**CA 15129, DiMoPEx**
**Di**agnosis, **Mo**nitoring, **P**revention of **Ex**posure Related Non-Communicable Diseases

COST is supported by the EU Framework Programme Horizon 2020

**WG1-WG3-WG5**

# SMRP and fibulin-3 as biomarkers in malignant mesothelioma

DiMoPEx


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## Introduction

Malignant mesothelioma (MM) is an aggressive malignant disease that has been associated with occupational and environmental exposure to asbestos (1,2). Since MM remains a fatal disease that is hard to treat, potential new biomarkers for earlier diagnosis and following the response to treatment have been intensively investigated. Among them are soluble mesothelin-related peptides (SMRP) and fibulin-3 (3,4,5).

**This study aimed to determine SMRP and fibulin-3 levels in patients with MM before treatment and in various responses to treatmen to investigate if SMRP and fibulin-3 levels could be useful in evaluating tumour response to treatment**.

## Methods

A panel study included 78 patients with MM treated and followed-up at the Institute of Oncology Ljubljana in the period between March 2007 and June 2011.

For all the patients, data on smoking were obtained using a standardized questionnaire. To determine occupational and/or environmental asbestos exposure, a semi-quantitative method was used. According to the cumulative asbestos exposure, the subjects were categorized into four groups: no exposure, low exposure, medium exposure and high exposure.

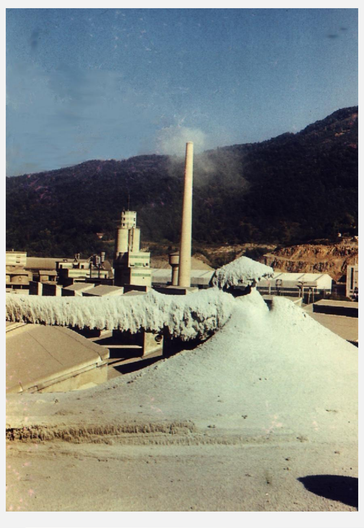
Serum samples were collected in all subjects before the treatment and/or at different responses to treatment (complete response, partial response, stable disease, progressive disease). Serum SMRP levels as well as fibulin-3 levels were determined using commercial ELISA assays.

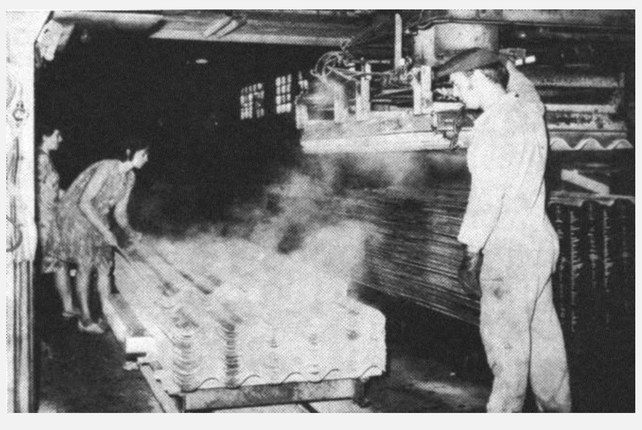
Standard descriptive statistics were used to describe each variable. Mann-Whitney test was performed to determine the differences in SMRP and fibulin-3 levels before treatment and in various responses to treatment. The correlations between fibulin-3 and SMRP levels were calculated using Pearson's correlation coefficient.

## Results – patients characteristics

The study included 78 patients with MM, 57 (73%) male and 21 (27%) female. The overall mean (min–max range) age was 64.48 (23.37–83.70) years. Among them, 35 (44.9%) were ever smokers and 43 (55.1%) of them never smoked.

Asbestos exposure was confirmed in 67 (85.9%) of the patients with MM. The assessed exposure was low in 24 (30.8%) patients, median in 21 (26.9%) patients, and high in 22 (28.2%) patients, while in 11 patients (14.1%) asbestos exposure could not be proved with certainty. In the exposed group, the mean duration of exposure was 141.32 (0.1–528) months.





Asbestos cement manufacturing plant of Salonit Anhovo, Slovenia.

## Results – biomarker analysis

Pre-treatment SMRP levels were significantly higher than in stable disease, partial response and complete response (U = 799.50, p = 0.008) as were the SMRP levels in progressive disease compared to stable disease, partial response and complete response to treatment or after surgery (U = 507.00, p = 0.000) (Table 1). Regarding fibulin-3, the levels were significantly higher in progressive disease as compared to the levels in stable disease, partial response and complete response to treatment or after surgery (U = 813.00, p = 0.001) (Table 2). No significant difference was observed between the fibulin-3 levels before treatment as compared to the levels in stable disease, partial response and complete response to treatment (U = 877.00, p = 0.299). No significant correlation was detected between SMRP and fibulin-3 levels

**Table 1. SMRP levels (nmol/l) before treatment and in different responses to treatment in 78 patients with malignant mesothelioma**

| Disease phase | Mean | SD | Median | Range | Inter-quartile | Mann-Whitney (U) test | P value |
|---|---|---|---|---|---|---|---|
| All phases (N=135) | 5.74 | 7.23 | 2.97 | 0.00–34.80 | 0.89–7.98 | | |
| Before treatment (N=33) | 5.75 | 7.77 | 2.80 | 0.00–34.80 | 0.71–8.76 | 799.50[a] | 0.008 |
| Complete response or after surgery (N=5) | 0.32 | 0.78 | 0.00 | 0.00–1.91 | 0.00–0.48 | | |
| Partial response (N=13) | 1.71 | 2.06 | 1.00 | 0.00–6.66 | 0.00–3.31 | | |
| Stable disease (N=39) | 2.87 | 3.85 | 1.79 | 0.00–20.71 | 0.51–3.33 | | |
| Progressive disease (N=45) | 9.56 | 8.20 | 7.05 | 0.28–31.56 | 3.38–12.67 | 507.00[b] | 0.000 |

N = number of serum samples; Mann-Whitney (U) test calculated for:
[a]SMRP before treatment vs. stable disease + partial response + complete response or after surgery;
[b]SMRP in progressive disease vs. stable disease + partial response + complete response or after surgery

**Table 2. Fibulin-3 levels (ng/ml) before treatment and in different responses to treatment in 78 patients with MM**

| Disease phase | Mean | SD | Median | Range | Inter-quartile | Mann-Whitney (U) test | P value |
|---|---|---|---|---|---|---|---|
| All phases (N=135) | 44.57 | 21.31 | 40.78 | 0.00–105.00 | 29.18–56.27 | | |
| Before treatment (N=33) | 40.57 | 22.26 | 35.09 | 1.65–92.32 | 24.23–56.21 | 877.00[a] | 0.299 |
| Complete response or after surgery (N=5) | 32.43 | 9.98 | 34.25 | 18.16–45.50 | 23.55–40.40 | | |
| Partial response (N=13) | 45.13 | 26.48 | 41.18 | 0.00–105.00 | 27.90–56.42 | | |
| Stable disease (N=39) | 40.00 | 16.11 | 37.10 | 6.52–73.44 | 29.40–47.56 | | |
| Progressive disease (N=45) | 53.56 | 21.67 | 47.19 | 16.26–105.0 | 37.78–67.93 | 813.00[b] | 0.001 |

N = number of serum samples; Mann-Whitney (U) test calculated for:
[a]fibulin-3 before treatment vs. stable disease + partial response + complete response or after surgery;
[b]fibulin-3 in progressive disease vs. stable disease + partial response + complete response or after surgery

## Discussion/Conclussions

Our findings suggest that SMRP may be a useful tumour biomarker for evaluating tumour response to treatment and detecting the progression of MM. The analysis also showed that fibulin-3 could be helpful in identifying the progression of the disease. However, to confirm these results more cases are needed to give power to the study and to conduct a thorough analytical follow-up study which will also include possible confounders and modifiers of exposure and disease.

## References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