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Abstracts' Service

The Asbestos Fibre Burden in Human Lungs: New Insights into the Chrysotile Debate

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The traceability of asbestos fibres in human lungs is a matter of discussion especially for chrysotile. This issue is of high significance for differential diagnosis, risk assessment and occupational compensation. At present no intra-individual longitudinal information is available. This study addresses the question whether the asbestos fibre burden in human lungs decreases with time after exposure cessation.

The database of the German Mesothelioma Register was screened for patients with asbestos body counts of at least 500 fibres per gram of wet lung, which had been analysed twice from different tissue excisions at minimum intervals of 4 years.

Twelve datasets with individual longitudinal information were discovered with a median interval of about 8 years (range 4-21 years). Both examinations were performed after exposure cessation (median: surgery, 9.5 years; autopsy, 22 years). Pulmonary asbestos fibre burden was stable between both examinations (median 1623/4269 asbestos bodies per gram wet lung). Electron microscopy demonstrated a preponderance of chrysotile (median 80%).

This study is the first to present longitudinal intra-individual data about the asbestos fibre burden in living human lungs. The high biopersistence of amphiboles, but also of chrysotile, offers mechanistic explanations for fibre toxicity, especially the long latency period of asbestos-related diseases.

Predicting Risk of Undiagnosed COPD: Development and Validation of the Target COPD Score

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Chronic obstructive pulmonary disease (COPD) is greatly underdiagnosed worldwide and more efficient methods of case-finding are required. We developed and externally validated a risk score to identify undiagnosed COPD using primary care records.

We conducted a retrospective cohort analysis of a pragmatic cluster randomised controlled case-finding trial in the West Midlands, UK. Participants aged 40-79 years with no prior diagnosis of COPD received a postal or opportunistic screening questionnaire. Those reporting chronic respiratory symptoms were assessed with spirometry. COPD was defined as presence of relevant symptoms with a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio below the lower limit of normal. A risk score was developed using logistic regression with variables available from electronic health records for 2398 participants who returned a postal questionnaire. This was externally validated among 1097 participants who returned an opportunistic questionnaire to derive the c-statistic, and the sensitivity and specificity of cut-points.

A risk score containing age, smoking status, dyspnoea, prescriptions of salbutamol and prescriptions of antibiotics discriminated between patients with and without undiagnosed COPD (c-statistic 0.74, 95% CI 0.68-0.80). A cut-point of $\geq$ 7.5% predicted risk had a sensitivity of 68.8% (95% CI 57.3-78.9%) and a specificity of 68.8% (95% CI 65.8.1-71.6%).

A novel risk score using routine data from primary care electronic health records can identify patients at high risk for undiagnosed symptomatic COPD. This score could be integrated with clinical information systems to help primary care clinicians target patients for case-finding.

Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma

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Rationale. Phenotypic distinctions between severe asthma (SA) and nonsevere asthma (NONSA) may be confounded by differential adherence or incorrect use of corticosteroids.

Objectives. To determine if there are persistent phenotypic distinctions between SA (as defined by 2014 American Thoracic Society/European Respiratory Society guidelines) and NONSA after intramuscular triamcinolone acetonide (TA), and to identify predictors of a corticosteroid response in these populations.

Methods. A total of 526 adults age 18 years and older (315 SA) and 188 children age 6 to less than 18 years (107 SA) in the NHLBI Severe Asthma Research Program III were characterized before and 3 weeks after TA. The primary outcome for corticosteroid response was defined as greater than or equal to 10-point improvement in percent predicted FEV_1.

Measurements and Main Results. Adult asthma groups exhibited a small but significant mean FEV_1% predicted improvement after TA (SA group mean difference, 3.4%; 95% confidence interval, 2.2-4.7%; P = 0.001), whereas children did not. Adult SA continued to manifest lower FEV_1 and worse asthma control as compared with NONSA after TA. In children, after TA only prebronchodilator FEV_1 distinguished SA from NONSA. A total of 21% of adults with SA and 20% of children with SA achieved greater than or equal to 10% improvement after TA. Baseline bronchodilator response and fractional exhaled nitric oxide had good sensitivity and specificity for predicting response in all groups except children with NONSA.

Conclusions. One in five patients with SA exhibit greater than or equal to 10% improvement in FEV_1 with parenteral corticosteroid. Those likely to respond had greater bronchodilator responsiveness and fractional exhaled nitric oxide levels. In adults, differences in airflow obstruction and symptoms between SA and NONSA persist after parenteral corticosteroids, suggesting a component of corticosteroid nonresponsive pathobiology in adults with SA that may differ in children.

HER2 Gene Protein Assay Is Useful to Determine HER2 Status and Evaluate HER2 Heterogeneity in HER2 Equivocal Breast Cancer

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Objectives. Approximately 15% of breast cancers show equivocal human epidermal growth factor receptor 2 (HER2) results on HER2 immunohistochemistry (IHC) and are reflexed for fluorescence in situ hybridization (FISH). However, some cases remain equivocal. In this study, we evaluated these double-equivocal cases by using a novel gene protein assay (GPA), which can simultaneously assess HER2 gene copy number and protein on a single slide using bright-field microscopy.

Methods. GPA was performed on 42 HER2 IHC and FISH double-equivocal cases.

Results. GPA was negative for amplification in 28 cases, equivocal in three cases, and positive in 11 cases. The GPA results showed excellent concordance with either repeat FISH using a chromosome 17 centromere probe or FISH using an alternative probe. Furthermore, HER2 heterogeneity was identified in three of 11 GPA-positive cases.

Conclusions. HER2 GPA performs accurately and is very useful to determine HER2 status in HER2 IHC and FISH double-equivocal breast cancer cases and identify HER2 heterogeneity.

A Study of Motivations and Expectations of Patients Seen in Phase 1 Oncology Clinics

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Background. To better inform clinical practice, this study was aimed at capturing patients' motivations for enrolling in phase 1 trials and at quantifying their expectations of the benefits, risks, and commitment associated with clinical trials and the impact of the initial consultation on their expectations.

Methods. This was a single-center, prospective, quantitative study of newly referred adult patients considering their first phase 1 oncology trial. Participants completed questionnaires before they were seen and an abbreviated follow-up version after their consultation.

Results. Questionnaires were completed by 396 (99%) and 301 (76%) before and after the clinic, respectively. Participants ranked the possibility of tumor shrinkage (84%) as the most important motivation for considering a phase 1 trial; this was followed by no alternative treatments (56%), their physician's recommendation (44%), and the fact that the research might benefit others (38%). When they were asked about the potential personal benefit, 43% predicted tumor shrinkage initially. After the consultation, this increased to 47%. Fourteen percent of patients expected a cure. When asked about risks, 71% of the participants expected moderate side effects. When asked about expectations of time commitments, a majority of patients did not anticipate weekly visits, although this was understood by 93% of patients after the consultation. Overall, patients were keen to consider trials and when asked before and after the consultation 72% and 84% were willing to enroll in studies, respectively.

Conclusions. This study reports that more than 80% of patients enroll in early-phase clinical oncology trials motivated by the potential of a clinical benefit, with approximately half expecting tumor shrinkage and approximately a tenth anticipating a cure. The typical phase 1 response rate is 4% to 20%, and this discrepancy exemplifies the challenges faced by patients and healthcare professionals during their interactions for phase 1 studies.

Monocytes Inhibit NK Activity via TGF-β in Patients with Obstructive Sleep Apnoea

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Obstructive sleep apnoea (OSA) is associated with cancer incidence and mortality. The contribution of the immune system appears to be crucial; however, the potential role of monocytes and natural killer (NK) cells remains unclear.

Quantitative reverse transcriptase PCR, flow cytometry and in vitro assays were used to analyse the phenotype and immune response activity in 92 patients with OSA (60 recently diagnosed untreated patients and 32 patients after 6 months of treatment with continuous positive airway pressure (CPAP)) and 29 healthy volunteers (HV).

We determined that monocytes in patients with OSA exhibit an immunosuppressive phenotype, including surface expression of glycoprotein-A repetitions predominant protein (GARP) and transforming growth factor-β (TGF-β), in contrast to those from the HV and CPAP groups. High levels of TGF-β were detected in OSA sera. TGF-β release by $GARP^+$ monocytes impaired NK cytotoxicity and maturation. This altered phenotype correlated with the hypoxic severity clinical score (CT90). Reoxygenation eventually restored the altered phenotypes and cytotoxicity.

This study demonstrates that $GARP^+$ monocytes from untreated patients with OSA have an NK-suppressing role through their release of TGF-β. Our findings show that monocyte plasticity immunomodulates NK activity in this pathology, suggesting a potential role in cancer incidence.