Screening for lung cancer – are we nearly there yet?

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Lung cancer remains a significant disease in men in the UK and worldwide. It is often diagnosed late when treatment options are limited. Early diagnosis is key. In this article the authors discuss the latest techniques in diagnosing lung cancer and the potential benefits of a lung cancer screening programme.

Lung cancer is the most frequently diagnosed cancer in men and the leading cause of cancer death worldwide. The majority (70%) of patients are diagnosed with stage 3 and 4 disease when curative treatment is not an option. When lung cancer is detected at its earlier stages, surgical resection (with or without adjuvant treatment) offers vastly improved survival rates (Figure 1). The need for early detection is therefore imperative to improve outcomes for this condition.

Investigating screening and early detection has been the objective of many trials since the 1970s. The earlier studies, using chest x-ray, failed to show any benefit. Thanks to continually improving technology in computed tomography (CT) image acquisition and processing, radiation doses for ‘low-dose chest CT’ (LDCT) have been brought down from 7mSv to around 1mSv, and more recently there is promise of an ‘ultra-low dose CT’ that utilises radiation doses of around 0.2mSv, the equivalent of just 20 chest x-rays.

As a result, CT screening has been under extensive investigation in recent years. In 2011 the US National Lung Screening Trial (NLST) investigators reported an improvement in lung cancer-specific mortality of 20% and all-cause mortality of 6.7% with LDCT compared with chest x-ray after three annual screens and seven years follow-up. Several other trials have been or are underway, but none have been sufficiently powered to confirm or refute this finding. The largest of these is the Dutch–Belgian Randomised Lung Cancer Screening Trial (NELSON), which has recruited mostly men and is due to publish in the next year.

Figure 1. CT scan showing an early lung cancer (red box) in an asymptomatic patient. It was proven to be an adenocarcinoma and successfully resected.
BENEFITS OF SCREENING

Based on the currently available evidence, lung cancer screening seems to be an effective intervention. The screening committee in the UK is waiting on the pooled results of more recent European trials to make a decision. The Centre for Medicare and Medicaid Services, US insurance providers, has initiated screening for its clients if asymptomatic and aged 55–77 with a 30 pack-year smoking history, including those having quit 15 years ago or less; however, much of the uninsured American population remains without access to lung cancer screening.

The impressive mortality benefit of screening, which rivals that of breast or bowel screening, is likely to be at least partly due to the high sensitivity of the screening test, which was reported at 94.4% by the NLST investigators. Although not the same as specificity (as an indeterminate test is not the same as a positive test), a drawback is the relatively high rate of indeterminate pulmonary nodules, which are frequently detected at screening and require further radiographic surveillance. This adds to the cost of screening and can cause a degree of anxiety in patients. The exact frequency of this occurrence varies with the threshold volume or diameter of a nodule deemed necessary for nodule surveillance. When the threshold is set at 5mm, as recommended by the British Thoracic Society (BTS) Guidelines, this figure is estimated to be around 25%.

Despite this disadvantage, LDCT screening is considered to be cost-effective, at an estimated cost per quality-adjusted life year gained of around £9000. At this figure, it would be likely to be accepted as a cost-effective intervention by NICE.

In order to enhance the benefits and cost-effectiveness and to reduce the harms of screening, various strategies can be implemented (Box 1), such as optimisation of nodule management algorithms, and refining the eligibility criteria of who should be screened and how frequently screening should occur.

IDENTIFYING THOSE AT RISK

The evidence suggests that if we identify and screen those at highest risk of lung cancer, we can reduce both the number of individuals to be screened to save one life from lung cancer and the number of false-positive results per screening-prevented lung-cancer death.

Various algorithms, including the PLCO2012 and LLPv2 models, have been proposed to predict risk of lung cancer based on clinical and demographic factors (Table 1). The most important factors are age and smoking history; factors such as previous malignancy or emphysema/bronchitis, family history of lung cancer, social deprivation and others are also of significance.

Using risk to determine eligibility for screening would be quite a challenge to introduce, given most current cancer screening programmes are population-based and use only age to determine eligibility. Assessing and determining risk is an additional step in a screening programme. How this is best carried out has not yet been determined and the options range from asking patients to complete a self-risk assessment, to a

<table>
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<tr>
<th>LLPv2</th>
<th>PLCO2012</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Smoking duration (years)</td>
<td>Education (1-6)</td>
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<td>Previous pneumonia/COPD/emphysema/bronchitis/tuberculosis</td>
<td>BMI</td>
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<td>Personal history of lung cancer</td>
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<td>Previous family history of lung cancer (and relative’s age at onset)</td>
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<td>Race (White, Black, Hispanic, Asian, Native American, Native Hawaiian)</td>
<td>Smoking status</td>
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<td>Smoking status</td>
<td>Average number of cigarettes smoked per day</td>
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<td>Duration smoked (years)</td>
<td>Years ago quit smoking</td>
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Table 1. The variables used in the LLPv2 and PLCO2012 algorithms to predict risk of lung cancer
telephone or a nurse consultation to carry out the risk assessment.

Whatever method for selecting and engaging patients is chosen, it is important to consider the issue of social deprivation. Individuals from more deprived communities are more likely to smoke, have higher nicotine dependence and subsequently have a higher risk for lung cancer. Engaging those at high risk improves the risk–benefit balance of screening for the individual, but conversely, it has been documented that these same individuals are less likely to attend screening. Special measures to engage individuals from deprived communities are therefore needed to prevent a screening programme increasing the existing social inequalities in lung cancer.

SMOKING CESSION VITAL
Early detection is not the same as prevention and this is a message that must be made clear. Smoking cessation is still vitally important to reduce lung cancer incidence in the long term, and any screening programme must have a means to implement smoking cessation alongside it. How best to go about this is still under debate. Data from the NELSON study showed those in the screened and control arms had higher rates of smoking cessation than the background population, suggesting those motivated to participate in the trials may be amenable to health promotion. Studies have also shown that smoking abstinence was increased in those with indeterminate and positive results compared with those with negative results, suggesting fear of a cancer diagnosis may motivate quit attempts. It is therefore imperative in those with normal scans to balance reassurance with the promotion of health-protective behaviours. Given the high number of incidental findings of smoking-related lung diseases such as emphysema and bronchiectasis picked up at the screening scan, it may be advantageous to use these to motivate patients to trigger a quit attempt.

Another incidental finding common in this demographic of smokers and ex-smokers in their 60s and 70s is coronary artery disease. As the NHS runs health checks for individuals aged 40–74 for cardiovascular risk assessment, it seems sensible to combine lung cancer screening and cardiovascular risk assessment, given the population at risk for both conditions. Furthermore, LDCT scans have been shown to be effective at picking up the presence of coronary calcification and it is possible that this may be a useful contributor to assessing cardiovascular risk.

CONCLUSION
While there is a clear need to promote early detection in lung cancer, it is vital that this occurs in asymptomatic patients to truly result in a stage shift to early disease with curative options. If screening is implemented for lung cancer, it must be carried out in an evidence-based manner with adequate resources available and stringent quality control to derive the maximum benefit for patients. If done properly, it has the opportunity to transform outcomes in lung cancer. While we wait for the results of the European studies and for policy makers in the UK to make a decision about implementation, we can continue further research to provide evidence to support future guidance around best practice for lung cancer screening, and hope that we are very nearly there.

Declaration of interests: none declared.

REFERENCES