Correspondence to: Dr C S Devulapalli, Ringerike Hospital, Hønefoss, Arnold Dybjords vei 1 Service Box 13, Hønefoss, NO-3504, Norway; c.s.devulapalli@medisin.uio.no

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Serum free DNA and COX-2 mRNA expression in peripheral blood for lung cancer detection

Lung cancer is the most frequently diagnosed tumour type and the leading cause of cancer mortality throughout the world. The prognosis of patients is strongly correlated with tumour stage,[1] hence the importance of an accurate, easily usable diagnostic tool for early detection.

Low-dose spiral computed tomography (CT) has opened up interesting prospects for early diagnosis but is expensive, invasive and presents some limitations, especially in terms of specificity.[2] Free circulating DNA levels have been shown to be higher in patients with lung cancer than in healthy individuals (including heavy smokers), suggesting that this marker could be an important tool to identify lung cancer in screening programmes.[3] More recently, our group[4] and other researchers[5] have shown that plasma or serum free DNA is also significantly higher in patients with other cancer histotypes than in healthy donors. Cyclooxygenase-2 (COX-2) has been implicated in the early stages of lung oncogenesis,[6] and increased levels are associated with a poor prognosis.[7]

In our case-control study on 128 cancer patients and 103 healthy donors, we aimed to define the potential of serum free DNA and COX-2 mRNA expression, determined singly or in combination, for non-small cell lung cancer detection. Serum free DNA levels and COX-2 mRNA expression in peripheral blood were significantly lower in healthy donors than in patients (8.8 vs 48.0 ng/ml, $z = -11.17$, $p<0.001$ for DNA; 1.5 vs 2.0, $z = -6.02$, $p<0.001$ for COX-2) and were not related to sex, age or smoking habits in either group.

Table 1 Diagnostic relevance of free circulating DNA (cut-off 25 ng/ml) alone or in combination with COX-2 mRNA (cut-off 2.5 characterised by 100% specificity)

	Sensitivity (%) (95% CI)		
	Free DNA	Free DNA and COX-2	Specificity (%) (95% CI)
All cases	83 (76 to 89)	91 (86 to 96)	92 (87 to 97)
Sex			
Male	80 (72 to 88)	89 (82 to 94)	88 (79 to 94)
Female	89 (76 to 96)	97 (88 to 100)	100 (–)
Age (years)			
⩽60	89 (76 to 96)	94 (84 to 99)	87 (75 to 95)
>60	80 (72 to 88)	90 (83 to 95)	96 (89 to 99)
Smoking habits			
Non-smokers	93 (81 to 99)	97 (86 to 100)	91 (79 to 98)
Smokers	80 (72 to 87)	90 (83 to 95)	93 (85 to 97)
Histotype			
ADC	83 (76 to 90)	89 (84 to 94)	
SCC	83 (76 to 90)	94 (90 to 98)	
Others	82 (75 to 89)	91 (86 to 96)	
Stage			
I	88 (82 to 94)	96 (93 to 99)	
II	73 (65 to 81)	91 (86 to 96)	
III	80 (73 to 87)	88 (82 to 94)	
IV	84 (78 to 90)	87 (81 to 93)	

ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Moreover, no significant differences were observed in patients in relation to tumour histotype or stage (see table 1 in online supplement). The area under the ROC curve (AUC) for free DNA was 0.917 (95% CI 0.877 to 0.957) (see fig 1 in online supplement) and very high predictivity was observed for a large range of cut-off values (see table 2 in online supplement). In particular, using a cut-off value of 25 ng/ml, sensitivity and specificity were 83% and 92%, respectively, and values were not significantly different for the subgroups categorised by clinical characteristics or smoking habits (table 1). The AUC value for COX-2 mRNA was 0.758 (95% CI 0.697 to 0.819) (see fig 1 in online supplement), and at the cut-off of 2.5 we observed 38% sensitivity and 100% specificity (see table 2 in online supplement) which did not change as a function of clinical characteristics or smoking habits.

DNA and COX-2 were not significantly correlated in healthy donors ($r_s = -0.04$, $p = 0.68$) or patients ($r_s = -0.05$, $p = 0.57$) and were analysed in combination. At the cut-off value of 25 ng/ml for free circulating DNA and 2.5 for COX-2 mRNA, significantly higher predictivity was observed compared with single marker analyses, with 91% sensitivity and 92% specificity for the overall series as well as for subgroups categorised for clinical characteristics or smoking habits. Moreover, using the combined analysis, the greatest increase in sensitivity was seen for squamous cell carcinoma (SCC) and for stage I and II tumours (table 1), reaching 100% in the subgroup of 31 patients with stage I and II SCC.

When the markers were analysed as continuous variables in a logistic regression model, each marker provided independent and therefore additive diagnostic information: a unit increase in log DNA or log COX-2 was associated with a 9-fold and 13-fold increase in cancer detection, respectively (see table 3 in online supplement), and similar results were obtained in multivariate analysis including clinical characteristics and smoking habits. The ROC curve of the combined marker algorithm confirmed the significantly higher diagnostic accuracy (AUC 0.940, 95% CI 0.908 to 0.972) than that observed for DNA alone (AUC 0.917, 95% CI 0.877 to 0.957) ($p = 0.035$).

We conclude that the combined approach could represent an important test for the early diagnosis of lung tumours.

P Ulivi,[1] L Mercatali,[1] W Zoli,[1] D Dell'Amore,[2] V Poletti,[2] G L Casoni,[2] E Scarpi,[1] E Flamini,[1] D Amadori,[1] R Silvestrini[1]

[1] Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy; [2] Department of Diseases of the Thorax, Morgagni-Pierantoni Hospital, Forlì, Italy

Correspondence to: Dr W Zoli, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Via Maroncelli 40, 47014 Meldola (FC), Italy; w.zoli@ausl.fo.it

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CORRECTIONS

doi:10.1136/thx.2007.086330corr1

L Paleari, A Cesario, P Granone, *et al*. Early detection of cancer: lessons from lung cancer CT screening. *Thorax* 2008;**63**:566. The correct affiliation for the fifth author, Patrizia Russo, is Lung Cancer Unit, National Cancer Institute, Genoa, Italy.

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P A Jenkins, I A Campbell, J Banks, *et al*. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. *Thorax* 2008;63:627–34. There is an error in the abstract of this article. It should read as follows. A trial was undertaken to compare clarithromycin (Clari) and ciprofloxacin (Cipro) as third drugs added to 2 years of treatment with R and E for pulmonary disease caused by *M avium-intracellulare* (MAC), *M malmoense* and *M xenopi* (REClari and RECiprol).

Pulmonary puzzle

ANSWER

From the question on page 802.

Two small opacities are seen in the nasopharynx.

Using fluoroscopy, an ENT surgeon was able to identify the presence of a nasal clip (fig 1) which was removed without difficulty, hence allowing NIV to continue. The patient had been using the device at night to keep his nasal flares patent to help alleviate snoring; he had nasally inhaled the clip with the added positive pressure of his ventilator. The presence of a foreign body either in the upper or lower respiratory tract must always be eliminated when signs of respiratory distress are observed. Assessment is particularly difficult in patients with limited communication such as those with bulbar disease of whatever cause.

Snoring is a extremely common condition that can cause significant difficulties in relationships and home life. Despite very limited evidence, there are numerous commercially available mechanical aids that attempt to keep the nasal air passages clear. When initiating non-invasive ventilation or continuous positive airways pressures therapy, one should check with the patient that these aids are not being used at night due to the risk of aspiration with added positive pressure.

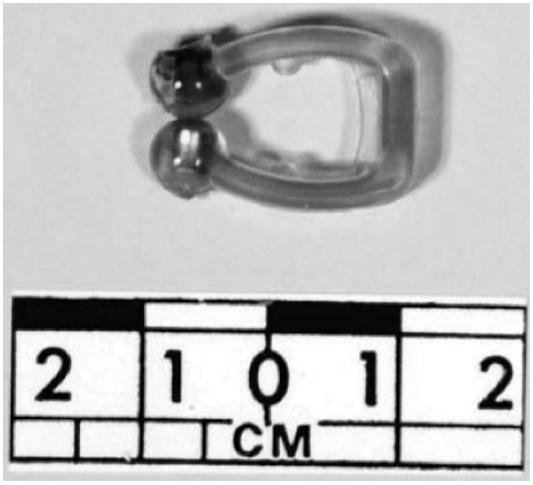

Figure 1 Nasal clip device after its removal.

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