Original Article

Follow-up of Soluble Mesothelin-Related Protein Levels in Participants With Asbestos-Related Disorders

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ABSTRACT

Background: Asbestos exposure is associated with the development of the cancer malignant mesothelioma (MM). Measurement of soluble mesothelin-related protein (SMRP) has been suggested as a method for detection of MM in its early stages. We prospectively examined SMRP levels in participants with asbestos exposure who are a group at a high risk of development of MM.
Methods: This study was a follow-up of our cohort of 322 asbestos-exposed participants. No further participants developed MM or malignancy over the study period. Mean follow-up time was 22.9 months.
Results: Mean (standard deviation) SMRP levels at baseline and follow-up were 0.94 (0.79) and 0.91 (0.86) nmol/L ($p = 0.1033$), respectively. Mean SMRP levels of the healthy individuals exposed to asbestos at baseline was significantly lower than those of participants with asbestosis and pleural plaques alone; similar patterns were found on follow-up measurements. There was a statistically significant effect of age on serial SMRP measurements. Our study confirms higher levels in participants with nonmalignant asbestos-related disorders. Levels decreased in asbestos-related disorders other than asbestosis, where a small increase was observed. We did not detect any further cases of malignancy.
Conclusion: Monitoring programs for early detection of MM need to take into account increased SMRP levels found in benign asbestos-related diseases.
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1. Introduction

Malignant mesothelioma (MM) is an aggressive and incurable cancer primarily attributable to previous occupational and environmental exposure to asbestos [1,2]. Asbestos still remains the most occupational carcinogen in the world [3]. Large amounts of asbestos were used in the past in a variety of applications, especially in Australia, where there was among the highest consumption of asbestos per capita in the world [4]. The MM cases in Australia have been reported to total 17,491 between 1982 and 2017 [5]. There is a need for an effective prevention program for a population with asbestos exposure and/or nonmalignant asbestos-related disorders (ARDs) who are at the highest risk of development of MM.

MM has a survival time of less than 18 months after diagnosis [6,7]. Making a diagnosis of MM is difficult in practice as it usually presents with nonspecific symptoms; subsequently, this tumor is often diagnosed late. There are no internationally agreed evidence-based screening guidelines. ARDs have long latency periods from time from first exposure to disease [8,9]; median latency for MM is now approximately 40 years [10]. Although no treatments have been proven to cure MM, early diagnosis could in theory allow early treatment with control of MM. Monitoring asbestos-exposed participants using a biomarker, or a combination of biomarkers, could potentially allow early diagnosis.

Several biomarkers including the calretinin, fibulin-3, megakaryocyte potentiating factor, osteopontin, soluble mesothelin-related protein (SMRP) have recently been examined with the

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aim of facilitating early diagnosis of MM [11−15]. Elevated levels of SMRP have been found to correlate with MM of the epithelioid subtype rather than the sarcomatoid form [16−18], and SMRP levels increase with tumor growth and response to treatment [16,19]. Some studies have shown that SMRP distinguishes MM from benign asbestos-related diseases in asbestos-exposed participants [11,13,16,20], but this has not been confirmed in others [21,22]. Several other large cohort studies have also subsequently been conducted which assess SMRP changes over time [22−25]. In our previous study evaluating the feasibility of SMRP for diagnosing MM in an asbestos-exposed population, we evaluated 535 asbestos-exposed participants over one year [26]. Overall, we found that SMRP had too low a negative predictive value to be useful for screening that it was nonspecific and that levels were higher in participants with ARDs. Here, we present the findings of the same cohort, which were followed for a further two years with complete clinical data.

2. Material and methods

2.1. Participants and study design

The study population was derived from a cohort study conducted at the Workers' Compensation (Dust Diseases) Board (DDB) of New South Wales, Sydney, Australia [26]. After the first visit with approximately one year, participants were invited to measure SMRP levels with a routine examination which included a standardized questionnaire, radiology, lung function, weight, a clinical examination by a thoracic physician, and blood collection. Between February 2007 and November 2008, 322 participants were invited by written notice for a follow-up examination. The study was approved by the Human Research Ethics Committee of St. Vincent's Hospital, Sydney, Australia. All participants gave written informed consent. Participants were not compensated for their participation.

Serum samples were coded and stored at $-80°C$ until further analysis. Serum SMRP levels were measured using the MESO-MARK® ELISA kit (Fujirebio Diagnostics, Malvern, PA, USA) in accordance with the manufacturer's guideline, and results were expressed in nmol/L. The limit of detection (LOD) of the assay was 0.3 nmol/L.

2.2. Statistical analysis

Comparison of SMRP levels between and within ARD groups (ARDGs) was tested with nonparametric Mann−Whitney tests and the paired Wilcoxon test, respectively. Spearman's rank analysis determined the correlation between the diagnosed ARDs. One-way analysis of variance (ANOVA) with the Bonferroni correction for multiple comparisons in posthoc tests and Student t test were used. We were interested in examining the association of certain participant characteristics that influence SMRP levels over time, particularly, age and BMI (body mass index). Change in SMRP levels over time was modeled in random coefficient mixed models using the SAS program, which has the capability of also handling repeated measurements at unequally spaced times. This model allows specification of the variance−covariance matrix of the measurement error within each study unit (i.e., participant) and thus be able to examine the intramarker and intermarker correlations of the measurement errors. The results of these mixed models with random coefficients are slope parameters that represent the average change per month in SMRP and the directional relationship (positive or negative) with the two characteristics (age and BMI) being examined. These models also adjusted for smoking (pack-years). Values are reported as means [standard deviation (SD)]. All statistical analyses were performed in GraphPad Prism (version 5,

Graphpad Software, San Diego, CA) and SAS (version 9.1, SAS Institute, Cary, NC). A *p value* < 0.05 was considered significant.

3. Results

A total of 322 participants were followed up across from February 2007 and November 2008. The mean follow-up time was 22.9 months (range 12−32 months). The great majority in the follow-up study were men (99%) with only 1% women (n = 2). Of a data set of 322 asbestos-exposed participants, we excluded participants with silicosis (n = 9) and those whose diagnosis had changed during the follow-up period (n = 16). Ultimately, data of 297 participants were used for statistical analysis.

Five disease groups were categorized as follows: 1) asbestosis (n = 7); 2) diffuse pleural thickening (DPT, n = 49); 3) asbestosis and DPT (n = 6); 4) pleural plaques alone (PPs, n = 90); 5) the healthy but asbestos-exposed population with no apparent asbestos-related disease (n = 145).

Demographic details and SMRP levels are shown in Table 1. Mean (SD) age of all participants at baseline was 65.4 (10.3) years and 67.1 (10.2) years at follow-up. Mean (SD) BMI of all participants at baseline and at follow-up were 27.8 (4.0) and 28.4 (3.9), respectively. Current and ex-smokers were 27 (9.1%) and 148 (49.8%) participants, respectively, and mean (SD) pack-years at baseline and follow-up were 22.6 (20.7) and 23.1 (21.5), respectively.

Overall, mean (SD) levels of SMRP at baseline and follow-up were 0.94 (0.79) and 0.91 (0.86) nmol/L ($p = 0.1033$), respectively. There was a significant difference in the mean serum SMRP levels between 5 disease groups at baseline ($p < 0.0001$) and at follow-up ($p = 0.0008$).

Mean (SD) levels of SMRP in the healthy population exposed to asbestos (n = 145) at baseline and follow-up were 0.75 (0.42) and 0.78 (0.46) nmol/L, respectively ($p = 0.1847$). Mean (SD) levels of SMRP in those with PPs alone (n = 90) at baseline and follow-up were 1.20 (1.09) and 1.12 (1.26) nmol/L, respectively ($p = 0.1182$). Mean (SD) levels of SMRP in those with asbestosis (n = 7) at baseline and follow-up were 1.66 (1.37) and 1.75 (1.31) nmol/L, respectively ($p = 0.7881$). Mean (SD) levels of SMRP in those with DPT (n = 49) at baseline and follow-up were 0.93 (0.65) and 0.72 (0.66) nmol/L, respectively ($p = 0.0003$). Mean (SD) levels of SMRP in those with asbestosis/DPT (n = 6) at baseline and follow-up were 1.32 (0.93) and 1.16 (0.51) nmol/L, respectively ($p = 0.4085$). Mean

Table 1
articipant characteristics and SMRP levels at baseline and follow-up

	Baseline	Follow-up
Number (female)	297 (2)	297 (2)
Age [Mean (SD), min−max]	65.4 (10.3, 36 - 86)	67.1 (10.2, 38 - 87)
BMI [Mean (SD), min−max]	27.8 (4.0, 18.9 − 43.8)	28.4 (3.9, 19.6 − 42.5)
Pack-years [Mean (SD), min−max]	22.6 (20.7, 0.5 - 120)	23.1 (21.5, 1 - 120)
SMRP [Mean (SD), min−max, nmol/L]	0.95 (0.79, 0.3 − 9.34)	0.91 (0.86, 0.3 − 10.4)
Asbestos-exposed Groups [n (%)]		
Healthy [145 (48.8)]	0.75 (0.42)	0.78 (0.46)
Asbestosis [7 (2.4)]	1.66 (1.37)	1.75 (1.31)
DPT [49 (16.5)]	0.93 (0.65)	0.72 (0.66)
Asbestosis/DPT [6 (2.0)]	1.32 (0.93)	1.16 (0.51)
Pleural plaques [90 (30.3)]	1.20 (1.09)	1.12 (1.26)

BMI: body mass index; DPT: diffuse pleural thickening; SD: standard deviation; SMRP: soluble mesothelin-related protein.

SMRP levels of the healthy individuals exposed to asbestos at baseline were significantly lower than those of participants with asbestosis ($p < 0.05$) and PPs ($p < 0.05$) which were similar patterns in follow-up measurements, but at follow-up the mean SMRP levels of participants with asbestosis was significantly higher than that of participants with DPT ($p < 0.05$). Serum SMRP levels were significantly correlated between two sampling points (Spearman r = 0.6064, 95% Confidence Interval [CI]: 0.5267 − 0.6756, $p < 0.0001$) (Fig. 1).

Age and BMI were included in random coefficient mixed models to adjust for their effects on the SMRP levels within the ARDGs. Table 2 shows the estimated correlation coefficients derived from the mixed models, modeling the effects of age and BMI on the SMRP levels over time. It shows the statistically significant effect of age (correlation coefficient = 0.083, $p < 0.001$) on serial SMRP measurements while BMI did not significantly affect change of SMRP level over time. The random effects in this mixed model represent the association between the two slopes and the correlation between the two variables, and our results show a nonsignificant relationship between age and BMI. Fig. 2 shows the change in SMRP levels for the five disease groups that were surveyed, only highlighting the two statistically significant comparisons. It shows that baseline SMRP levels for the asbestosis/DPT group are significantly higher than those of the healthy individuals exposed to asbestos. The second interesting finding is that the follow-up SMRP levels for participants with PPs are statistically lower than baseline measurements. The reasons for this change are difficult to discern for our study but may represent regression to the mean or potential selection bias. This issue needs to be examined in future studies.

A composite variable that combined the four ARDGs to form a new variable called the "ARDG" was also included in the comparisons. Comparing participants in the ARDG with healthy participants, the only statistically significant comparison ($p < 0.05$) is shown (Fig. 3).

There were 16 participants excluded from the study because the classification of their ARDs had changed. The SMRP levels in six healthy individuals exposed to asbestos at baseline and reclassified as PPs at follow-up were 1.06, 1.26, 1.19, 1.03, 0.54, and 1.17 nmol/L at baseline and 0.3, 1.3, 2.04, 1.05, 0.63, and 1.34 nmol/L at follow-up, respectively. The SMRP level in one healthy individual exposed to asbestos at baseline and reclassified as asbestosis at follow-up were 0.66 and 1.47 nmol/L, respectively. The SMRP levels in two participants with asbestosis at baseline and reclassified as asbestosis/DPT at follow-up were 3.45, 0.86 nmol/L at baseline and 1.73, 0.63 nmol/
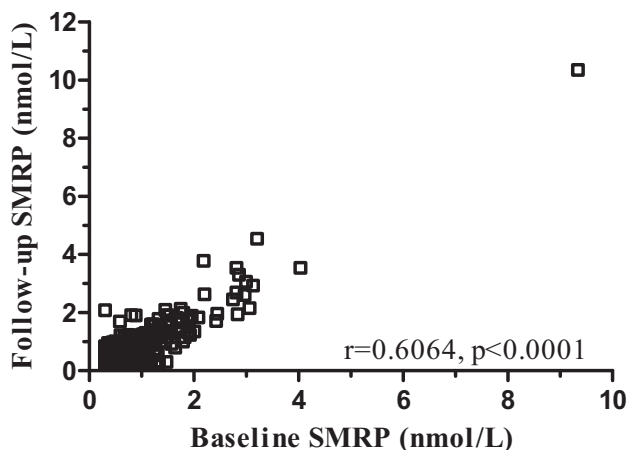
Table 2
Estimated correlation coefficients of the within-individual effect of age and BMI on SMRP levels

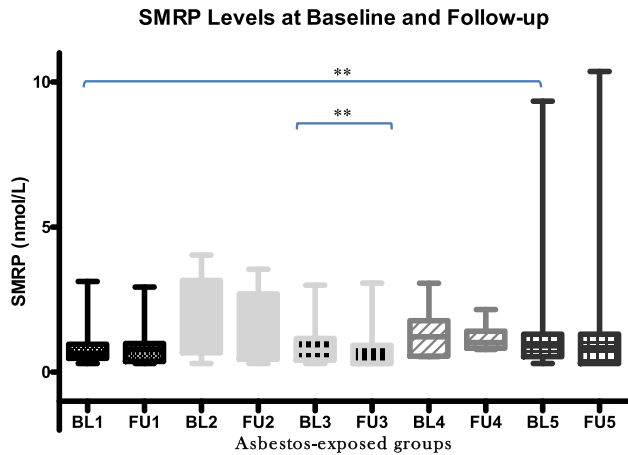| Features	Estimated correlation coefficients of age (X) and BMI (Y)	p
Fixed effects		
Slope$_x$	0.083***	<0.001
Slope$_y$	−0.001	0.103
Random effects		
Px	−0.048	0.414

BMI: body mass index; SMRP: soluble mesothelin-related protein.
***p < 0.001.

L at follow-up, respectively. The SMRP level in one participant with DPT at baseline and reclassified as asbestosis/DPT at follow-up were 0.42 and 0.3 nmol/L, respectively. Six participants who had been classified as PPs alone at baseline were later subsequently also reclassified as four DPT and two asbestosis in addition to PPs. The SMRP levels in two participants with PPs at baseline and reclassified as asbestosis at follow-up were 1.07 and 0.50 nmol/L at baseline and 0.3 and 0.3 nmol/L at follow-up, respectively. The SMRP levels in four participants with PPs at baseline and reclassified as DPT at follow-up were 0.3, 0.4, 0.52, and 0.34 nmol/L at baseline and 0.3, 0.3, 0.52, and 0.34 nmol/L at follow-up, respectively.

4. Discussion

Our study has examined the reproducibility of SMRP in participants with asbestos-related diseases compared with that in asbestos-exposed normal individuals. There is currently limited information available which includes good clinical data on this topic; yet, is it of importance when SMRP is considered as a potential screening tool in a clinical setting? The incidence of MM is highest in populations with asbestos exposure. Here, we present serial long-term biomarker measurements which confirm that SMRP has good reproducibility and that levels are affected by the presence of ARDs and by age. Our study confirms that SMRP levels are increased in participants with ARDs and also shows that these change within the different groups depending on the type of ARDs. Mean SMRP levels were stable in the whole group who did not develop any malignancy during the study period. This provides new data on SMRP in ARDs which may be of clinical utility.

The strengths of our study include a well-documented population with the full range of different nonmalignant ARDs, and longer term follow-up. There were no findings of any malignancy among our cohort during the study period, probably reflecting the size of the cohort and the length of follow-up as well as the fact that these participants had already been previously screened. The estimated lifetime risk of developing MM in a population with a history of asbestos exposure ranges 4.5−10.0%, but we did not document such an incidence [27]. SMRP levels among our cohort showed a wide variation, confirming that changes in individual levels need to be considered. As a group, mean (SD) levels of serum SMRP at baseline and follow-up were very closely correlated at 0.94 (0.79) and 0.91 (0.86) nmol/L ($p = 0.1033$). SMRP levels between the five ARDGs, however, differed significantly at baseline ($p < 0.0001$) and at follow-up ($p = 0.0008$), whereas differences emerged on subgroup analysis. Interestingly, there were significant differences in mean levels of SMRP in those with DPT (n = 49) at baseline and at follow-up ($p = 0.0003$), with mean levels actually falling. Mean levels rose in cases of asbestosis and fell in those with asbestosis and DPT. This is a helpful observation because it can be difficult to detect the development of MM in participants with extensive pleural disease, and an increase in the SMRP level in these groups should therefore

Fig. 1. Spearman rank correlation between baseline and follow-up levels of SMRP levels.

SMRP Levels at Baseline and Follow-up

Fig. 2. The box plot of SMRP levels of the five asbestos-exposed groups (1-5) taken at baseline (BL) and at follow-up (FU). 1 = Healthy; 2 = Asbestosis; 3 = Diffused Pleural Thickening (DPT); 4 = Asbestosis/DPT; 5 = Pleural Plaques. Only statistically significant comparisons (**$p < 0.05$) in the Mann−Whitney test for dependent groups and paired Wilcoxon test for independent groups are shown.

be interpreted seriously. It is interesting to speculate that changes within the different groups of ARDs may relate to their different underlying pathophysiologies, but our study cannot further examine this issue. Levels in healthy individuals showed no change with follow-up and remained significantly lower than those of participants with asbestosis ($p < 0.05$) and PPs ($p < 0.05$). This confirms the suggestion that SMRP levels correlate with severity of compensable ARDs such as asbestosis and could potentially be applied to monitor progress in the ARDs [28]. Our study has several limitations in that blood sampling and computed tomography were not mandatory because of the observational and voluntary nature of the study. As a consequence, the time of follow-up and time between blood samplings were not uniform across participants. Nonetheless, the study is probably more representative of the real world clinical situation rather than a selected epidemiological research cohort.

There have been several previous studies on this topic, most of which agree broadly with our findings. MM patients' SMRP level

SMRP Levels at Baseline and Follow-up

Fig. 3. The box plot of SMRP levels of the healthy group (HG) and the four asbestos-related diseased groups combined together as one group (ARDG), taken at baseline (@ BL) and at follow-up (@ FU). The only statistically significant comparison (**$p < 0.05$) by the Mann−Whitney test is shown. ARDG, asbestos-related disorder group; BL, baseline; FU, follow-up; HG, healthy group; SMRP: soluble mesothelin-related protein.

increased with the tumor growth, but that SMRP levels were stable in MM patients who underwent an objective response. Median SMRP values of 11 MM patients who had below 1 nmol/L at the time of diagnosis increased from 0.58 nmol/L at diagnosis to 0.73, 1.3, and 3.75 nmol/L at 2 months, 4 months, and 6 months after diagnosis, respectively. Sixteen MM patients with greater than 1 nmol/L at the time of diagnosis showed a median increase in serum SMRP levels to 2.1 nmol/L at 2 months, 5.2 nmol/L at 4 months, and 1.3 nmol/L at 6 months [23]. SMRP levels in participants with nonmalignant ARDs and no radiologically evident ARDs were thrice over 2 years. Median serum SMRP levels increased from 0.96 nmol/L at baseline to 1.18 nmol/L at 12.2 months (11.8−13.0) and 1.21 nmol/L at 24.2 months (22.0−24.6) [24]. Mean (SD) levels of SMRP in a population with formerly asbestos-exposed workers ($n = 1,884$), with an unknown history of asbestos exposure ($n = 256$) and with no asbestos exposure ($n = 102$) were 0.689 (0.433), 0.782 (0.644) and 0.561 (0.367) nmol/L, respectively. Four consecutive measurements of SMRP levels in 55 participants with a history of asbestos exposure showed no significant change over 2 years. Using criteria of an overall increase of more than 10 % during the 1-year interval between the first and last test as indicating no malignancy, mean (SD) of SMRP levels of 290 participants with a history of asbestos exposure over 765 days changed by 0.308 (0.353) nmol/L with an annual increasement of 0.172 nmol/L [25]. Filiberti et al. [22] also studied a cohort of 1,715 asbestos-exposed participants, finding that the median SMRP level at the first visit was significantly lower in healthy participants ($n = 1,227$) (median 0.43 nmol/L) than in participants ($n = 176$) with asbestos-related diseases (asbestosis, pleural thickening or plaques, median = 0.65 nmol/L; $p < 0.001$). SMRP was measured three times in 1,536 participants over a median time of 47.1 months. Epithelial MM developed in three cases, where SMRP levels at the first visit had ranged 0.17−0.52 nmol/L. There were 61 cases of other types of cancer during the study. Median SMRP levels in participants who developed cancer over follow-up changed little (0.41 nmol/L at the first and second visits to 0.46 nmol/L ($p = 0.2$) at the third visit). Overall, there was no significant change in SMRP levels over the study period [22].

SMRP levels among participants with ARDs have previously also been reported in different studies that SMRP levels were influenced by nonmalignant ARDs [22,25]. In this study, participants with pleural thickening or plaques had SMRP levels higher than those in healthy participants with a history of asbestos exposure [22]. A SMRP-based screening approach for early detection of MM could benefit from incorporation of serial measurements and individual-specific adjustments for age and kidney function (Glomerular Filtration Rate [GFR]), and our study would support these conclusions [24]. Our study differs from that of Filiberti et al. [22]; however, in that, they reported serum SMRP levels were influenced by age and BMI, whereas our further analysis suggests that BMI is a confounder rather than a primary factor affecting SMRP levels.

Our original study suggested that a single measurement of SMRP was unhelpful for screening for MM in asbestos-exposed individuals [26]. This has been confirmed in several subsequent studies [22−25]. In our current study, we did not observe any further cases of MM, which was good for our participants but did decrease the relevance of our study to MM screening. Our study is larger than that of Hollevoet et al. [24], who followed 215 participants, 137 of whom attended for a third SMRP sample at 2 years. The authors concluded that single measurements of SMRP were not likely to be helpful in screening for MM but that serial measurements and individual-specific screening might be of use [24]. We agree with these findings but would point out that our study has not been able to shed further light on this area in view of the lack of further cases of MM.
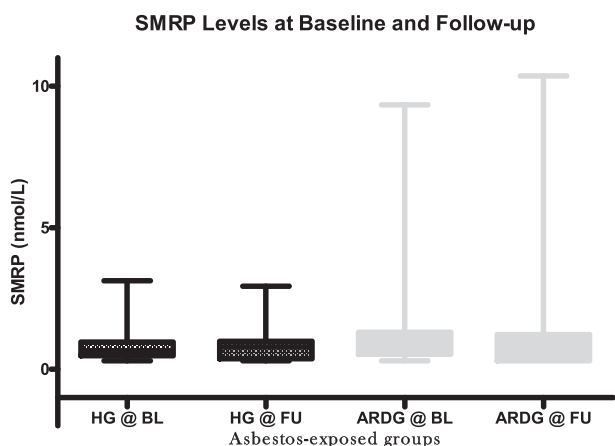
Despite limited treatment options for MM, new surgical and combined modality treatments for MM are becoming available, and early diagnosis should, in theory, offer the best hope for long-term survival in MM. Recently, there has been renewed interest in the potential for early resection in MM patients, and selected patients have been reported to survive for 5 years if the tumor is detected and promptly resected [29]. The majority of these patients have epithelial-type MM, which has a better prognosis than sarcomatous and mixed forms, and should be detected by SMRP assessment. Although standard treatment with pemetrexed in combination with a platinum agent improves survival in MM patients and has been incorporated into treatment guidelines [30], overall survival after diagnosis is still very poor [6,7]. SMRP analysis, alone or in combination with several other biomarkers, could eventually still prove useful for early detection of epithelial-type MM, but the many factors affecting its use need to be carefully documented. Recent reviews have highlighted several other potentially useful biomarkers [15,31], but SMRP is currently the only biomarker approved by the FDA for mesothelioma and thus the only biomarker for MM which can be used as a clinical tool.

To improve the survival rate in participants with MM, early detection and effective surveillance of the population at high risk is important, but in reality this is not an easy task. An ideal biomarker would accurately identify patients with MM, differentiate MM from benign pleural disease or other types of cancer, include all different histological subtypes of MM, and correlate with disease extent. The biomarker should be easily measurable in samples collected non-invasively and should be useful for predicting prognosis and treatment response. It should also be realistically priced. Although it can be measured in pleural fluid and in urine, it seems likely that serum measurements are most useful for early disease [32,33]. SMRP has emerged as a more useful biomarker for monitoring response to treatment in established epithelial-type MM and for detection of early MM [15,22–25,34]. SMRP has good specificity but suboptimal sensitivity for detection of MM. Nonetheless, it is important to describe the factors which affect its levels to further elucidate its proper clinical role. Many studies have not been able to contribute complete clinical data, often enrolling patients diagnosed with MM and also controls rather than prospectively monitoring asbestos-exposed participants. In addition, factors known to affect SMRP levels such as renal function may not be included.

Given the fact that MM is a fatal cancer, our aim must be to prevent MM altogether. Until asbestos exposure can be ceased altogether, optimal management of the people who have been exposed to asbestos is important. Those with a history of asbestos exposure and nonmalignant ARDs represent a well-defined group at risk of development of MM in the future, in whom screening would be possible, but in whom this has not yet been implemented. SMRP is not the perfect biomarker, but emerging information about its clinical application can only assist in the overall understanding of ARDs and their management.

Ethical approval

The study was approved by the Human Research Ethics Committee of St. Vincent's Hospital, Sydney, Australia. All participants gave written informed consent. Participants were not compensated for their participation.

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Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2020.07.009.

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