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HBM4EU project

SERUM BIOMARKERS IN ASBESTOS RELATED DISEASES

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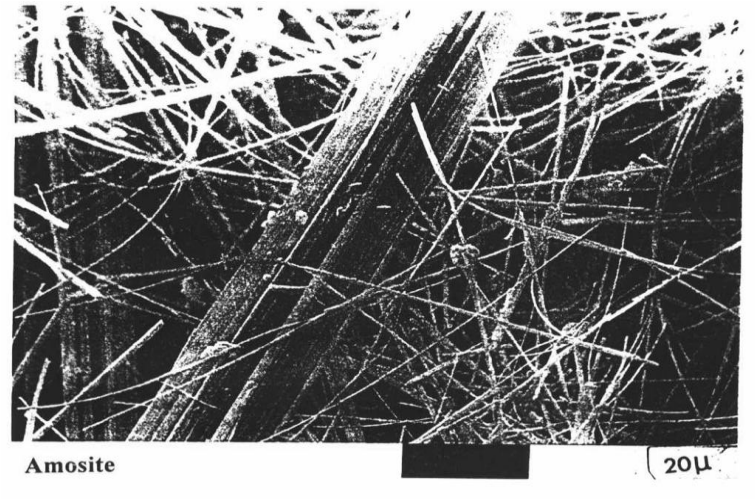
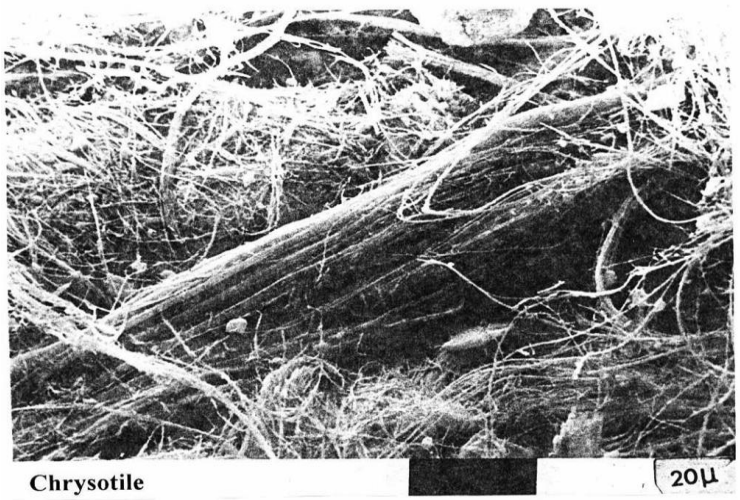
Asbestos





- ability to produce inflammation
- fibrous scarring
- cancer

Asbestos exposure

Has been associated with the development of:

- asbestosis
- pleural diseases, such as pleural plaques, diffuse pleural thickening and pleural effusion

Asbestos exposure

Has been associated with the development of several types of cancer:

- bronchogenic carcinomas
- diffuse malignant mesothelioma of the pleura and peritoneum
- cancer of the larynx, buccal mucosa, the pharynx,
- cancer of the ovary
- of the gastrointestinal tract
- the kidney

Malignant mesotelioma (MM)

- is a highly aggressive tumour of serosal surfaces, such as the pleura and the peritoneum
- the major cause and carcinogen associated with the development of this disease is asbestos
- MM is still difficult to diagnose
- potential serum biomarkers that could facilitate early diagnosis and help to follow the response to treatment have been investigated

Potential biomarkers

Soluble Mesothelin Related Protein (SMRP)

Fibulin-3

Survivin

Soluble Mesothelin Related Protein

- Mesothelin is a 40-kDa glycoprotein attached to the cell surface that is thought to have a role in cell adhesion and possibly in cell-to-cell signaling
- It exists in a variety of forms that can be detected in serum by using monoclonal antibody techniques in the form of soluble mesothelin-related peptides (SMRP)

Soluble Mesothelin Related Protein

- Mesothelin is highly expressed in malignant mesothelioma
- Several studies reported higher levels of SMRP in patients with malignant mesothelioma and suggested that SMRP may be a useful marker for the diagnosis of malignant mesothelioma and in monitoring the disease progression

SMRP-the aim of the study

- was to determine the differences in serum SMRP levels in subjects with MM before the treatment and at various responses to treatment (complete response, partial response, stable disease and progressive disease)
- to investigate if SMRP could play an important role in evaluating tumour response to treatment

SMRP-the methods

- The study included patients with malignant mesothelioma treated at the Institute of Oncology Ljubljana between March 2007 and December 2009
- Blood samples were collected before treatment and/or in various responses to treatment

SMRP-the methods

- SMRP levels were determined using ELISA assay based upon a combination of two monoclonal antibodies
- Mann-Whitney test was used to determine the differences in SMRP levels in various responses to treatment

SMRP-the results

- Pre-treatment SMRP levels were significantly higher than in stable disease, partial response and complete response, as were SMRP levels in progressive disease compared to stable disease, partial response and complete response

SMRP-the conclusion

- Our findings suggest that SMRP may be a useful tumor marker for detecting the progression of malignant mesothelioma and evaluating tumor response to treatment

Fibulin-3

- also known as epidermal growth factor containing fibulin-like extracellular matrix protein 1 (EFEMP1), is suggested to be a potential biomarker for malignant mesothelioma
- it belongs to a family of extracellular matrix glycoproteins that have recently been shown to act as tumour suppressors or activators in different cancers

Fibulin-3

- the levels have been found to be decreased in many cancer types due to promote hypermethylation
- has been correlated with poor survival of patients with lung cancer, breast cancer, and hepatocellular carcinoma
- on the other hand, an increase in fibulin-3 was observed in malignant gliomas, cervical carcinomas, and pancreatic cancer

Fibulin-3-the aim of the study

- to determine fibulin-3 levels in plasma of patients with MM before treatment and in various responses to treatment (complete response, partial response, stable disease, and progressive disease)
- to evaluate its potential applicability as a biomarker of tumour response to treatment
- to assess if plasma level of fibulin-3 could predict the probability of progressive disease after the response to treatment in the period of 18 months

Fibulin-3-the methods

- the study included patients with MM treated at the Institute of Oncology Ljubljana in the period between March 2007 and June 2011
- data on smoking were obtained using a standardized questionnaire
- blood specimen collection was carried out in patients before treatment and/or after treatment and/or at the progress of the disease

Fibulin-3-the methods

- Fibulin-3 levels in plasma were measured with the use of enzyme-linked immunosorbent assay
- The median value of fibulin-3 in complete response or after the surgery was chosen as the cut-off level
- Standard descriptive statistics were used to describe each variable
- Mann-Whitney test (U) test was performed to determine the differences in fibulin-3 levels before treatment and in various responses to treatment

Fibulin-3-the results

- in patients evaluated before the treatment fibulin-3 levels were not influenced by histopathological subtypes, tumour stages or the presence of metastatic disease
- significantly higher fibulin-3 levels were found in progressive disease as compared to the levels before treatment, in complete response to treatment, and in stable disease

Fibulin-3--the results

- patients with fibulin-3 levels exceeding 34.25 ng/ml before treatment had more than four times higher probability for developing progressive disease within 18 months .
- patients with fibulin-3 levels above 34.25 ng/ml after treatment with complete response or stable disease had increased odds for progressive disease within 18 months.

Fibulin-3 -the conclusion

Our findings suggest that in addition to SMRP fibulin-3 could also be helpful in detecting the progression of MM.

Survivin-the methods

- is a key member of the inhibitor of apoptosis protein (IAP) family, encoded by the *BIRC5* (baculoviral inhibitor of apoptosis repeat containing 5) gene
- is involved in the regulation of both apoptosis and cell division IAPs bind and inhibit caspases, reducing their activity and leading to suppression of programmed cell death

Survivin

survivin is usually not expressed in normal differentiated tissues, but is highly expressed in several cancers

Cisplatin

- Cisplatin is used in chemotherapy of several cancer types, including malignant mesothelioma

Survivin-the aim of the study

- to evaluate if serum survivin levels influence outcome of cisplatin-based chemotherapy in patients with MM

Survivin-the methods

- this panel study included patients with histologicaly proven MM treated with cisplatin-based chemotherapy at the Institute of Oncology, Ljubljana
- serum samples were collected before the start of the first day of chemotherapy, after the last cycle of chemotherapy and at disease progression

Survivin-the methods

- smoking status and exposure to asbestos were obtained during the clinical interview
- exposure to asbestos: patients were classified into following groups: occupational, environmental, and occasional asbestos exposure or no known asbestos exposure
- influence on tumor response and survival was evaluated using nonparametric tests and Cox regression

Survivin-the results

- patients with progressive disease had significantly higher survivin levels before chemotherapy
- median serum survivin level after chemotherapy was higher than median serum level at diagnosis
- if survivin levels increased after chemotherapy, patients had, conversely, better response
- unexpectedly, patients with increased survivin levels after chemotherapy also had longer progression-free and overall survival

Survivin -the conclusion

- These results suggest serum survivin levels before and during chemotherapy could serve as a biomarker predicting MM treatment response

Biomarkers-conclusions

Our findings suggest that:

- SMRP may be a useful tumour biomarker for evaluating tumour response to treatment and detecting the progression of MM
- fibulin-3 could be helpful in identifying the progression of the disease
- survivin levels before and during chemotherapy could serve as a biomarker predicting MM treatment response

Diseases

new serum biomarkers for developing of the risk for asbestos related diseases (MM) need to be further investigated

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Thank you for your attention

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Alenka Franko, PhD, MD, works as an associate professor at the Clinical Institute of Occupational Medicine, University Medical Centre Ljubljana, Slovenia. Dr Franko's research and teaching follow up several themes: Occupational and environmental toxicology, molecular epidemiology, genetics and gene-environment interactions, occupational medicine. She conducts this work nationally and internationally. In HBM4EU, she is involved in WP2.

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