

## Nicotine clearance: genetic and environmental influences

The renal clearances of nicotine and cotinine, its proximate metabolite, vary considerably between individuals. This twin study looked at the influences of genetic and environmental factors on renal clearance.

One hundred and ten monozygotic and 29 dizygotic healthy twin pairs with a mean age of 37.7 years were recruited. The group was predominantly female (69.9%) and Caucasian (76.1%). An intravenous infusion of deuterium-labelled nicotine and cotinine was administered after an overnight fast. In smokers, the dose was dependent upon their plasma cotinine concentration. Blood samples were taken at intervals and urine was collected over 8 h. These compounds demonstrate minimal protein binding, so their glomerular filtration was estimated by the glomerular filtration rate (GFR).

Analysis using twin methods revealed the presence of non-additive genetic effects on GFR and net secretory/reabsorptive clearance. Additive genetic effects seemed to be more important in the renal clearance of cotinine. The study was not powered sufficiently to allow biometric models to separate additive

genetic effects from non-additive genetic effects and shared environmental factors.

Renal clearance comprises passive glomerular filtration/reabsorption, previously shown to be largely under environmental control, and active secretion which has been found to be heritable. This study showed that, at uncontrolled urine pH, there was net reabsorption of both compounds in most subjects. Therefore, there may be an overriding genetically-controlled active secretory process despite net reabsorption or, in this case, reabsorption may be genetically influenced. Furthermore, the results suggest that nicotine and cotinine are cleared in slightly different ways and are likely to be influenced by different factors.

Future studies to determine the factors influencing renal drug clearance may make it possible to individualise drug prescribing, increasing effectiveness and safety.

► Benowitz NL, Lessov-Schlaggar CN, *et al.* Genetic influences in the variation in renal clearance of nicotine and cotinine. *Clin Pharmacol Ther* 2008;**84**:243–7.

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## Mutations in the LKBI tumour suppressor gene linked to non-small cell lung cancer in Caucasians

Lung cancer remains the most common cause of cancer-related death in the UK. However, patients with non-small cell lung cancer (NSCLC) may benefit from surgery or radiotherapy, providing a cure in a small proportion. Mutations in the LKBI tumour suppressor gene have been found in several human cancers including NSCLC. This study explores the incidence of LKBI mutations in patients with NSCLC, the frequency in different ethnic groups and associations with other clinicopathological characteristics (sex, smoking, tumour stage, histology and outcome).

Tumour tissue collected from 310 patients at curative surgical resections was screened for LKBI mutations. These were present in 11% of the tumours, which was more than other common solid malignancies (0–4%). Mutations were more prevalent in the Caucasian group (17%) than the Asian group (5%), with an

association between smoking (>10 pack-years) and the presence of mutations. Despite this, the study fails to address fully the fact that smokers were predominantly Caucasian, confounding the ethnic divide. Surprisingly, LKBI mutations were more common in adenocarcinomas (13%) as, histologically, this is the most frequent lung cancer in non-smokers. Statistically, LKBI mutation status was not found to affect outcomes in patients with stage I and II NSCLC treated with surgery alone, although the study showed shorter survival rates.

The complexity of this study and numerous influencing factors highlight the multifactorial aetiology of NSCLC and an important genetic link, raising the question whether genetic screening in the future could help detect those at risk of developing a potentially curable cancer.

► Koivunen JP, Kim J, Lee J, *et al.* Mutations in the LKBI tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. *Br J Cancer* 2008;**99**:245–52.

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## PF-3512676 may enhance the clinical activity of taxane/platinum chemotherapy in advanced non-small cell lung cancer

Current first-line therapy for stage IIIB–IV non-small-cell lung cancer (NSCLC) is taxane plus platinum-based chemotherapy. With this regime the 1-year survival rate is less

than 40%. Toll-like receptors (TLR) can stimulate innate and antigen-specific acquired immunity. PF-3512676 is a TLR9-activating oligodeoxynucleotide and has confirmed antitumour activity against a variety of cancers.

This randomised phase II study examined the safety and antitumour action of the combination of PF-3512676 and taxane/platinum chemotherapy in stage IIIB–IV NSCLC. One hundred and twelve patients were included from 26 centres. All patients had adequate blood counts, renal and hepatic function and had received no previous chemotherapy. Patients with autoimmune diseases or brain metastasis were excluded.

Seventy-three patients received chemotherapy plus PF-3512676 and 37 patients received chemotherapy alone.

The observed response rate (assessed as a complete or partial response based on investigator assessment) was higher in the PF-3512676 group than in the group receiving chemotherapy alone (38% vs 19%). Although not all responses were confirmed radiologically, the authors felt that the response rate would have been even higher in the PF-3512676 arm if this had been the case. Despite more patients with stage IV disease in the PF-3512676 group, the median survival was 12.3 months compared with 6.8 months in the group receiving chemotherapy alone, with 1-year survival rates of 50% and 33%, respectively.

The addition of PF-3512676 was generally well tolerated. Phase III trials are in progress and may provide further evidence that the addition of PF-3512676 to taxane/platinum chemotherapy is safe and may prolong survival.

- Manegold C, Gravenor D, Woytowicz D, *et al.* Randomized phase II trial of a Toll-like receptor 9 agonist oligodeoxynucleotide, PF-3512676, in combination with first-line taxane plus platinum chemotherapy for advanced-stage NSCLC. *J Clin Oncol* 2008;**26**:3979–86.

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## Functional limitations of COPD

Chronic obstructive pulmonary disease (COPD) affects both pulmonary and non-pulmonary systems and results in a wide range of physical functional limitations in sufferers. This study is an attempt to characterise the impact of COPD on non-pulmonary function.

One thousand and two patients from the Kaiser Permanente Medical Care Program (KPMCP) aged 40–65 years who met the criteria for a diagnosis of COPD and who had also received two or more prescriptions for COPD-related illness in the previous 12 months were recruited. The study participants were matched by age, sex and race with a reference group of 302 patients from the KPMCP who did not meet either of the criteria for a COPD diagnosis. Subjects participated in a series of validated assessments of physical function including short physical performance battery, 6-minute walk test and skeletal muscle strength testing. In addition, semi-structured interviews were used to provide information on self-reported functional limitation.

Not only was pulmonary function found to be significantly poorer in the study group, the patients with COPD were also

found to have significantly greater deficits in lower extremity functioning, exercise performance, muscle strength and had a higher rate of self-reported functional limitations. These deficits remained after potential confounding factors were accounted for—such as age, sex, race, height, educational attainment and cigarette smoking.

The authors conclude that the functional limitations found are specifically attributable to COPD; however, the impact of any co-morbidities is unclear. Interestingly, the majority of patients with COPD studied were GOLD stage 0–2 and therefore it seems that systemic manifestations have an impact even in mild patients. The age range of the participants means that the applicability of the study findings to those aged >65 years is uncertain and most likely underestimated.

- Eisner MD, Blanc PD, Yelin EH, *et al.* COPD as a systemic disease: impact on physical functional limitations. *Am J Med* 2008;**121**:789–96.

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## Influenza vaccine may not protect elderly subjects from pneumonia

Influenza and complications associated with influenza including pneumonia impose a significant burden on the healthcare system, particularly in elderly individuals. Although the influenza vaccine could potentially reduce the risk of complications, its benefit in this group remains doubtful.

This population-based nested case-control study investigated whether the influenza vaccine reduced the risk of community acquired pneumonia in immunocompetent elderly individuals. The cohort comprised people aged 65–94 years who had enrolled in a health maintenance organisation in Washington State during the pre-influenza and influenza seasons in 2000, 2001 and 2002.

A total of 1173 individuals with pneumonia confirmed by medical records or chest radiography were included (714 of whom had been vaccinated against influenza). 2346 individuals without pneumonia (two age- and sex-matched for each case) served as controls (1838 of whom had not received the influenza vaccination). The presence of heart and lung diseases, frailty

indicators, smoking history, use of respiratory medications and routine prescriptions were reviewed and adjusted to reduce confounding factors. After adjustment, influenza vaccination was not associated with a reduction in community acquired pneumonia during the influenza season. The authors suggested two potential explanations; either influenza caused a small proportion of pneumonia in elderly people or the available vaccine was less effective in reducing the risk of pneumonia.

Although this was a large population-based study and raises important questions, more robust randomised controlled trials are needed to determine the effectiveness of the influenza vaccine in reducing influenza-related morbidity in this age group. Until this happens, the influenza vaccination will continue to be used as a health protective measure worldwide.

- Jackson ML, Nelson JC, Weiss NS, *et al.* Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study. *Lancet* 2008;**372**:398–405.

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