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202. Early detection of lung cancer

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Interval lung cancers not detected on screening chest x-rays: How are they different?

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Background: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial provides us an opportunity to describe interval lung cancers not detected by screening chest x-ray (CXR) compared to screen-detected cancers.
Methods: Participants were screened with CXR at baseline and annually for two (never smokers) or three (ever smokers) more years. Putative interval cancers were those with a negative CXR screen but with a diagnosis of lung cancer within 12 months. Screen-detected cancers were those with a positive CXR and diagnosed within 12 months. Potential interval cancers were re-reviewed to determine whether lung cancer was missed and probably present during the initial interpretation or whether the lesion was a "true interval" cancer.
Results: 77,445 participants were randomized to the intervention arm with 70,633 screened. Of 5,227 positive screens from any screening round, 298 resulted in screen-detected lung cancers; 152 had potential interval cancers with 128 CXR available for re-review. Cancer was probably present in 45/128 (35.2%) at time of screening; 83 (64.8%) were "true interval" cancers. Compared to screen-detected cancers, true interval cancers were more common among males, persons with <12 years education and those with a history of smoking. True interval lung cancers were more advanced stage IV (31.0% vs. 16.7%, p<0.007), more often small cell, 27.7% vs. 7.4%, and less often adenocarcinoma, 25.3% vs. 56.4% (p<0.0001), and less likely to be in the right upper lobe, 16.9% vs. 36.2% (p<0.001).
Conclusion: True interval lung cancers differ from CXR-screen-detected cancers with regard to demographic variables, stage, cell type and location.

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The effect of route of presentation on lung cancer outcome

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Background: Lung cancer is the commonest cause of cancer death in the UK, with one year survival lagging behind the rest of Europe. Early lung cancer diagnosis is imperative in achieving the highest chance of curative therapy. Recent Public Health Campaigns have highlighted importance of early lung cancer detection and early presentation to primary care, allowing onward referral.
The Luton and Dunstable Hospital is situated north of London, covering a population of 320,000. Observations show when patients present as an emergency, instead of through outpatient referral, disease is at a later stage and limited treatment, if any, available.
Aims: To compare stage of lung cancer, treatment intent and survival, between patients referred from primary care and emergency inpatient presentations.
Methods: 2010 LUCADA data from Luton and Dunstable NHS Trust were analysed, including 144 patients. 63 primary care referrals, and 81 inpatient presentations. Performance status, stage, survival and treatment were compared using the Chi-Squared contingency test.
Results: Patients referred through outpatients had a significantly better performance score (p<0.0001) and an earlier stage disease (p=0.0005)compared to those diagnosed following emergency admission. Survival data (at time of analysis), revealed a greater likelihood of death within the inpatient population (p<0.0001). A trend existed for more active treatment in outpatient referrals, although this failed to reach statistical significance.
Conclusions: Our data shows outpatient diagnosis is associated with better performance scores, earlier cancer stage and prolonged survival. Early symptom recognition, with early referral is vital in improving life expectancy from lung cancer.

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The results of the prevalence screen in Lung SEARCH: A UK based screening trial for lung cancer based on sputum cytology and cytometry, by the Lung SEARCH screening group

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Lung SEARCH is a screening trial in 9 UK centres of 1658 subjects with a >20 pack year smoking history, mild or moderate chronic obstructive pulmonary disease (COPD). Randomisation was to a control group who had no active intervention, but an exit chest X-ray (CXR) at the end of 5 years; or a surveillance group who provide sputum samples annually for 5 years, for cytological and cytometrical analysis, and if normal for the duration of the study, an exit CXR. Samples showing abnormalities would undergo annual low-dose computed tomography (CT) and autofluorescent fibreoptic bronchoscopy (AFB) for the remaining years of the five. Our aim is to identify more early stage cancers in the surveillance arm (>50%) than the control (<10%) and literature on COPD suggested we would need 37 cancers in each study group.
We entered 785 subjects into the surveillance, and 783 in the control arms. The two groups were well matched with 52% of men in both groups, 56% and 44% in each group were current or ex-smokers, and their mean ages were 63 years. 75% in each group had moderate COPD and 25% were mild.
Results: Of the 785 subjects in the surveillance arm, 92% provided a sputum sample. Of these only 132 of 742 were inadequate for analysis. 532 (73%) were normal, 128 (17%) were abnormal: 16 were high grade and 112 low grade. All 128 are being followed by CT and AFB.
Conclusions: Sputum cytology/cytometry performed within a high risk population gave a higher than expected yield of abnormal samples. The study may prove a promising and cost effective method to identify those at very high risk of developing early lung cancer.

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**Detection of lung cancer using ion mobility spectrometry in Japan: A pilot study**

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Background: National Lung Screening Trial (NSLT) reported screening with low-dose CT could reduce mortality from lung cancer. Breath analysis such as canine scent, electronic nose and ion mobility spectrometry (IMS) could detect volatile organic compounds (VOC).
Objectives: To detect specific VOC peaks in lung cancer then compare lung cancer and healthy subjects.
Methods: IMS coupled to a multi-capillary column (MCC/IMS) (BioScout: B&S Analytik, Dortmund, Germany) with a 95MBq β-radiation source was used to detect VOC peaks. For the Japanese market, regulations restrict 63Ni β-radiation sources to under 100MBq. Exhaled breath samples were collected at quite breathing in 30 patients with lung cancer and 13 healthy volunteers. Peaks were characterized using Visual Now 2.2 software (B&S Analytik, Dortmund, Germany).
Results: Patients included 17 adenocarcinoma, 3 squamous cell carcinoma, 6 small cell carcinoma and 4 unclassified carcinoma. Forty-seven VOC peaks were detected and 10 VOC peaks showed significant differences between lung cancer and healthy volunteers (p<0.05).
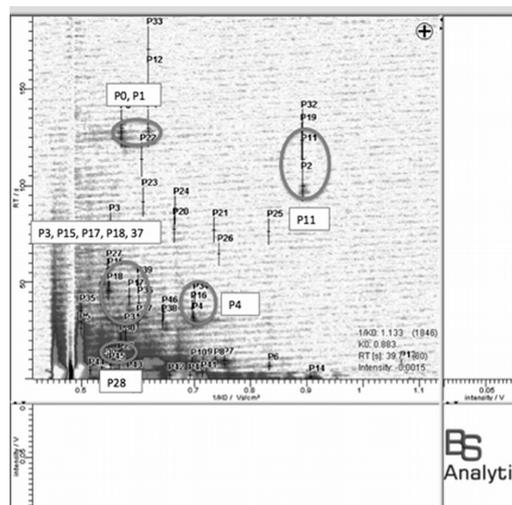
Conclusions: IMS using 95MBq β-radiation source is a feasible screening test in the detection of lung cancer. In the future, IMS may detect histological types of lung cancer and molecular mutation.

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Cancer-associated oncogenic BARD1 isoforms: From biomarker expression studies to development of a blood test for early detection of lung cancer

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BARD1 protein binds to, stabilizes, and enhances the tumor suppressor functions of BRCA1. However, highly upregulated expression of aberrant BARD1 isoforms correlates with decreased patient survival in NSCLC.

BARD1 isoforms are tumor drivers and act antagonistically to E3 ubiquitin ligase functions of BARD1-BRCA1 heterodimer. In particular, isoform BARD1β is promoting cell proliferation by stabilizing Aurora kinases. Since BARD1β and BARD1π are upregulated and correlated with poor prognosis in lung cancer they might act as suitable biomarkers of NSCLC detection/progression.

We developed a blood test based on BARD1 isoforms by performing ELISA tests with antibodies against different regions of BARD1 for detection of BARD1 isoforms in blood of NSCLC patients. We also generated a peptide library representing 60 epitopes mimicking BARD1 isoforms, for detection of autoimmune antibodies recognizing epitopes expressed by BARD1 isoforms.

Significant differences between serum samples from 60 chemotherapy-naive NSCLC patients and from 40 healthy volunteers have been found. Applying a combination of seven peptides, lung cancer was detected with 87 percent sensitivity and 68 percent specificity. Thus, antibodies against BARD1 isoforms are telltales of NSCLC and their detection can be further developed towards a blood test.

Experiments including larger patient and control group numbers, different types of lung cancer are currently ongoing, and should optimize test conditions and define the target patient set.

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Electronic nose detects early stage and peripheral lung cancers

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We have reported that exhaled volatile organic compound (eVOC) profile of lung cancer (LC) subjects differed from healthy ever smokers (HS).

Aim: To determine if eVOC profile of LC subgroups (1) peripheral tumours and (2) early stage disease differ from HS.

Method: LC (n=53) and HS (n=177) subjects provided a breath sample after tidal breathing through an inspiratory port filter for 5 mins. It was analysed with a 32 sensor Cyranose 320 (Smiths Detection). Tumours were staged (7th ed TNM system), and defined as peripheral if located in the outer 1/3 of lung fields on axial CT images. LC subgroups were: Stages I/II (n=27), III/IV (n=25), central (n=32) and peripheral tumors (n=21). Data were reduced to principal components for canonical discriminant analysis to determine differences between groups. Accuracy was calculated using SPSS V17.0 with leave one out cross validation.

Results: The eVOC profile distinguished between LC and HS with a cross validation (CVV) accuracy of 79%, (p<0.0001). Analysis of HS, early (I/II) and late (III/IV) stage LC showed an eVOC profile CVV accuracy of 77%. A principal component vector was significantly different between early (I/II) stage LC and HS (p<0.0001). eVOC profile CVV accuracy was 77% when analysing central, peripheral and HS cases. A principal component vector was significantly different between peripheral LC and HS (p=0.03).

Conclusion: These data indicate the ability of exhaled breath VOC profiles to distinguish early stage and peripheral lung cancer cases from healthy ever smokers, and therefore support its potential as a non-invasive screening tool for early detection of lung cancer.

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An electronic nose in the discrimination of patients with lung cancer and controls

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Background: Lung cancer is a leading cause of death in men suffering from oncological diseases. Exhaled breath contains hundreds of volatile organic compounds (VOCs) that could serve as biomarkers of lung disease. Electronic nose can distinguish VOC mixtures by pattern recognition.

Objective: We hypothesized that an electronic nose can discriminate exhaled air of patients with lung cancer from healthy controls.

Methods: 25 patients with clinicaly and histologicaly verified lung cancer and 45 controls were included in a study with sampling of exhaled breath. Subjects inspired VOC-filtered air by tidal breathing for 5 minutes, and a single expiratory vital capacity was collected into polyethylene terephthlate bag that was sampled by electronic nose (Cyranose 320) within 5 minutes. Smellprints were analyzed by multifactorial logistic regression analysis (MLRA). Optimal detector parameter combination for diagnosis of laung cancer was calculated by MLRA backward stepwise method. Sensitivity, specificty, PPV and NPV of the method were calculated.

Results: Optimal detector parameters for discrimination of lung cancer were maximum of detectors number 6, 13. and 23. and area under curve of detectors 2, 6, 24 and 29. 22 out of 25 or 88.0% of lung cancer cases were predicted correctly by MLRA. Sensitivity of the method was 88.0%, specificity 91.1%, PPV 84.6% and NPV 93.2%.

Conclusions: The electronic nose appears to be able to discriminate exhaled breath from subjects with lung cancer and healthy controls. Analysis of exhaled breath coud be used as the lung cancer screening method in the future.

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Hyaluronan: A novel sputum marker for the screening and diagnosis of lung cancer patients

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Introduction: Hyaluronic Acid (HA) is elevated in several cancers, but there is no data regarding its concentration in the sputum of lung cancer patients.In this study, we examined the HA concentrations in the sputum and its impact on the screening and diagnosis of lung cancer patients.

Methods: HA was examined in sputum samples of 90 lung cancer patients, 25 COPD patients and 15 healthy controls.All the patients and healthy controls selected underwent a sputum induction.Sputum samples were incubated with urea 7M at 60°C and afterwards incubated with a proteolytic enzyme.The levels of HA were measured by a noncompetitive ELISA-like fluorometric assay.

Results: A significant different concentration pattern of HA in the sputum was found among lung cancer, COPD and healthy individuals (p<0.001; Fig. 1A). ROC curve between lung cancer and healthy volunteers furnished an area of 0.821 (0.727–0.915). Assuming a cut off value of 31.44ng/mg, the specificity was 100% and the sensitivity was 51% (Fig. 1B). ROC curve to distinguish COPD patients from lung cancer patients showed an area of 0.698 (0.600-0.797) and the cut off
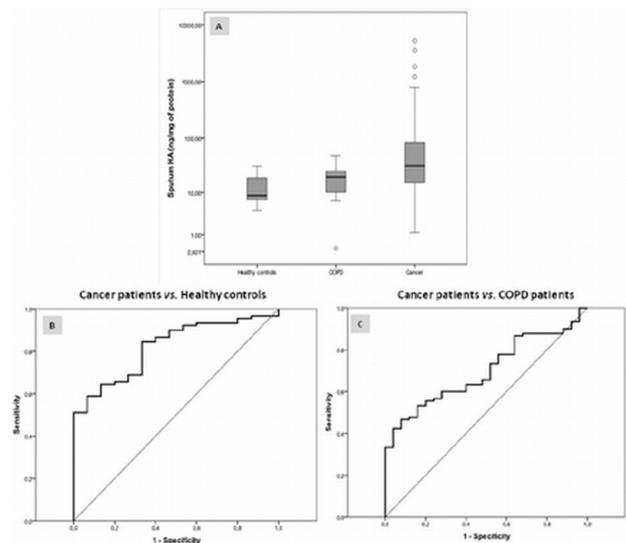

Cancer patients *vs.* Healthy controls   Cancer patients *vs.* COPD patients

Figure 1: A - Patients with lung cancer had a significantly higher hyaluronan levels in sputum than that in the COPD and healthy controls (Log10 scale; p<0.001) **B/C -** ROC curves for sputum levels of hyaluronan. **B-** The cut off level of hyaluronan that result in the highest diagnostic accuracy was >31.44ng/mg. The cut-off point of hyaluronan discriminated between healthy controls and lung cancer patients, with 100% specificity and 51% sensitivity. The diagnostic accuracy was 82%. **C-** The cut-off point of hyaluronan that discriminated COPD and lung cancer patients, with 100% specificity and 33% sensitivity was >48.3ng/mg. The diagnostic accuracy was 69%.

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value of 48.3ng/mg presented 100% of specificity and 33% of sensitivity (Fig. 1C).

Conclusions: The results presented suggest a promising role of HA quantification in the sputum as a novel screening and diagnostic marker for differentiating normal and other type of fibrotic pulmonary problems from lung cancer patients.