yes	No
Myojin et al. 2012	Mesothelioma mortality	Japanese men with an occupational history of asbestos exposure	2003–50	Risk function model that incorporated risk of death from mesothelioma as a function of past exposure	Indirect; asbestos imports	Yes	No
Lopez-Abente et al. 2013	Pleural cancer (mesothelioma) deaths	Spanish males and females	2011–20	Age-period-cohort model	Indirect; asbestos consumption	Yes	No
Girardi et al. 2014	Mesothelioma incidence	Males/females Veneto, Italy	2011–26	Bayesian age-period-cohort model	Indirect; asbestos consumption	Yes	No
Miranda et al. 2015	Mesothelioma mortality	Males in Great Britain	1990–40	Age-period-cohort model without offset	None	Yes	No
Soeberg et al. 2016	Mesothelioma incidence	Males/females in Australia	2012–30	Age-period-cohort model with natural cubic splines	None; instead predicted incidence rates from historical trends	Yes	No

Environmental exposure

Study	Disease predicted	Population studied	Prediction period	Prediction method	Asbestos exposure	Model sensitivity tested w observed data (past mesothelioma/other cases)	Model revisited to check accuracy of prediction
Azuma et al. 2009	Mesothelioma mortality	Males/females in Japan	2005–70	Mesothelioma risk model	Indirect; historical asbestos exposure and mesothelioma rate attributed to environmental exposure	Yes; model underestimated past cases	No

Study	Disease predicted	Population studied	Prediction period	Prediction method	Asbestos exposure	Model sensitivity tested w observed data (past mesothelioma/other cases)	Model revisited to check accuracy of prediction
Furlan et al. 2011	Mesothelioma mortality	Population of the Casale Monferrato Local Health Area, Italy	2008–40	Cellular Automata model (more commonly used in epidemic diseases)	Indirect – based on number of people living in the LHA area at the same time	Yes	No
Finity 2015 (covers occupational and environmental exposure predictions)	Mesothelioma incidence	Australian population	2015–2100	Mesothelioma risk model	Indirect – asbestos volume index (equal to 100% of asbestos consumed each year + 30% of the asbestos removed each year	Yes; back fit asbestos exposure allocation to cases from 1988 – by Wave of exposure	No
Other asbestos-related disease predictions							
dos Santos Antao et al. 2009	Asbestosis mortality	Males/females in United States of America	2005–27	Generalised additive model	Indirect; asbestos consumption	Yes	No
Van der Bij et al .2016	Lung cancer	Males/females in the Netherlands	2011–30	3 different models: 1. Age-period-cohort model based on mesothelioma cases 2. Past cases of lung cancer extrapolated forward 3. Life table analysis	1. Past mesothelioma cases used as a proxy for exposure 2. Population Attributable Risk of asbestos exposure taken from earlier study 3. JEM used to estimate current exposure	Compared with an earlier Dutch study (Segura et al) method 1 estimated 20% higher number of cases	No