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Original Article

Association of Biomarker Levels with Severity of Asbestos-Related Diseases

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Objectives: Asbestos-related diseases (ARDs) have increased globally over the decades, causing an economic burden and increased health care costs. It is difficult to predict the risk of development of ARDs and of respiratory disability among workers with a history of asbestos exposure. Blood based biomarkers have been reported as promising tools for the early detection of malignant mesothelioma. This study investigated whether serum soluble mesothelin-related peptide (SMRP) would reflect severity of disablement in compensable ARDs.
Methods: SMRP levels were measured in a cohort of 514 asbestos-exposed subjects. Severity of ARDs was assessed by a Medical Authority comprising four specially qualified respiratory physicians. Severity of ARDs and SMRP levels were compared.
Results: Mean (standard deviation) serum SMRP level in the population with compensable ARDs (n = 150) was 0.95 (0.65) nmol/L, and was positively associated with disability assessment ($p = 0.01$). Mean SMRP level in healthy asbestos-exposed subjects was significantly lower than those with pleural plaques ($p < 0.0001$) and in subjects with ARDs who received compensation ($p < 0.01$).
Conclusion: This study indicates that serum SMRP levels correlate with severity of compensable ARDs. Serum SMRP could potentially be applied to monitor progress of ARDs. Further prospective work is needed to confirm the relationship between SMRP and disability assessment in this population.

Key Words: Asbestos-related diseases, Compensation, Disability, SMRP

Introduction

Asbestos is a carcinogenic substance [1], which causes malignant mesothelioma (MM) and lung cancer. It also induces benign diseases, such as pleural plaques, asbestosis, and diffuse pleural thickening. These diseases, simply called asbestos-related diseases (ARDs) are well described and the annual death attributable to asbestos exposure is estimated to be approximately 107,000 worldwide [2]. Compensation costs in the USA and Europe in the next decade are estimated at USD 280 billion [3].

If ARDs could be detected in their early stages, they might be managed and treated more effectively. MM, in particular, has no cure, but novel treatments are under development and early detection might eventually prove helpful in controlling this neoplasm [3,4]. Blood based biomarkers, such as soluble mesothelin-related peptide (SMRP), have been reported to be useful in the differential diagnosis and in monitoring the progress of epithelial type MM, but not for early detection [5-10].

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There are several studies that have suggested that an elevated serum SMRP level is also related to the duration of past asbestos exposure [10,11], although contrary findings have also been reported [8], possibly due to the difficulty in quantifying asbestos exposure [12]. If SMRP can be used as a surrogate for past asbestos exposure, this might be helpful in predicting the severity of disablement because the risk of these disease developments is related to cumulative asbestos exposure [13].

To date, the relationship between SMRP level and degree of severity of ARDs has not been investigated. Therefore, the aim of this study was to assess whether serum SMRP levels reflect disablement assessment and severity of ARDs.

Materials and Methods

Study population

These data are derived from a cohort population, which has been previously described [7]. In brief, the study was conducted at the Workers' Compensation (Dust Diseases) Board (DDB) of New South Wales, Sydney, Australia. This study was approved by the Human Research Ethics Committee of St. Vincent's Hospital, Sydney, Australia. All participants provided written informed consent followed by blood collection and they were not compensated for their participation. Serum samples were stored at -80°C until analysis. A routine medical examination for asbestos-exposed workers conducted at the DDB included a standardized questionnaire, a clinical examination by a thoracic physician, a chest radiograph, a computed tomography (CT) scan if indicated, and full lung function tests. Subjects were categorized into 5 diagnostic groups according to the American Thoracic Society criteria [14].

Compensation scheme and assessment of disability

Under the Workers' Compensation (Dust Diseases) Act 1942, workers who had occupational asbestos exposure as an employee in New South Wales, Australia, are eligible to apply for compensation to the DDB. The Medical Authority (MA) at the DDB consists of a panel of four respiratory physicians. The MA certifies that an individual has an ARDs and is entitled to compensation after a consideration of occupational history, radiological evidence, lung function test results, and (where required) the caring respiratory physician's medical report. The severity of compensable ARDs is measured as a percentage respiratory disability between 0% and 100%, based on American Medical Association (AMA) IV criteria [15]. These criteria are based on symptoms, lung function tests and, where necessary, further tests. Respiratory disablement was classified into 4 different classes (0-9%, 10-25%, 26-50%, and 51-100%). MM and lung cancer due to asbestos exposure are always assessed as having 100% respiratory disablement. Non-malignant occupational respiratory disorders are assessed according to symptoms, lung function test results, and radiological findings. Subjects awarded compensation are entitled to a regular pension and their disablement assessment is reassessed approximately every two years on the basis of repeat examinations and investigations.

SMRP measurement

Serum SMRP levels were determined using the commercial ELISA kit (Mesomark; Fujirebio Diagnostics Inc., Malvern, PA, USA) according to the manufacturer's instructions, and results were expressed in nmol/L. The limit of detection (LOD) for SMRP assay was 0.3 nmol/L. Samples less than LOD were reported as 0.3 nmol/L for statistical purposes. Assays were performed in duplicate and in blinded fashion at a single laboratory.

Statistical analysis

The association between SMRP levels and degree of severity of ARDs were determined using analysis of variance (ANOVA), chi-square test, Pearson regression, and the Students' t-test. A Bonferroni correction was applied for multiple comparisons in *post hoc* tests. Statistical analyses were performed in GraphPad Prism (version 5; Graphpad Software, San Diego, CA, USA). A p-value less than 0.05 was considered significant.

Results

Study population

The study population has been previously described [7]. Briefly, study participants (n = 514) were categorized into 5 diagnostic groups: asbestosis (n = 24), diffuse pleural thickening (DPT) (n = 113), asbestosis and DPT (n = 13), pleural plaques (PPs) only (n = 141), and apparently healthy subjects with past asbestos exposure (n = 223). Mean age (stnadard deviation, SD) of this population (n = 514) was 66.9 (10.1) years. A total of 150 subjects were diagnosed with asbestosis, DPT, and asbestosis + DPT by the MA which are the compensable ARDs. Of these, 81 subjects were deemed disabled due to their disease and had respiratory disablement assessed as between 10-100% and they were thus eligible for compensation (Table 1). Sixty-nine subjects were assessed as 0% disability although ARDs were diagnosed. There was no statistical difference in age or body mass index between the two groups of subjects with compensable ARDs; however, the group with compensated ARD had significantly more ex-smokers than those with non-compensated

Table 1. Basic characteristics of study subjects by group

	Healthy asbestos-exposed population (n = 223)	Pleural plaques (n = 141)	Non compensated ARDs* (n = 69)	Compensated ARDs* (n = 81)
Age, mean (standard deviation), year	61.2 (10.2)	69.7 (8.7)	70.7 (7.3)	73.2 (6.2)
Body mass index, % (n)				
< 18.5	0.5 (1)	0.7 (1)	0 (0)	1.2 (1)
18.5-24.9	20.6 (46)	24.1 (34)	13.0 (9)	11.1 (9)
25-29.9	48.9 (109)	51.1 (72)	53.6 (37)	59.3 (48)
≥ 30	30.1 (67)	24.1 (34)	33.3 (23)	28.4 (23)
Smoking status, % (n)				
Never-smoker	46.6 (104)	35.9 (51)	18.8 (13)	23.5 (19)
Ex-smoker	42.6 (95)	56.0 (79)	5.8 (4)	72.8 (59)
Current-smoker	10.8 (24)	7.8 (11)	75.4 (52)	3.7 (3)

ARDs: asbestos-related diseases.
*ARDs include asbestosis, diffuse pleural thickening (DPT), and asbestos/DPT. Entitlement of compensation is based on severity of ARDs from 0-100%.

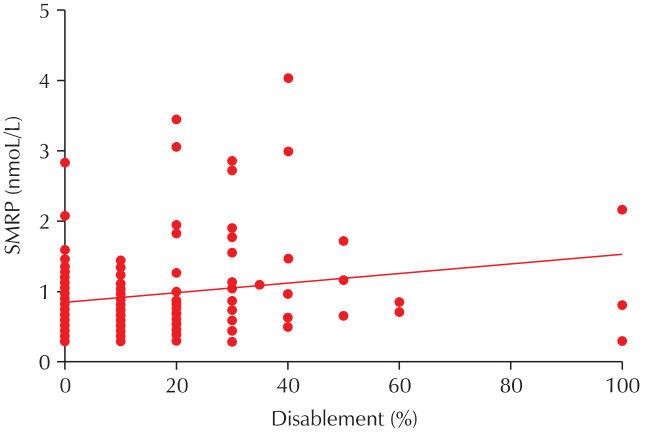

Fig. 1. Association between SMRP concentration and disablement due to asbestos-related diseases as assessed by the Medical Authority (n = 150, Pearson r = 0.209, p = 0.01). SMRP: soluble mesothelin-related peptide.

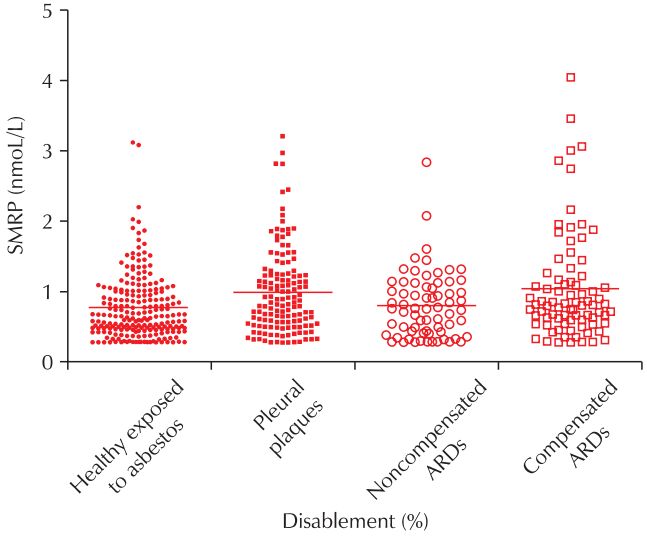

Fig. 2. SMRP concentration in subjects. (1) Exposed to asbestos but apparently healthy, (2) with pleural plaques, (3) with asbestos-related diseases (includes asbestosis, diffuse pleural thickening [DPT] and asbestosis/DPT) but not eligible for compensation due to their 0% disablement, (4) with compensated asbestos-related diseases due to their 10-100% disablement. Horizontal scale bars denote mean concentrations. There was a significant difference between the groups (analysis of variance, p < 0.0001). SMRP: soluble mesothelin-related peptide, ARDs: asbestos-related diseases.

ARDs (p < 0.0001).

SMRP measurements

Mean (SD) serum SMRP level in the population with compensable ARDs (0-100%, n = 150) was 0.95 (0.65) nmoL/L. A significant positive correlation between SMRP level and severity of compensable ARDs (0-100%, n = 150) was found (Pearson r = 0.209, p = 0.01, Fig. 1).

Mean (SD) serum levels of SMRP differed between the four groups; 1) subjects with a history of asbestos exposure but apparently healthy (n = 223, 0.79 [0.45] nmoL/L); 2) subjects with PPs (n = 141, 1.00 [0.60] nmoL/L); 3) subjects who were diagnosed with compensable ARDs but were not awarded compensation due to their 0% disability (n = 69, 0.82 [0.46] nmoL/L); and 4) subjects who received compensation due to their 10-100% disability (n = 81, 1.06 [0.76] nmoL/L) (ANOVA, p < 0.0001, Fig. 2). Mean SMRP level in the healthy subjects was significantly lower than in subjects with PPs (p < 0.01) and in subjects who were entitled to compensation due to

their 10-100% disability ($p < 0.01$).

Discussion

Our study has demonstrated a relationship between disablement from non-malignant ARDs (as assessed according to AMA criteria) and a blood biomarker, SMRP. This is not unexpected because disablement is awarded to those who are suffering from an established disease due to asbestos and who are symptomatic, and is strongly linked to a severity of the diseases, which in turn is related to previous cumulative exposure to asbestos. Severity of disability, as determined by the MA using AMA V criteria [15], takes into account the symptoms, lung function, and radiological change, but is highly reliant on lung function. Mean (SD) serum levels of SMRP differed between four groups examined and the mean SMRP level in the healthy subjects was significantly lower than in subjects who were entitled to compensation due to their 10-100% disability ($p < 0.01$). Thus, SMRP, which is an entirely objective marker, seems likely to reflect different stages or severity of ARDs and could potentially be used for monitoring progress or disablement assessment in ARDs. To our knowledge, this is the first report of such an association.

Asbestos usage has declined substantially in the Western world over the last four decades, but ARDs are predicted to increase due to the long latency period for development of the disease [13,16,17]. New technologies and increasing awareness of the adverse health effects of asbestos exposure are also likely to increase the diagnosis of these diseases. Thus, it is likely that the measurable prevalence of ARDs will increase over the next decades. Improvements in diagnostic methods (including blood biomarker usage) are also likely to occur. Although improvement in diagnostic methodologies have allowed earlier diagnosis of benign ARDs, such as pleural plaques, it is still difficult to diagnose MM in its early stages [4]. Accurate non-invasive tests for asbestos-related malignancies would be of considerable clinical benefit. Several biomarkers have been suggested for MM detection in its early stages and SMRP has received significant research attention [5-10,12]. However, biomarker analysis has not yet been applied to the assessment of disease severity or to compensation status.

Along with diagnostic studies, several recent reports have investigated the association between SMRP levels and past history of asbestos exposure [8,9,11,12]. These studies were not uniform in their findings. Pass et al. did not find an association between SMRP and duration of past asbestos exposure [8] but others found a significant relationship [9,11]. In these later studies, higher levels of serum SMRP were significantly related to the duration of past asbestos exposure.

Overall, the development of ARDs is related to duration of asbestos exposure in most populations, probably because this is a surrogate for intensity of exposure [13]. Disablement severity is assessed on the basis of symptoms as well as objective measures, such as lung function testing, and usually reflects an established disease that is more severe and thus highly likely to be related to past intensity of asbestos exposure. Thus, it is expected that SMRP would be related to the severity of disease and therefore to disablement status. It was not possible for us to assess past asbestos exposure in our study because of incomplete previous occupational exposure history records of the previous occupational exposure history in our cohort population. However, this would ideally be performed using an evidence-based methodology, such as a standardized questionnaire and an occupational exposure matrix [18].

There are several potential confounding factors in our study. The population was derived from a compensation and screening registry, and it is therefore biased to include those with symptomatic diseases. Our findings are not reflective of the population in general, and in particular, for those with ARDs who do not apply for compensation. All our study subjects were men. Smoking habits differered between the groups. Interestingly, SMRP levels in subjects with PPs were similar to those with compensable disease. The reasons for this are uncertain, but it is possible that some patients with PPs also had other ARDs, particularly asbestosis and/or DPT. High resolution CT scans are required for diagnosis and assessment in such cases, but these were not always available in our study. Currently, PPs alone (or with chest pain) are not accepted for compensation in the absence of other ARDs, as they are not associated with lung function abnormalities [19,20], although this has been questioned [21].

Lung function measurements were performed as part of an assessment for compensation, and it is possible that this could have confounded the results. We have previously found an association between lung function and SMRP levels [22], although the mechanism for this is unclear. It would be expected that SMRP would reflect severity if this were the case. However, it is also possible that SMRP reflects an inflammatory or another process which has been activated by asbestos exposure and which eventually results in an established disease. If SMRP or other biomarkers are found to be an accurate reflection of disablement, this could be helpful in providing an objective method of assessment. Further prospective work is needed in this area to substantiate our findings and clarify the underlying pathophysiological mechanisms of raised SMRP after asbestos exposure.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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