The risk of malignant pleural mesothelioma

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25 September 2023

Although the use of asbestos-containing building materials was banned in the UK in 1999, this carcinogenic mineral continues to be a serious health threat. Daniel J. Murphy from the University of Glasgow tells us more

The UK currently endures the highest incidence of Mesothelioma worldwide: 45 annual fatalities/million population; 1/212 male lifetime risk [(1)], making asbestos the leading cause of occupation-related mortality in the UK. [(2)] Although the use of asbestos-containing building materials was banned in the UK in 1999, an estimated 1.5 million UK buildings are thought to contain up to six million tons of asbestos – including 94% of hospitals, 80% of schools and 74% of university buildings. [(3)]

This legacy of asbestos-containing buildings continues to drive new cases of MPM through passive environmental exposure of long-term building occupants, for instance, teachers and nurses, who develop Mesothelioma at five and three times the rate of the general public, respectively.[(4)] The projected decline in UK Mesothelioma by 2035 [(5)] appears to be based largely on the timing of legislation banning new use of asbestos but fails to adequately account for the continued threat of passive exposure arising from pre-1999 construction, as acknowledged by the UK Health & Safety Executive. [(6)]

Indeed, the projected decline in UK incidence looks increasingly unlikely to occur without government action to remove all forms of asbestos from UK buildings. Worldwide, mining and use of asbestos continue in many countries with inadequate labour protection, and Mesothelioma rates are rising rapidly. [(7, 8)]

Mesothelioma is difficult to diagnose, leading to delayed treatment

Unlike most cancers, Mesothelioma doesn't grow in a discrete focal mass – instead, it spreads insidiously over the lining of the chest cavity, presenting a diffuse multifocal field of cancer that, on the surface, appears very similar to benign pleural inflammation.

To date, there is no well-defined precursor lesion, and molecular diagnostics have failed to provide greater certainty than a microscopic examination of biopsied tissue by a trained pathologist. Diagnosis of Mesothelioma thus relies almost entirely on the manual detection of Mesothelioma cells invading into underlying tissue. [(9)]

A major difficulty is that even multiple biopsies taken with the assistance of an endoscope inserted into the chest can still fail to capture invading cells, leading to false negative diagnosis. Moreover, because only 12-15% of patients who present with symptoms of pleural inflammation develop Mesothelioma within two years of first presentation, international guidelines mandate observation, rather than therapeutic intervention, for patients whose biopsies show no signs of invasive disease. [9]

This “watch and wait” approach thus prevents immediate treatment of patients with early-stage disease that may be at high risk of developing Mesothelioma, or indeed those where Mesothelioma was missed at initial biopsy. Recent therapeutic advances such as immunotherapy [10] have shown significant survival benefits in patients with malignant disease and could be deployed earlier in the patients’ journey if definitive diagnostic tools are developed to reliably differentiate low-risk inflammation from high-risk pre-malignancy.

How mouse models of Mesothelioma can help

The onset of clinical symptoms of Asbestosis that sometimes precedes Mesothelioma can take up to 40 years following exposure. However, experiments in rodents have shown that the biopersistence of Asbestos fibres in the chest cavity drives chronic inflammation that persists from the time of exposure through to the onset of symptomatic disease and development of Mesothelioma. [11, 12]

The clinical picture of Mesothelioma is thus limited to the last mile of a long journey, and eventual Mesothelioma victims are typically symptom-free until their disease is very advanced. There is consequently a huge gap in the clinical understanding of what happens between exposure and onset of symptoms.

To address this gap, my lab has developed genetically engineered mouse models of Mesothelioma that combine controlled introduction of the same mutations that commonly arise in human Mesothelioma with a single injection of Asbestos to incorporate chronic inflammation in our models.

A single exposure to microgram levels of Asbestos (a microgram is one-millionth of a gram) dramatically accelerates the onset of malignancy in all of our models, demonstrating a vital role for Asbestos-driven inflammation in Mesothelioma development beyond mutagenesis. [13] Our mouse models resemble human mesothelioma in microscopic appearance, molecular characteristics, and crucially, in response to clinically relevant therapies, attesting to their relevance for human Mesothelioma.

However, because of their highly reproducible, genetically accelerated cancer development, we can investigate the entire course of disease progression, from initial exposure and the first appearance of cancer-causing mutations all the way through to terminal cancer. Our mouse models thus provide vitally needed insight into stages of cancer development that are simply impossible to follow in human subjects at risk of developing Mesothelioma.

IAMMED-Meso: Understanding the biological basis of risk

We have identified combinations of mutations that give rise to Mesothelioma in 100% of mice (this is called full penetrance) and other combinations that result in variable incidence of malignancy (this is called partial penetrance and is reflective of the risk of developing Mesothelioma).

Knowing that mice with fully penetrant mutation combinations are certain to develop Mesothelioma enables us to sample and examine tissue prior to the onset of symptoms and to compare those samples with fully developed Mesothelioma to determine what changes have taken place in between. Similarly, knowing how long it takes for Mesothelioma to emerge in fully penetrant mice allows us to compare samples from partially penetrant mice at the same time since tumour initiation (which is under experimental control).

This enables us to determine how high-risk pre-malignancy differs from lower-risk pre-cancerous lesions. The molecular and cellular characteristics of these comparisons give us clues of what to look for in samples from human patients with symptoms of Asbestosis that are at risk of developing Mesothelioma. In collaboration with the clinical teams of PREDICT-Meso [(14)], led by Prof. Kevin Blyth, we have access to tissue and pleural fluid samples from a projected cohort of up to 500 symptomatic patients at risk of developing Mesothelioma, along with follow-up samples from those whose disease does indeed progress to Mesothelioma, and from those with stable non-progressing benign disease.

Through cross-species comparisons, we hope to zero in on key molecular features than can be used to definitively distinguish high risk from low risk of Mesothelioma development, enabling earlier treatment of high-risk patients than is currently possible and provided solace and reassurance to patients at low risk of progression to Mesothelioma.

IAMMED-Meso and PREDICT-Meso are funded by Cancer Research UK. DEBiT-Meso is funded by Asthma + Lung UK

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Investigating the underlying biology of asbestos-driven mesothelioma

Inhalation exposure to Asbestos remains the number 1 cause of pleural Mesothelioma, a lethal cancer of the lining of the chest cavity, diagnosed in approximately 31,000 people annually worldwide.