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Original Article

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Validation of an Asbestos Job-Exposure Matrix (AsbJEM) in Australia: Exposure–Response Relationships for Malignant Mesothelioma

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Abstract

Objectives: An asbestos job-exposure matrix (AsbJEM) has been developed to systematically and cost-effectively evaluate occupational exposures in population-based studies. The primary aim of this study was to examine the accuracy of the AsbJEM in determining exposure–response relationships between asbestos exposure estimates and malignant mesothelioma (MM) incidence (indirect validation). The secondary aim was to investigate whether the assumptions used in the development of the original AsbJEM provided accurate asbestos exposure estimates.

Methods: The study population consisted of participants in an annual health surveillance program, who had at least 3-month occupational asbestos exposure. Calculated asbestos exposure indices included cumulative asbestos exposure and the average exposure intensity, estimated using the AsbJEM and duration of employment. Asbestos and MM exposure–response relationships were compared between the original AsbJEM and its variations based on manipulations of the intensity, duration and frequency of exposure. Twenty-four exposure estimates were calculated for both cumulative asbestos exposure and the average exposure intensity using three exposure intensities (50th, 75th and 90th percentile of the range of mode exposure), four peak durations (15, 30, 60 and 120 min) and two patterns of peak frequency (original and doubled). Cox proportional hazards models were used to describe the associations between MM incidence and each of the cumulative and average intensity estimates.

Results: Data were collected from 1602 male participants. Of these, 40 developed MM during the study period. There were significant associations between MM incidence and both cumulative and average exposure intensity for all estimates. The strongest association, based on the regression-coefficient from the models, was found for the 50th percentile of mode exposure, 15-min peak duration and the doubled frequency of peak exposure. Using these assumptions, the hazard ratios for mesothelioma were 1 (reference), 1.91, 3.24 and 5.37 for the quartiles of cumulative asbestos exposure and 1 (reference), 1.84, 2.31 and 4.40 for the quartiles of the average exposure intensity, respectively.

Conclusion: The well-known positive exposure–response relationship between MM incidence and both estimated cumulative asbestos exposure and average exposure intensity was confirmed. The strongest relationship was found when the frequency of peak exposure in the AsbJEM was doubled from the originally published estimates.

Keywords: asbestos; exposure–response relationship; job-exposure matrix; mesothelioma; occupational exposure

Introduction

Asbestos is a known cause of a number of diseases, including malignant mesothelioma, lung cancer and asbestosis (Jamrozik et al., 2011). Exposure–response relationships have been established between asbestos exposure and these asbestos-related diseases (ARDs) (Paris et al., 2009; Clin et al., 2011; Lenters et al., 2011; Olsson et al., 2017). However, there has been a considerable variation in the exposure–response slope of these relationships across individual studies, which is partly due to the diversity of the quality of the exposure assessments in different studies (Lenters et al., 2011). A robust measure of exposure is important as poor-quality exposure estimates will lead to exposure misclassification obscuring exposure–response relationships.

A job-exposure matrix (JEM) is a standardized method to assign specific exposure estimates to job histories (Pannett et al., 1985). JEMs have been designed to systematically and cost-effectively evaluate occupational exposures within the wider workforce for a variety of agents in various industries and occupations over different time periods and can be specific to different countries (Coughlin and Chiazze, 1990; Peters et al., 2016b). The use of a JEM provides standardized exposure assessment and reduces reporting bias (Peters et al., 2011). However, JEMs are subject to intra-occupational miscalculation since workers with the same job title are not necessarily exposed to the same amount of asbestos (Coughlin and Chiazze, 1990; Bouyer et al., 1995). Due to variability within tasks within the same title, accuracy of estimates within a JEM varies. Bouyer and Hémon (1993) and Goldberg et al. (1993) have suggested that estimates derived from a JEM can be indirectly validated if they allow the detection of a known association between risk factors and a disease, for example the well-established association between asbestos exposure and malignant mesothelioma because it is almost invariably attributed to asbestos exposure.

A JEM to estimate occupational asbestos exposure in Australian workers (AsbJEM) was recently published (van Oyen et al., 2015). However, the accuracy of exposure estimation in this AsbJEM was questioned as relatively low exposure estimates were indicated for some job titles for which there are many reported cases of asbestos-related diseases (Kottek and Kilpatrick, 2016). Of particular concern was the duration and frequency of peak exposure (Kottek and Kilpatrick, 2016). The aims of this study were (i) to validate (indirectly) the AsbJEM by assessing the well-established exposure–response relationship with malignant mesothelioma and (ii) to investigate the effects of changing the designated estimates of intensity, duration and frequency of peak and mode exposures so as to refine the AsbJEM if required. This study was approved by the University of Western Australia Human Research Ethics Committee.

Methods

Participants

Participants came from an annual health surveillance programme for people with significant occupational exposure to asbestos [the Asbestos Review Programme (ARP)] (Hansen et al., 1997, 1998; Musk et al., 1998; Murray et al., 2016). Individuals eligible to join the ARP have had at least 3-month cumulative full-time equivalent occupational exposure to asbestos or those with evidence of pleural plaques. This includes trades such as carpenters, builders, boilermakers, electricians and dockyard workers.

Asbestos exposure estimations

Cumulative asbestos exposure (fibre ml^{-1}-year) for each participant in our cohort was estimated using the AsbJEM (van Oyen et al., 2015). Exposure estimates for occupation–industry combinations over four time periods (1943–1966, 1967–1986, 1987–2003 and ≥2004) were evaluated by an expert panel. 'Mode' was the most common exposure level, and 'peak' was the short-term intense exposure in a particular job. 'Background' was the same as exposure from the general environment. The frequency and intensity of mode, peak and background exposures were pre-defined for each time period, except for the frequency of background exposure, which was calculated by subtracting the mode frequency from the total number of working days in the year (240 days assuming 2 days off a week and 4 weeks of holidays). The background, peak and mode exposures were each calculated as the product of intensity and frequency. The daily average exposure was calculated as the sum of all these exposures divided by 240. Accordingly, cumulative asbestos exposure for an individual in a specific occupation was calculated as the daily average exposure for that job (fibre ml^{-1}) multiplied by the length of employment (year) (fibre ml^{-1}-year) (van Oyen et al., 2015).

Examination of the AsbJEM

The AsbJEM was manipulated regarding the intensity of mode exposure, and the duration and frequency of peak exposure. The exposure–response relationship (estimated using methods described below) was iteratively examined to determine the best estimate of exposure, which was determined by the slope of the relationship: a steeper slope was considered to indicate a better estimation of asbestos exposure as it suggests less-exposure misclassification and less underestimation of exposure–response relationships (Lenters et al., 2011).

Intensity of mode exposure

The intensity of exposure was classified into background (0.0001 fibres ml^{-1}), low (0.01–0.1 fibres ml^{-1}), medium (0.1–1 fibres ml^{-1}), high (1–25 fibres ml^{-1}) and very high (25–50 fibres ml^{-1}) (van Oyen et al., 2015). The AsbJEM adopted the mid-point of the range of exposure in each category to represent the intensity of mode exposure. However, it is possible that for ARP participants, that value may have underestimated exposure because these people joined the ARP due to their awareness that they may have undertaken tasks which were at the higher end of the occupation-exposure combination. Therefore, we assessed whether the 75th and 90th percentile of the range of exposure better represented the level of exposure for this cohort than the 50th percentile.

Duration of peak exposure

During the development of the AsbJEM, the duration of peak exposure was arbitrarily set at 15 min. This had been discussed extensively at that time and was finalized based on the expertise of the occupational hygienists (Peters et al., 2016a). However, as pointed out by Kottek and Kilpatrick (2016), 'many of the historic reports of peak exposure are short-term measurements made during a task that was carried out for a much longer period'. Therefore, we further assessed other peak exposure durations, specifically 30, 60 and 120 min.

Frequency of peak exposure

Frequency of peak exposure was distributed at 1, 2, 11 or 48 days per year across various industry–occupation combinations in the AsbJEM, which was built on the experts' assessment of exposure in a particular job or industry. However, Kottek and Kilpatrick (2016) mentioned the possibility of the expert panel underestimating the frequency. Therefore, we also investigated whether twice the original frequency of peak exposure, in particular for the first time period (1943–1966), would result in a stronger exposure–response relationship with mesothelioma.

Case ascertainment

All incident cases of mesothelioma and related deaths in Western Australia are reported to the Department of Health Cancer Registry. Cases were determined by data linkage of ARP participants with the Cancer Registry. The Registry records both the date of diagnosis and the date of death, if appropriate. Data were available until 31 December 2014, which served as our censor date for this study.

Statistical analysis

Exposure–response relationship between asbestos exposure and the occurrence of malignant mesothelioma was evaluated in two different multivariate statistical models using Cox Proportional Hazards regression. The risk of mesothelioma incidence with particular cumulative asbestos exposures and the average exposure intensity was calculated in each model, respectively. Time to mesothelioma diagnosis since the entry to the ARP was defined as the underlying time scale with diagnosis of mesothelioma as the outcome variable, while explanatory variables included cumulative asbestos exposure in the first model, and the average exposure intensity and duration of exposure (length of employment) in the second model. Duration of exposure was not included in the first model due to high collinearity with cumulative asbestos exposure.

Cumulative asbestos exposure was re-calculated based on new assumptions of the intensity of mode exposure and the duration and frequency of peak exposure. The average exposure intensity was calculated as the division of cumulative asbestos exposure estimated using the AsbJEM by duration of exposure, which was defined as the total number of years of occupational asbestos exposure above the background level.

For all calculations, the distribution of cumulative asbestos exposure and the average exposure intensity were skewed, and natural logarithmic transformation was performed and used for the analyses. The incidence rate of mesothelioma was calculated as the number of mesothelioma cases divided by person-years since the entry to the ARP. Age at first exposure was also included in all models as this is known to influence mesothelioma incidence (Reid et al., 2007).

Continuous data were expressed as either mean and SD or median and interquartile range. Student's *t*-test or Wilcoxon rank sum test was performed for a comparison of the mean or median of two independent groups, respectively. For categorical data, chi-square test was conducted. Statistical significance was set at $P \leq 0.05$ (two tailed). The risk of developing the outcome was estimated by the hazard ratio (HR). The strongest association of mesothelioma incidence with cumulative asbestos exposure and the average exposure intensity was identified by the largest value of the coefficient estimated from the Cox regression models. Accordingly, the AsbJEM model that provided the steepest slope of the relationship was considered as the best estimate of occupational asbestos exposure because mesothelioma is caused exclusively by asbestos exposure. The shape of the exposure–response relationship was tested using fractional polynomials (Royston and Sauerbrei, 2005). Model fitting was evaluated using *C*-index (Harrell et al., 1996). Participants lost to follow-up were assumed to have lived to the end of the study or to 90 years of age. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 2084 people had attended the ARP. After excluding participants with additional non-occupational asbestos exposure (mostly from home renovation) (n = 373), uncertain occupational history (n = 81), only background exposure (n = 15) and women (n = 13), 1602 participants with occupational asbestos exposure were included in the analyses. There were 40 cases of mesothelioma (209 cases per 100 000 person-years). Compared with participants who did not develop mesothelioma, the mean age at first exposure was significantly younger for mesothelioma cases (15.7 ± 2.2 versus 17.0 ± 4.6, P = 0.0008) and the mean duration of exposure was significantly longer (37.5 ± 11.2 versus 31.9 ± 13.9 years, P = 0.01) (Table 1).

For all of the exposure estimates that were calculated through the manipulation of the AsbJEM, Spearman's correlation coefficients were examined to investigate whether the new estimates were just a re-scaling of the original estimates. To confirm that the manipulations did not constitute just a re-scaling, the standard deviation of within-person ranking for all of these exposure estimates was also examined against the null hypothesis that it was zero using one-sample *t*-test. Spearman's correlation coefficients calculated for all 24 patterns of the exposure estimates ranged from 0.8914 to 0.9998 (see Supplementary Table S1). They were highly correlated, but still not perfect. In addition, the standard deviation of within-person ranking for all of these exposure estimates was significantly deviated from zero for both calculated cumulative asbestos exposure and average intensity exposure (see Supplementary Figure S1). Both of these findings verified that the manipulation of the AsbJEM was not due to a re-scaling of the exposure estimates.

Table 1. Comparison of exposure characteristics for participants with and without mesothelioma

	Mesothelioma (n = 40)	No mesothelioma (n = 1562)	P-value
Age at first exposure	15.7 ± 2.2	17.0 ± 4.6	0.0008
Duration of exposure	37.5 ± 11.2	31.9 ± 13.9	0.01
Time since first exposure	55.1 ± 8.2	56.8 ± 10.5	0.33
Time since entry to the ARP	8.7 ± 6.1	12.1 ± 7.6	0.001

Data are expressed as mean ± SD (years).

Both the median calculated cumulative asbestos exposure and average intensity exposure were significantly higher for mesothelioma cases compared with non-cases for all estimations of the AsbJEM (see Supplementary Tables S2 and S3).

Asbestos exposure indices such as cumulative asbestos exposure and the average exposure intensity were fitted as linear functions in the models as testing fractional polynomials demonstrated that they were better than quadratic functions for all assumptions of the AsbJEM ($P > 0.05$). After adjusting for age at first exposure, there was a significant association of mesothelioma incidence with cumulative asbestos exposure for all calculations of the AsbJEM (Table 2). A revised AsbJEM with doubled peak frequency and no change for other indices (the 50th percentile of the range of each exposure category as mode intensity and peak duration of 15 min) produced the strongest exposure–response relationship of 0.2723 or an HR of 1.31 [95% confidence interval (CI): 1.12–1.53] for every log fibre ml^{-1}-year increase of cumulative asbestos exposure (Tables 2 and 3). The largest value of *C*-index was also demonstrated with this assumption (Table 2).

After adjusting for duration of exposure and age at first exposure, there was also a significant association of mesothelioma incidence with the average exposure intensity for all calculations of the AsbJEM with the maximum coefficient of 0.2367 or an HR of 1.27 (95% CI: 1.08–1.49) for every log fibre ml^{-1} increase of the average exposure intensity occurring under the same AsbJEM assumptions as with cumulative exposure (Tables 3 and 4). Duration of exposure was also significantly associated with mesothelioma incidence with the coefficient ranging from 0.0363 to 0.0374 or an HR of

Table 2. Age-adjusted regression coefficients of cumulative asbestos exposure and *C*-index for different assumptions of mode intensity and peak duration and frequency[a]

Assumptions to calculate cumulative exposure		β-coefficient (SE)	*C*-index	*P*-value
Mode intensity	Peak duration			
Original peak frequency				
50%	15 min	0.2683 (0.0777)	0.6900	0.0006
	30 min	0.2668 (0.0809)	0.6862	0.0010
	60 min	0.2595 (0.0832)	0.6811	0.0018
	120 min	0.2472 (0.0837)	0.6740	0.0032
75%	15 min	0.2588 (0.0748)	0.6899	0.0005
	30 min	0.2606 (0.0781)	0.6891	0.0008
	60 min	0.2579 (0.0810)	0.6837	0.0015
	120 min	0.2497 (0.0827)	0.6778	0.0025
90%	15 min	0.2546 (0.0737)	0.6891	0.0005
	30 min	0.2576 (0.0769)	0.6897	0.0008
	60 min	0.2566 (0.0801)	0.6850	0.0014
	120 min	0.2503 (0.0822)	0.6793	0.0023
Doubled peak frequency				
50%	15 min	**0.2723 (0.0794)**	**0.6907**	0.0006
	30 min	0.2712 (0.0826)	0.6877	0.0010
	60 min	0.2648 (0.0845)	0.6836	0.0017
	120 min	0.2550 (0.0848)	0.6778	0.0026
75%	15 min	0.2629 (0.0764)	0.6903	0.0006
	30 min	0.2653 (0.0798)	0.6889	0.0009
	60 min	0.2631 (0.0826)	0.6862	0.0015
	120 min	0.2565 (0.0840)	0.6823	0.0023
90%	15 min	0.2587 (0.0753)	0.6899	0.0006
	30 min	0.2623 (0.0787)	0.6895	0.0009
	60 min	0.2618 (0.0818)	0.6869	0.0014
	120 min	0.2568 (0.0836)	0.6829	0.0021

Fifty percent, 75% and 90% indicate the 50th, 75th and 90th percentile of the range of mode intensity, respectively. The bold value indicates the largest number.
[a]Models including age at first exposure.

Table 3. Age-adjusted mesothelioma risk associated with cumulative asbestos exposure and the average exposure intensity

Cumulative exposure (fibre ml^{-1}-year)[a]	Mesothelioma cases (n)	Hazard ratio (95% confidence interval)[c]
Continuous		1.31 (1.12–1.53) per log fibre ml^{-1}-year
Categorized [median (range)][e]		
0.09 (0.002–0.67)	10	1 (reference)
0.93 (0.67–2.01)	12	1.91 (0.82–4.41)
2.23 (2.01–4.95)	8	3.24 (1.27–8.24)
12.3 (4.95–169.3)	10	5.37 (2.22–12.98)
Average exposure intensity (fibre ml^{-1})[b]	**Mesothelioma cases (n)**	**Hazard ratio (95% confidence interval)[d]**
Continuous		1.27 (1.08–1.49) per log fibre ml^{-1}
Categorized [median (range)][e]		
0.003 (0.0001–0.018)	9	1 (reference)
0.03 (0.018–0.04)	10	1.84 (0.75–4.53)
0.06 (0.04–0.12)	11	2.31 (0.96–5.60)
0.42 (0.12–5.74)	10	4.40 (1.78–10.91)

[a]Cumulative asbestos exposure was calculated using the AsbJEM with a modification (peak duration of 15 min, mode intensity at the 50th percentile of the range and doubled peak frequency during the first time period).
[b]Average exposure intensity was calculated using the AsbJEM with a modification (peak duration of 15 min, mode intensity at the 50th percentile of the range and doubled peak frequency during the first time period).
[c]Models including age at first exposure.
[d]Models including duration of exposure and age at first exposure.
[e]Grouping by quartiles of natural logarithmic transformed-exposure estimates.

1.04 under all assumptions of the AsbJEM. The largest value of C-index was also demonstrated with this assumption (Table 4).

Grouping by quartiles of exposure gave HRs of 1.91, 3.24 and 5.37 for the second, third and fourth quartile groups of cumulative asbestos exposures (0.93, 2.23 and 12.3 fibres ml^{-1}-years, respectively) compared with the reference exposure of 0.09 fibres ml^{-1}-years (Table 3) and HRs of 1.84, 2.31 and 4.40 for the second, third and fourth quartile of average exposure intensity (0.03, 0.06 and 0.42 fibres ml^{-1}, respectively) compared with the reference exposure of 0.003 fibres ml^{-1} (Table 3).

Discussion

The AsbJEM provided estimates of occupational asbestos exposure, enabling the detection of an exposure–response relationship with mesothelioma incidence in Australian workers. This was consistent with previously published literature (Hansen et al., 1998; Iwatsubo et al., 1998; Gasparrini et al., 2008; Clin et al., 2011; Offermans et al., 2014; Lacourt et al., 2014; Ferrante et al., 2016). As the association of mesothelioma incidence with asbestos exposure has been established, this study shows that the AsbJEM provides realistic estimates for occupational asbestos exposure in a wide range of jobs throughout Australia. The significant finding for average exposure intensity reinforces the effectiveness of the AsbJEM because intensity can only be estimated with the AsbJEM, whereas cumulative exposure also contains information obtained irrespective of the tool, i.e. duration of occupation/exposure, which was demonstrated to be significantly associated with mesothelioma incidence in this study and thus must have affected the effect of cumulative asbestos exposure. Furthermore, various assumptions of the AsbJEM were explored, and it was found that the published formula could be refined with some modification to the frequency of peak intensity since the strongest exposure–response relationship was demonstrated when it was doubled in the first period of time in the AsbJEM.

Mesothelioma incidence was estimated to be 209 cases per 100 000 person-years in this study. This finding should be interpreted with caution when it is compared with previous reports as the incidence was calculated from the entry to the ARP in this study. If it was calculated from first exposure, mesothelioma incidence would have been estimated to be 45 cases per 100 000 person-years. This figure is lower than 135–203 per 100 000 person-years among former asbestos miners and millers in Western Australia (Berry et al., 2012), while it is higher than 5.8 per 100 000 person-years from a population-based study in Italy (Mensi et al., 2016). However, previous studies of railway rolling

Table 4. Age-adjusted regression coefficients of both average exposure intensity and duration of exposure and *C*-index for different assumptions of mode intensity and peak duration and frequency[a]

Assumptions to calculate average intensity		β-coefficient (SE) for average intensity	*P*-value	β-coefficient (SE) for duration of exposure	*P*-value	*C*-index
Mode intensity	Peak duration					
Original peak frequency						
50%	15 min	0.2344 (0.0795)	0.0032	0.0374 (0.0136)	0.006	0.6849
	30 min	0.2291 (0.0824)	0.0054	0.0371 (0.0136)	0.006	0.6847
	60 min	0.2181 (0.0841)	0.0095	0.0367 (0.0136)	0.007	0.6827
	120 min	0.2033 (0.0841)	0.0157	0.0364 (0.0136)	0.007	0.6812
75%	15 min	0.2275 (0.0765)	0.0029	0.0374 (0.0136)	0.006	0.6839
	30 min	0.2259 (0.0796)	0.0046	0.0372 (0.0136)	0.006	0.6839
	60 min	0.2191 (0.0822)	0.0076	0.0368 (0.0136)	0.007	0.6830
	120 min	0.2077 (0.0833)	0.0127	0.0365 (0.0136)	0.007	0.6822
90%	15 min	0.2243 (0.0753)	0.0029	0.0374 (0.0136)	0.006	0.6835
	30 min	0.2239 (0.0784)	0.0043	0.0372 (0.0136)	0.006	0.6838
	60 min	0.2190 (0.0813)	0.0070	0.0369 (0.0136)	0.007	0.6828
	120 min	0.2091 (0.0829)	0.0116	0.0366 (0.0136)	0.007	0.6822
Doubled peak frequency						
50%	15 min	**0.2367 (0.0811)**	0.0035	0.0373 (0.0136)	0.006	**0.6860**
	30 min	0.2317 (0.0839)	0.0057	0.0369 (0.0136)	0.006	0.6850
	60 min	0.2220 (0.0851)	0.0091	0.0366 (0.0136)	0.007	0.6845
	120 min	0.2101 (0.0849)	0.0134	0.0363 (0.0136)	0.007	0.6835
75%	15 min	0.2300 (0.0780)	0.0032	0.0373 (0.0136)	0.006	0.6848
	30 min	0.2286 (0.0812)	0.0049	0.0370 (0.0136)	0.006	0.6856
	60 min	0.2226 (0.0835)	0.0077	0.0367 (0.0136)	0.007	0.6849
	120 min	0.2132 (0.0843)	0.0115	0.0364 (0.0136)	0.007	0.6840
90%	15 min	0.2268 (0.0769)	0.0032	0.0373 (0.0136)	0.006	0.6843
	30 min	0.2268 (0.0801)	0.0046	0.0371 (0.0136)	0.006	0.6852
	60 min	0.2224 (0.0827)	0.0072	0.0368 (0.0136)	0.007	0.6845
	120 min	0.2142 (0.0840)	0.0108	0.0365 (0.0136)	0.007	0.6841

Fifty percent, 75% and 90% indicate the 50th, 75th and 90th percentile of the range of mode intensity, respectively. The bold value indicates the largest number.
[a]Models including age at first exposure.

stock workers in Italy and shipyard workers in Sweden reported mesothelioma incidence as 22 and 54 per 100 000 person-years, respectively (Sandén et al., 1992; Gasparrini et al., 2008), which were comparable with the rate observed in this study. These findings indicate that the ARP cohort is representative of people at risk of developing mesothelioma from occupational asbestos exposures and that the AsbJEM can adequately estimate the level of such exposures for this group. Furthermore, mesothelioma was also observed in workers with relatively low cumulative occupational asbestos exposure, again consistent with previous studies. The lowest quartile of cumulative asbestos exposure for mesothelioma cases in this study was 0.67 fibres ml^{-1}-years with 10 cases occurring below this level. Offermans et al. (2014) described an HR of 2.69 for cumulative asbestos exposure of 0.20 fibres ml^{-1}-years compared with never-exposed subjects. Lacourt et al. (2014) demonstrated that when cumulative asbestos exposure ranged from 0 to 0.1 fibres ml^{-1}-years, the risk of mesothelioma became four times higher than in never-exposed subjects. They also stated that 15% of men with mesothelioma had cumulative asbestos exposure below 0.1 fibres ml^{-1}-years. In addition, Ferrante et al. (2016) reported that the odds ratio (OR) of mesothelioma rose to 4.4 when cumulative asbestos exposure increased from the background level below 0.1 to a range of 0.1–1 fibres ml^{-1}-years. The present study identified four cases of mesothelioma with cumulative asbestos exposure ranging from 0.002 to 0.1 fibres ml^{-1}-years (data only shown as the range of

0.002–0.67 fibres ml^{-1}-years). Iwatsubo et al. (1998) reported an OR for mesothelioma of 1.2 with cumulative exposure in the range of 0.001–0.49 fibres ml^{-1}-years. Therefore, the AsbJEM should inform the estimation of risk of mesothelioma for Australian workers with relatively low cumulative occupational asbestos exposure.

There were some differences between the present study and earlier studies elsewhere. Most previous studies were population based and thus subjects who were never occupationally exposed to asbestos could be included in the analysis (Lacourt et al., 2014; Offermans et al., 2014; Ferrante et al., 2016). This was also true for a hospital-based study (Iwatsubo et al., 1998). However, in the present study, a cohort with known occupational asbestos exposure was used, and participants with only background/non-occupational levels of asbestos exposure were not included. If such minimally exposed subjects had been included in our analyses, the association would have been greater because those people would have been at extremely low risk of developing mesothelioma. This would then be analogous to a previous study where a significant exposure–response relationship was obtained only when never-exposed subjects were included in the analysis (Offermans et al., 2014).

There are some caveats in the interpretation of the findings of this study. First, this is an indirect validation of the AsbJEM using the well-established association between exposure to asbestos and mesothelioma. It may be argued that an exposure metric should be assessed against a 'gold standard' such as counting the number of asbestos fibres in lung tissue samples to confirm the exposure level (Tuomi et al., 1991). However, it is unrealistic to apply such an invasive procedure to exposed populations, and adopting an alternative non-invasive measurement is more practical to estimate exposure (Hardt et al., 2014). Second, refining the AsbJEM was based on the assumption that the strongest exposure–response relationship, identified through the steepest slope, would indicate the best estimation of asbestos exposure. This assumption seems reasonable as exposure–response relationships are expected to improve if the misclassification of the estimation can be reduced (Lenters et al., 2011) as non-differential exposure misclassification is most likely to shift the slope towards the null (Höfler, 2005). A limitation of JEMs is the lack of precision for individual exposures as they assume workers undertaking similar job tasks in a particular industry receive the same or similar level of exposure, while there is known exposure heterogeneity within jobs (Kromhout et al., 1993). However, exposure misclassification is not expected to be associated with level of exposure, and we assumed that exposure misclassification was non-differential and, as such, not affecting our conclusions. However, there were no large differences in the slopes (β coefficients) of all the model variations, which suggests that the original AsbJEM would have been sufficient to estimate the association between occupational asbestos exposure and mesothelioma. Third, there was some uncertainty regarding the level of asbestos exposure before 1943. We assumed that exposure levels before 1943 were the same as the subsequent period from 1943 to 1966. This decision was supported by the expert panel, which was involved in the development of the AsbJEM although it is recognized that there was uncertainty present in some industries. However, this extrapolation was only necessary for a small number of jobs (n = 88) and thus would not have appreciably affected the findings.

Conclusions

The AsbJEM has been validated using a cohort with diverse occupational asbestos exposures. All variations of the AsbJEM, including the original, identified an exposure–response relationship between asbestos and malignant mesothelioma. The strongest relationship was found when the frequency of peak exposure in the AsbJEM was doubled from the originally published estimates. Therefore, this modification will be used for future application of the AsbJEM. It is expected that the results of this study will facilitate more widespread use of the AsbJEM in future research including risk assessment of other ARDs in Australia. The AsbJEM may therefore have a role for estimation of exposure and thus risk and attribution of causality of asbestos-related diseases.

Supplementary data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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Conflict of interest

The authors declare no conflict of interest relating to the material presented in this article. Its contents, including any opinions and conclusions expressed, are solely those of the authors. The study's sponsors did not influence the way the study was structured or carried out, the results or review of the manuscript prior to publication.

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