Lung and pleural cancer

S104 THE NATIONAL LUNG CANCER AUDIT: PROGRESS IN THE FIRST 3 YEARS—DATA COMPLETENESS

[1]PA Beckett, [2]R Stanley, [1]MD Peake. *[1]Clinical Effectiveness and Evaluation Unit, Royal College of Physicians, London, UK; [2]The Information Centre for Health and Social Care, Leeds, UK*

Introduction: The National Lung Cancer Audit is an audit of lung cancer run jointly by the Royal College of Physicians and The Information Centre for Health and Social Care. Its development was driven by the realisation that lung cancer outcomes vary widely across the UK and are poor compared with other western countries. The aim of the audit is to record outcomes in lung cancer on a large scale and through case-mix adjustment, start to explain the wide variations noted. Although Wales and Scotland have recently been submitting data to the audit, this abstract presents results for England only from the first 3 years of the audit, focusing on the quality of the data.
Results: Support for the audit has grown steadily. Currently, all cancer networks in England and Wales submit data to the audit and only two trusts have never contributed. In 2005, there were 10 920 evaluable cases submitted, rising to 16 922 in 2006 and 20 639 in 2007. As seen in the table, the quality of the data has also improved.
Conclusions: The aims of collecting data on the majority of incident cases of lung cancer and mesothelioma in the UK have been achieved. Participation is now very high and data completeness has started to improve. This will allow case-mix adjustment of outcomes by trust and network to be published in the forthcoming annual report. It is hoped that this will explain previously observed geographical variations in lung cancer outcomes.

Abstract S104 Table

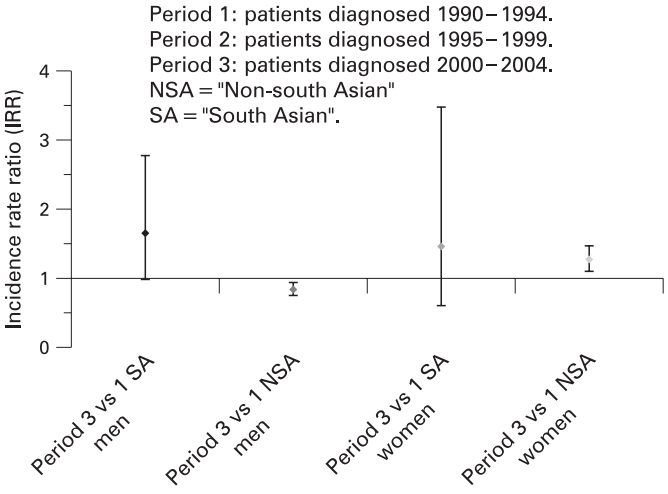
	2005 (%)	2006 (%)	2007 (%)
Date of diagnosis field	92.4	92.5	95.1
Histology field	79.6	78.4	82.4
PS field (overall)	65.7	76.5	80.3
PS field (actual*)	53	56	62.1
Staging field (overall)	51.3	54.6	69.6
Staging field (actual*)	47	50	57.6
PS, stage, comorbidity (actual*)	24	29	45†
Treatment recorded	66	72	79

*Actual refers to completeness when "unknown" has been excluded. †Comorbidity removed from this for 2007 therefore direct comparison not possible. PS, performance status

S105 CHANGES IN LUNG CANCER INCIDENCE IN SOUTH ASIANS IN LEICESTER 1990–2005

[1]M Day, [1]J Poole, [1]D Meechan, [2]LK Smith, [3]CM Free, [3]JA Bennett, [3]MD Peake. *[1]Trent Cancer Registry, Sheffield, UK; [2]University of Leicester, Leicester, UK; [3]Glenfield Hospital, Leicester, UK*

Introduction: In a previous study we demonstrated that lung cancer incidence in the Leicester south Asian population was approximately 60% lower then the rest of the population for men and 70% lower for women. However, our data suggested that the incidence was rising in this population between 1990 and 1999.[1] We expanded the original data to determine if the reported increased trend of lung cancer incidence in south Asians has continued to rise.
Methods: Leicester patients diagnosed with lung cancer between 1990 and 2005 were identified from Trent Cancer Registry data. Ethnicity was assigned using nam-pechan software, deprivation by Townsend score (2001). Ward level population estimates by 5-year age band, sex and ethnicity were obtained from the 2001 census. Using Poisson regression, variations in incidence by ethnicity, deprivation and period of diagnosis were then assessed, calculating the interaction between period of diagnosis and ethnicity to compare trends over time.



Abstract S105 Figure

Results: In south Asian men, the risk of lung cancer has increased by nearly 70% for patients diagnosed between 2000 and 2005 compared with those diagnosed between 1990 and 1994 (incidence ratio (IR) 1.67, 95% CI 1.0 to 2.8) with a small fall seen in non-south Asian men (IR 0.84, 95% CI 0.8 to 0.9). The increases for south Asian men are seen across all deprivation groups, with the greatest increase in the least deprived group. There was a non-significant increase in the risk of lung cancer in south-Asian women, although numbers were small (IR 1.46, 95% CI 0.61 to 3.78), and a significant rise in lung cancer incidence in non-south Asian women (IR 1.27, 95% CI 1.1 to 1.5) (see fig).
Conclusions: Lung cancer in UK resident south Asians is increasing and may represent changing smoking habits. South Asians presenting with "red flag" respiratory symptoms and/or abnormal chest *x* rays should be assessed urgently and lung cancer should be considered as a possible diagnosis.

1. **Smith, *et al***. Recent changes in lung cancer incidence for south Asians: a population based register study. *BMJ* **326**:81–2.

S106 SOCIAL DEPRIVATION AND LUNG CANCER CHARACTERISTICS: THE INSIDE STORY

J Greenwood, A Ponnuswamy, E Othman, VS Sreeguru Lakshman, I Whittle, MJ Ledson, MJ Walshaw. *Liverpool Heart And Chest Hospital, Liverpool, UK*

Introduction: There is a well-recognised association between deprivation and ill health and less affluent individuals are at greater risk of developing lung cancer. Using tools based on postcode to estimate deprivation, we looked at factors that might contribute to its development within the catchment of our large lung cancer unit (>400 cases per year), serving a city population of varying economic status.
Patients and Methods: We looked at smoking history, spirometry, WHO performance status, cancer stage, tumour cell type and treatment; and correlated these with the deprivation indices IMD and Health IMD provided by the local public health department in all 3441 patients (1811 men) diagnosed with lung cancer from January 2000 to April 2008.
Results: Only 6.4% were non-smokers, and 42% were still smoking at diagnosis. As regards performance status, 28% were WHO 0, 22% 1, 26.6% 2, 3.2% 3 and 3.7% 4. Although 30% had clinical diagnoses, 23% were adenocarcinoma, 22% squamous, 10.5% small cell and 14.5% miscellaneous. Stage at presentation was 1a 3%, 1b 5.2%, 2a 0.6%, 3a 4%, 3b 6.7% and 4 15.6%. Although 11% were resected and

30% underwent radical oncological treatment, the remainder were offered palliation only. As regards deprivation, IMD and Health IMD scores ranged from 8.45 and 0.8 to 87.4 and 3.6 (least deprived to most deprived, respectively). Univariate analysis revealed that the most deprived had a worse performance status and spirometry (paired data available for 1504 patients), were more likely to be smokers and had a more advanced stage of cancer (paired data available for 643 patients) and were more likely to be clinical diagnoses, but when histology was obtained there was a preponderance of small cell and squamous subtypes.

Conclusion: In this large cohort of lung cancer patients, those who were socially and economically deprived presented later in the course of their disease and were less fit than more affluent patients. Such factors militate against effective treatment for this patient group and illustrate the urgent need for strategies to improve the economic and social wellbeing of population groups who are at risk of lung cancer.

S107 PLEURAL FLUID MESOTHELIN LEVELS: DIAGNOSTIC ACCURACY, REPRODUCIBILITY AND RELIABILITY AFTER PLEURODESIS

[1]HE Davies, [2]RS Sadler, [1]CE Manners, [1]RJO Davies, [2]BL Ferry, [1]YCG Lee. *[1]Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK; [2]Department of Immunology, Churchill Hospital, Oxford, UK*

Serum measurement of soluble mesothelin, a new biomarker for mesothelioma, is FDA approved for clinical use. Mesothelin is released from pleural mesotheliomas; thus the measurement of pleural fluid mesothelin has potential advantages over serum quantification.

Aims: To determine the utility of pleural fluid mesothelin level by assessing its diagnostic value in unselected patients with undiagnosed pleural effusions, short-term reproducibility and longitudinal change with time and variation after pleurodesis.

Methods: Mesothelin concentrations were determined in 408 pleural fluid and 64 serum samples by ELISA (CIS Bio, France). Pleural fluid was prospectively collected from patients (n = 167) presenting with an undiagnosed pleural effusion. Serial pleural fluid samples were obtained from patients (n = 34) who had an indwelling pleural catheter or repeated thoracentesis. Pleural fluid and blood mesothelin levels were measured in 32 patients before and after talc pleurodesis.

Results: Pleural fluid mesothelin concentrations were significantly higher ($p<0.001$) in mesothelioma patients (n = 24) than those with metastatic carcinomas (n = 67) and benign effusions (n = 75): median (interquartile range) 40.3 (18.3–68.1) versus 6.1 (1.5–13.2) versus 3.7 (0–12.4) nmol/l, respectively. At the optimal cutoff (20 nmol/l), pleural fluid mesothelin has an excellent diagnostic sensitivity (71%) and specificity (90%) for mesothelioma. Pleural fluid mesothelin measurement provided additional value over cytological analysis. In pleural fluids with "suspicious" (but not definite malignant) cytology (n = 11), pleural fluid mesothelin levels greater than 20 nmol/l were 100% specific in diagnosing mesothelioma. In cytology-negative effusions (n = 94), pleural fluid mesothelin offered negative and positive predictive values of 94% and 75%, respectively, for mesothelioma. Intra-individual reproducibility was excellent. In serial pleural fluid samples obtained within 7 days, mean (SD) variation of mesothelin was −0.11 (8.42) and 0.76 (6.02) nmol/l in mesothelioma and non-mesothelioma patients, respectively. Pleural fluid mesothelin levels increased significantly with time ($r = 0.60$, $p<0.001$) in mesothelioma patients. Talc pleurodesis did not significantly alter mesothelin levels in pleural fluid or serum (median change −5.78 and 0.0 nmol/l, respectively).

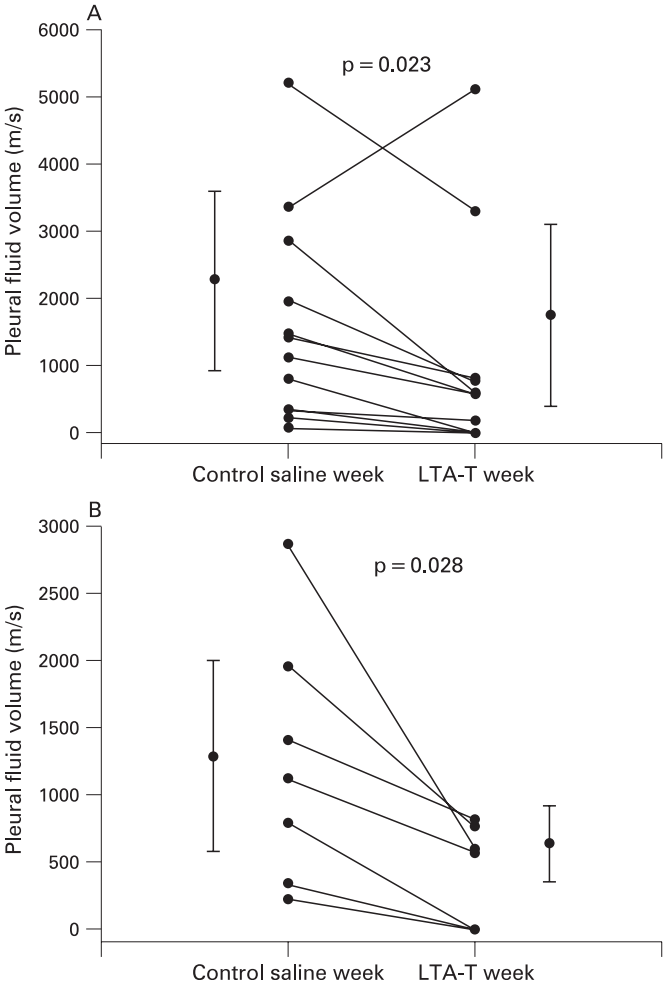
Conclusion: Pleural fluid mesothelin provides additional diagnostic value for mesothelioma over cytological examination. Mesothelin measurements are highly reproducible in the short term (<7 days), are not affected by pleurodesis and increase over time in mesothelioma patients reflecting disease progression.

S108 A PHASE I TOXICITY, DOSE FINDING AND PRELIMINARY EFFICACY ASSESSMENT OF LIPOTEICHOIC ACID-T FOR PLEURODESIS IN MALIGNANT PLEURAL EFFUSION

[1]NM Rahman, [1]HE Davies, [2]M Salzberg, [1]EL Hedley, [3]P Truogg, [4]R Midgley, [5]D Kerr, [6]C Clelland, [1]RJO Davies. *[1]Oxford Centre for Respiratory Medicine, Oxford, UK; [2]Pharma Brains Ltd, Basel, Switzerland; [3]Lunamed, Switzerland; [4]Cancer Research UK, Oxford, UK; [5]Department of Clinical Pharmacology, Oxford University, Oxford, UK; [6]Department of Clinical Pathology, Oxford Radcliffe Hospitals, Oxford, UK*

Background: Lipoteichoic acid T (LTA-T) is a pro-inflammatory Gram-positive bacterial cell wall motif that acts through the Toll-like receptor pathway. LTA-T may be a trigger for the pleural inflammation seen after pleural infection, resulting in a fibrosed pleural cavity. We hypothesised that intrapleural LTA-T administration could control malignant pleural effusion (MPE) by inducing pleurodesis.

Method: This study was a dose escalation and toxicity study performed in 13 patients with MPE requiring drainage. An indwelling pleural catheter was placed and a "control" (intrapleural saline) was administered; pleural fluid production then was recorded for 7 days (week 1). An escalating single dose of intrapleural LTA-T was administered on day 7; fluid production was recorded over the next week (week 2), and long-term fluid



Abstract S108 Figure (A) Pleural fluid production by week of study in all patients. Individual patient results are shown in addition to mean and error bars for each group. p Value derived from Wilcoxon signed rank test. (B) Pleural fluid production by week of study in patients receiving 750μg LTA-T or more. Individual patient results are shown in addition to mean and error bars for each group. p Value derived from the Wilcoxon signed rank test.

control assessed. The primary outcome measure was toxicity and safety profile.
Results: Dose was limited by toxicity at 3000 μg single dose (systemic inflammatory reaction requiring hospital admission). Therapeutic dose was 750–1500 μg with only mild and inconsistent side effects at this dose. Pleural fluid production decreased significantly after intrapleural LTA-T compared with saline alone (fig), and this was due to a reduction in those receiving 750 μg or more LTA-T (saline control week 1244 ml, SD 933, LTA-T week 394 ml, SD 375, diff 850 ml, SD 699, 95% CI 204 to 1497, p = 0.018, fig). 86% of patients treated with LTA-T achieved pleural fluid control for at least one month.
Conclusion: A single dose of intrapleural LTA-T has a mild and favourable toxicity profile when compared with standard pleurodesis agents and may induce effective pleurodesis in MPE. Further larger scale studies are now required using this agent.

Understanding asthma pathogenesis

S109 PATHOGENIC BACTERIA IN INDUCED SPUTUM IN SEVERE ASTHMA

[1]B Green, [1]V Kehagia, [1]D Sammut, [2]S Wiriyachaiporn, [1]M Carroll, [2]K Bruce, [1]P Howarth. *[1]Southampton University Hospitals NHS Trust, Southampton, UK; [2]King's College London, London, UK*

Introduction: The role of bacterial airway colonisation in chronic stable asthma is unclear. However, there is increasing evidence for the role of bacterial pathogen-associated molecular patterns such as lipopolysaccharide in the activation of the innate immune system, which may lead to the expression of a neutrophilic asthma phenotype.
Aims: We aimed to use terminal restriction fragment length polymorphism (T-RFLP) profiling to identify pathogenic bacteria in induced sputum from severe asthmatic patients and correlate findings with clinical characteristics and differential cell counts.
Methods: Induced sputa were obtained from chronic, stable, severe asthmatic patients (N = 21). All patients were at BTS asthma treatment step 4 or 5 with a minimum of 6 weeks since last exacerbation. All patients were on high-dose inhaled corticosteroids and nine were on long-term maintenance oral prednisolone treatment. Sputa obtained were split for differential cell counts and 16S ribosomal DNA T-RFLP. Using this process bacterial nucleic acids are extracted from the sputum, 16S ribosomal RNA gene PCR products, specific to domain bacteria, are amplified then digested using a specific endonuclease. Ribosomal gene fragments are produced and separated by gel electrophoresis, forming a T-RFLP profile of the diversity of the colonising bacterial community.
Results: 18 out of 21 specimens contained at least one of either *Haemophilus* sp, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. The presence of at least one of these species was associated with the earlier onset of disease (p = 0.039), duration of disease (p = 0.030) and increased peak flow variability over a 2-week period (p = 0.022). There was no significant association between inhaled corticosteroid dose, maintence oral prednisolone treatment, atopy, asthma symptom scores, exhaled nitric oxide or degree of airways obstruction and colonisation with these species. Colonisation with at least one of these species was associated with significantly increased neutrophil differential cell counts (median neutrophil count 76.0% vs 38.5%, p = 0.043).
Conclusion: Airway colonisation with potentially pathogenic bacteria is a common feature of severe asthma and is associated with a neutrophilic phenotype of airways inflammation.

S110 EP2 PROSTANOID RECEPTOR-MEDIATED SUPPRESSION OF KCa3.1 AND MIGRATION IN HUMAN LUNG MAST CELLS

SM Duffy, G Cruse, P Bradding. *University of Leicester, Leicester, UK*

Mast cells play an important role in the pathogenesis of asthma. Human lung mast cells (HLMC) express the Ca^{2+}-activated K^+ channel $K_{Ca}3.1$, which is opened following IgE-dependent activation, and which promotes Ca^{2+} influx, secretion and migration. $K_{Ca}3.1$ in HLMC is closed by the β_2-adrenoceptor and the adenosine A_{2A} receptor via a G_s-coupled mechanism independent of cyclic AMP. Prostaglandin E_2 (PGE_2) promotes degranulation and migration of mouse bone marrow-derived mast cells through the G_i-coupled EP_3 prostanoid receptor, and induces LTC_4 and cytokine secretion from human cord blood-derived mast cells. However, PGE_2 binding to the G_s-coupled EP_2 receptor on HLMC inhibits their degranulation. In this study we have used the patch-clamp technique to measure ion channel function in isolated HLMC in response to PGE_2. $K_{Ca}3.1$ was opened using the specific opener, 1-EBIO. Following $K_{Ca}3.1$ activation by 1-EBIO, the addition of 10^{-8} to 10^{-5} mol PGE_2 produced rapid, dose-dependent and partly reversible channel suppression in 90% of HLMC. The addition of 10^{-5} mol PGE_2 reduced $K_{Ca}3.1$ membrane current at +40 mV from 155.4 ± 20.9 to 92.6 ± 13.7 pA (p = 0.001, n = 22 cells), with a corresponding shift in reversal potential (Vm) from −69.5 ± 2.8 to –56.3 ± 3.9 mV. The selective EP_2 prostanoid receptor agonist butaprost also suppressed $K_{Ca}3.1$ (146.0 ± 18.3 pA to 61.2 ± 6.1 pA by 10^{-5} PGE_2, p = 0.001, n = 20). Half maximal suppression (IC_{50}) of $K_{Ca}3.1$ by PGE_2 and butaprost occurred at 4.0×10^{-7} mol and 2.1×10^{-7} mol, respectively. Conversely, the competitive EP_1 and EP_2 receptor antagonist AH6809 antagonised the suppression of $K_{Ca}3.1$ by PGE_2 and butaprost. HLMC migration induced by chemokine-rich airway smooth muscle conditioned media was suppressed by the EP_2 agonist butaprost ($p<0.05$, n = 4). PGE_2 alone was chemotactic in high concentrations (10^{-6} mol, $p<0.05$ compared with control, n = 4). Also PGE_2-dependent chemotaxis was enhanced in the presence of the $EP_{1/2}$ receptor antagonist 10^{-5} mol AH6809 ($p<0.05$ compared with control, n = 4). In summary, the G_s-coupled EP_2 receptor closes $K_{Ca}3.1$ in HLMC and attenuates both chemokine and PGE_2-dependent HLMC migration. EP_2 receptor agonists with $K_{Ca}3.1$ modulating function may be useful for the treatment of mast cell-mediated disease.

S111 CHEMOKINE RELEASE IN RESPONSE TO *DERMATOPHAGOIDES PTERONYSSINUS* ALLERGEN 1, BY PRIMARY RESPIRATORY BASAL CELLS OF PATIENTS WITH SEVERE ASTHMA AND HEALTHY CONTROLS

B Thomas, RA Hirst, G Williams, J Bankart, P Haldar, A Wardlaw, CE Brightling, C O'Callaghan. *University of Leicester, Leicester, UK*

Introduction: Sensitisation and allergy to the house dust mite *Dermatophagoides pteronyssinus* is common among patients with asthma. Injury and disruption of airway epithelium that may occur in patients with asthma potentially exposes the airway basal cells to inhaled allergens.
Aim: To determine the chemokine release by primary respiratory basal cells of patients with severe asthma and healthy controls, in response to Der p 1.
Methods: Eight adult patients with severe asthma and six healthy adult control subjects were studied. Bronchoscopic brush biopsies were obtained from the bronchus intermedius. From the brushing, basal cells were cultured to confluency in collagen coated glass chamber slides (Nunc) in bronchial epithelial growth medium. The cells were exposed to LoTox Der p 1 (Indoor Biotechnologies) at concentrations of 1 μg/ml and 5 μg/ml in the presence of dithiothreitol and supernatants harvested at 8 h and 24 h following