

SCIENTIFIC REPORTS **OPEN** Prediagnostic detection of mesothelioma by circulating calretinin and mesothelin – a case-control comparison nested into a prospective cohort of asbestos-exposed workers

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Malignant mesothelioma (MM) is strongly associated with a previous asbestos exposure. To improve timely detection of MM in asbestos workers, better screening tools – like minimally-invasive biomarkers – are desirable. Between 2008 and 2018 2,769 patients with benign asbestos-related diseases were recruited to participate in annual screens. Using a nested case-control design the protein markers calretinin and mesothelin were determined by enzyme-linked immunosorbent assays in prediagnostic plasma samples of 34 MM cases as well as 136 matched controls from the cohort. Conditional on a pre-defined specificity of 98% for calretinin and 99% for mesothelin the markers reached individual sensitivities of 31% and 23%, respectively, when including the incident cases with samples taken between one and 15 months before diagnosis. The combination of both markers increased the sensitivity to 46% at 98% specificity. Marker complementation increased with earlier sampling. The marker combination improves the sensitivity of the individual markers, indicating a useful complementation and suggesting that additional markers may further improve the performance. This is the first prospective cohort study to evaluate a detection of MM by calretinin and its combination with mesothelin up to about a year before clinical diagnosis. Whether an earlier diagnosis will result in reduced mortality has yet to be demonstrated.

Asbestos is still used in many countries despite being classified as a human carcinogen by the International Agency for Research on Cancer (IARC) in 1977^{1,2}. Because of the continued use of asbestos and the long latency period ranging from less than ten to more than 70 years, asbestos-related cancers like malignant mesothelioma (MM) remain a global health issue^{3,4}. Estimates of the global annual number of MM deaths are in the range of 32,000 to 59,000⁵. In Germany, more than 1,600 new MM cases are diagnosed annually and over 1,000 are recognized as occupational disease, despite of an asbestos ban in 1993^{6,7}.

The so-called secondary prevention aims at an early detection of cancer in high-risk groups like occupationally asbestos-exposed individuals to improve therapy options. The diagnosis of MM can be difficult and is based on examination of tissue or cellular material by an experienced pathologist, generally supported by a panel of immunohistochemical markers⁸. For screening of an at-risk population, only less invasive methods like imaging can be employed. Unfortunately, imaging methods for MM screening are currently not available^{9,10}. The non-circular tumor growth pattern of MM and the differentiation of pleural changes, especially between early MM and plaques, is challenging when interpreting computed tomography (CT) scans¹¹. Moreover, a benefit

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