Commentary

Personalized lung cancer screening: the value of spirometry and emphysema as risk modifiers

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In 2011 the National Lung Cancer Screening Trial (NLST) showed that screening lowered lung cancer mortality from 1.66% in the computed tomography (CT) arm to 1.33% in the chest X-ray arm (1). Based on the NSLT results the US Preventive Services Task Force (USPSTF) recommended annual screening with chest CT in current smokers (or former smokers quitted less than 15 years) of 55 to 77 years with a smoking history of 30 pack years in the USA (2). Several prominent medical societies like the American Thoracic Society and American College of Chests Physicians subsequently endorsed lung cancer screening with CT. Critics have argued that the USPSTF eligibility criteria lead to a too high rate of false-positives resulting in an unfavorable risk-benefit ratio. Of the positive screening CT's in NLST almost 96% was false positive. There are proven effective strategies to lower false positives such as short-term follow-up of indeterminate nodules with calculation of volume doubling time. Additional to these personalized screening methodologies may decrease the high rate of false-positive CT's.

In a screening setting selecting participant with the most favorable a-priori risk of the disease screened for, i.e., lung cancer is crucial for the effectiveness of screening. Identifying the (former) smoker with the highest a-priori risk will inevitably improve the risk-benefit ratio of screening (3). Well-known risk factors for lung cancer are age, smoking and number of pack years smoked. de Koning *et al*. examined which screening scenario has the most favorable benefit-harm ratio based on the age of screening participants, pack years smoked, years quitted and screening intervals using NLST and Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial data. They showed that the most favorable screening scenario is annual CT for individuals aged 55 through 80 years with 30 or more pack-years (4). Retrospective analysis of NLST data showed that the most lung cancer deaths were prevented in those with the highest risk of lung cancer (5). Lung cancer risk was calculated based on a number of risk factors including age, pack-years, years since quitting smoking, family history of lung cancer, previous or current occupation with dust exposure, previous or current occupation with asbestos exposure and a diagnosis of emphysema as visually assessed on chest X-ray. The results were impressive as the number of participants who would need to be screened to prevent one lung-cancer death decreased from 5,276 among the 20% of participants at lowest risk to only 161 among the 20% of those at highest risk. It might well be that subjects meeting lung cancer screening eligibility criteria but with a low risk on lung cancer could suffice with longer screening intervals.

How could a more personalized screening work? Next to well-known risk factors chronic obstructive pulmonary disease (COPD) is also associated with lung cancer. However, whether this has to do with the fact that COPD and lung cancer share the same risk factor, i.e., smoking, is not well elucidated yet. Young *et al*. showed in a retrospective case-control study that COPD was more prevalent in current and former smokers with lung cancer compared to current and former smokers without lung cancer. Half of the current and former smokers with lung cancer had COPD GOLD 2 or higher compared to only 8% in the control group (6). Interestingly, in the current and former smoking group with lung cancer there were significantly more current smokers, 39% versus only 22% in the group without lung cancer. In a post-hoc analysis of the Danish Lung Cancer Screening Trial (DLCST), Wille *et al*.

reported that participants with COPD and more than 35 pack years had a significantly increased risk of dying from lung cancer. However, because the DLCST was statistically underpowered, also in this specific subgroup of the DLCST there was no significant reduction in mortality in the CT screening group compared to the control group.

Spirometry requires additional testing which can complicate the screening. Especially when spirometry is performed in dedicated certified laboratories after bronchodilation. Could the baseline CT provide an opportunity to personalize the screening? Adding emphysema presence on CT to the NSLTS lung cancer screening eligibility criteria increased the number of lung cancers detected in a retrospective analysis of a small European lung cancer screening study in Pamplona (P-IELCAP) (7). Maybe even important is that adding the presence of emphysema as eligibility criterion decreased the numbers of persons needed to screen to detect one lung cancer in P-IELCAP. de-Torres *et al*. developed a COPD lung cancer screening score (COPD LUCS) in order to predict the risk of lung cancer in COPD patients (8). Two risk categories were created: low and high risk based on body mass index (BMI), pack years, age and the presence of emphysema on CT. High risk COPD patients had a 3.5 fold increase on lung cancer compared to the low risk subjects.

Also in the general population presence of emphysema on CT is associated with lung cancer mortality. In a large meta-analysis visually assessed emphysema was associated with lung cancer (9). In the Multi-Ethnic Study of Atherosclerosis (MESA) quantitatively assessed emphysema on cardiac CT was associated with greater lung cancer mortality, independent of age, gender, BMI, smoking status and pack years (10). Interestingly from this study is the fact that participants were from the general population of which the vast majority was not familiar with a diagnosis of COPD. It might thus be that there is an association of emphysema with lung cancer, independent from COPD.

Emphysema presence on CT thus might be used as risk modifier in personalized screening strategies. However, per definition it only can be of use if someone has undergone a first CT screening round, which makes it an unpractical criterion for eligibility for lung cancer screening. This brings us to an important aspect of personalized screening methodologies, which is making use of information from the first screening CT to improve the risk-benefit of screening subsequent lung cancer screening.

Data from the Dutch-Belgian Lung Cancer Screening (NELSON) trial showed that one of the decisive characteristics associated with lung cancer probability after a first screening CT is performed is the presence and size of pulmonary nodules (11). Participants without a pulmonary nodule on the first screening CT had a very low risk (0.4%) of developing lung cancer during two years of follow-up. Remarkably, this risk did not significantly differ from participants with a pulmonary nodule smaller than 5 mm (0.6%). Likewise, in participants with nodules of 5–10 mm the risk remained less than 1.3%.

In addition, given the high costs of lung cancer screening personalized screening methodologies may also offer a solution in an attempt to reduce and control costs. In the US, Medicare have agreed to reimburse the screening costs in eligible subjects according to the USPSTF recommendation, however, Medicare stresses that eligibility criteria need to be refined in the near future. According to the current eligibility criteria it is projected that in the next 5 years 10.7 million more low-dose CT scans will be performed in the US only. In NLST costs per quality adjusted life-years (QALY's) were significantly lower in participants with high lung cancer risk compared to those with low lung cancer risk (12). In a participant in the lowest lung cancer risk quintile a QALY costs 169,000 USD while in a patient in the highest lung cancer risk quintile a QALY costs only a third (52,000 USD).

In conclusion, there is substantive evidence supporting personalized screening methodologies to increase the risk-benefit ratio of lung cancer screening. An important point of concern remains the very high rate of false-positive screens. COPD and emphysema may show to be important risk modifiers in lung cancer screening. After the primary results of the NELSON trial study are reported, important post-hoc analyses in the NELSON trial may elucidate the role of COPD and emphysema on lung cancer risk in lung cancer screening CT.

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Footnote

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to declare.

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