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Circulating nucleosomes to identify non-smoker subjects at risk of lung cancer and triage them for low-dose CT scan.

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Background: Lung cancer (LC) is the leading cause of cancer death worldwide and the most frequently occurring in men and the second most diagnosed cancer in woman after breast cancer. The primary risk factor leading to LC is tobacco smoke. Nevertheless, several studies in the US, UK and Asia reported an increasing rate of LC in non-smokers. 15-20% of LC patients worldwide are non-smokers with this percentage rising to 60% in non-smoking women in Asia. Current LC screening guidelines recommend a CT scan only for high-risk smokers. Despite there being no guidelines to recommend LC screening in non-smokers those with increased risk factors could be monitored. Therefore, a blood-test could offer a simple way to identify non-smokers at high-risk of LC and triage them to go for low-dose CT scan. **Methods:** We measured circulating levels of nucleosomes and CEA in 722 non-smoker subjects referred for CT scan at National Taiwan University Hospital. The patients were later confirmed to have either a LC (n = 509, including 401 patients at stage 0-1), non-malignant nodules (n = 142), or no-nodules (n = 71). Whole blood was collected in EDTA plasma tubes for analysis by six different Nu.Q chemiluminescent magnetic microparticle immunoassays (Belgian Volition SRL, Belgium) targeting H3.1-nucleosomes or different histone modifications (H3K9Me3-, H3K27Me3-, H3K36Me3-, H3K9Ac-, H3K14Ac-nucleosomes). CEA was analyzed on the Abbott ARCHITECT analyzer. We defined by logistic regression the best combination of biomarkers to identify LC cases in this non-smoking population in a rule-in approach. **Results:** At 95% specificity, none of the individual biomarkers exceed 24.8% of sensitivity for LC vs non-malignant nodules and no nodules. A combination of 2 nucleosome biomarkers: H3K9Me3- and H3K9Ac-nucleosomes with CEA in a logistic regression model showed improved sensitivity detecting 32.4% of LC in the non-smoker subjects at 95% specificity for LC vs non-malignant nodules and no nodules (area under the curve (AUC): 0.76, R^2: 19.1%). In a non-smoking women sub-group by adding a third nucleosome biomarker: H3K36Me3-nucleosomes to the model we could detect 34.3% of the women who have lung cancer at 95% specificity (AUC: 0.75; R^2: 20.2%). **Conclusions:** Our results indicate that a blood test combining circulating nucleosomes targeting different epigenetic modifications with CEA allow the detection of LC cases in a non-smokers population. This blood test could be part of the screening criteria for the non-smoking population at risk to develop LC and could help to triage them for low-dose CT scan. Research Sponsor: Belgian Volition SRL.