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LUNG ALERT

Tumour suppressor gene methylation and screening for lung cancer

▲ Belinsky SA, Klinge DM, Dekker JD, *et al*. Gene promoter methylation in plasma and sputum increases with lung cancer risk. *Clin Cancer Res* 2005;**11**:6505–11

Bronchial carcinoma is the leading cause of cancer death and often presents at an advanced stage. This study explored the exciting possibility of developing a screening tool for lung cancer. It assessed the level of inhibitory methylation of specific tumour suppressor genes in three groups of women with different levels of lung cancer risk. Plasma and sputum samples were taken from 74 never smokers (lowest risk with $<1 \times 10^{-4}$ lifetime risk), 121 current and former smokers (intermediate risk with 0.3% yearly risk), and 56 patients who had undergone surgical resection of stage I lung cancer (highest risk with 6.0% risk per patient year). Once DNA had been extracted from the samples, methylation specific polymerase chain reaction (PCR) was used to detect inhibition of specific genes: CDKN2A (p16), O⁶-methylguanine-DNA methyltransferase (MGMT), and ras effector homologue 1 (RASSF1A) in plasma and sputum, with additional genes in sputum.

The prevalence of methylation was found to be greater in those with an increased cancer risk. In plasma the largest difference between the groups was seen for MGMT and p16 where lung cancer survivors had increased odds of 5.0 ($p = 0.07$) and 3.2 ($p = 0.04$) fold for methylation compared with never smokers. Those with the highest risk were also more likely to have at least one gene affected ($p < 0.01$). In sputum, lung cancer survivors had a 6.2 fold greater odds for methylation of three or more genes than smokers. Levels of RASSF1A and MGMT methylation in lung cancer survivors were significantly higher in sputum than in plasma samples ($p < 0.05$). The authors conclude that the methylation of multiple gene promoters in sputum is strongly associated with the increased risk of lung cancer.

These results suggest that, with further work, the detection of gene methylation in sputum could be developed as a screening test for lung cancer. Larger studies evaluating this technique are urgently required.

R Stretton

Senior House Officer, Aberdeen Royal Infirmary, UK; r.stretton@nhs.net