Screening for lung cancer

Lung cancer is the most common cause of cancer death, both in the UK and worldwide. It accounts for around 35 000 deaths in the UK alone each year and there has been little change in survival over the past 20 years. Furthermore, around three quarters of all patients present with locally advanced and metastatic disease, when any treatment is palliative. There has been increasing interest in screening for lung carcinoma as early stage disease may be treated with curative intent. This article provides an overview of lung cancer screening and reviews the main questions and considerations associated with implementation of a programme in the UK.

What is screening?

The UK National Screening Committee (2015) defines screening as '… a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.' For cancer screening this means detection of early stage cancer in those who are asymptomatic so that more effective treatment can be offered. There are three NHS cancer screening programmes currently available in the UK: cervical, breast and bowel.

Background to lung cancer screening

Four categories of screening have been studied in lung cancer: imaging, bronchoscopy, sputum analysis and biomarkers in serum and other fluid. To date only computed tomography screening has been shown to be effective in reducing mortality.

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Biomarkers and gene technology

The area of biomarker research and identification of genomic abnormalities to try to detect lung cancer at an early stage is a rapidly growing area of cancer research. No specific blood, sputum or exhaled breath test has yet been shown to be effective in clinical trials. It may be that biomarkers will have a place in the risk stratification or identification of patients suitable for entry into screening or who may require more rigorous investigation (Vansteenkiste et al, 2012). A greater appreciation of the different genomic abnormalities in different lung tumours may also allow more targeted and personalized therapies but currently there is no evidence that screening for lung cancer in this way is effective (Cancer Genome Atlas Research Network, 2012; Collisson et al, 2014).

Chest X-ray screening

Initial work performed from the 1950s to 1970s focussed on the use of the chest X-ray, with several studies showing that cancers were detected at an earlier stage and suggesting that there was a survival benefit in the screened group. However, the Prostate Lung Ovarian and Colorectal screening trial randomized subjects to chest X-ray and showed no reduction in mortality compared to controls (Hocking et al, 2010).

With the advent and widespread use of computed tomography, recent randomized controlled trials have used this as the screening tool of choice for lung cancer. However, before looking at the results of screening trials it is important to understand the main biases that apply to screening trials.

Understanding the biases operating in screening trials

Many of the earlier non-randomized lung cancer screening trials did not take into account the biases that are associated with screening trials specifically, resulting in apparently longer overall survival but no reduction in mortality. These three biases can be minimized by ensuring that the main outcome measure is survival. *Figure 1* illustrates these biases.

Key trials in lung cancer screening

There have been several randomized controlled trials of screening for lung cancer using low dose computed tomography. Many of the European trials, including the largest (NELSON), are still in the follow-up period. These are summarized in *Table 1*.

The only trial that has shown a mortality reduction to date is the National Lung Cancer Screening Trial (NLST), performed in the USA. It recruited almost 53 500 people aged between 55 and 74 years, who had smoked within the past 15 years and who had a smoking history of at least 30 pack years, and randomized them to annual screening by low dose computed tomography or chest X-ray. There were 247 deaths from lung cancer per 100 000 person years in the low dose computed tomography arm compared with 309 deaths per 100 000 person years in the chest X-ray group. This trial finished 1 year earlier than planned as it reached its prespecified lung cancer mortality reduction of 20% in the low dose computed tomography arm. There was also a 6.7% reduction in all-cause mortality (1877 deaths in the low dose computed tomography arm *vs* 2000 deaths in the chest X-ray arm) (National Lung Screening Trial Research Team et al, 2011).

Based on this study the US Preventative Services Taskforce has recommended that lung cancer screening should be offered to patients aged between 55 and 80 years who have the same smoking history as those included in NLST (Humphrey et al, 2013). A decision regarding implementation of a screening programme in Europe is pending the results of NELSON, alongside pooled data from all of the European randomized controlled trials, and also evidence regarding which selection criteria should be used, associated harms and cost-effectiveness analyses (Field et al, 2014).

Figure 1. Biases operating in screening trials. a. Lead time bias. Note that the patients die at the same time but because the patients in the screened arm were diagnosed earlier as a result of early detection, the survival appears longer. b. Overdiagnosis bias. Here there are tumours diagnosed that do not influence the individual patient's survival, but because they are diagnosed in the screened group they contribute to an overall apparent improvement in survival. c. Length time bias. The blue arrows represent the asymptomatic growth of tumours before diagnosis and the red arrows after diagnosis. Longer arrows indicate more indolent tumours. It can be seen that screening is more likely to detect the indolent tumours.

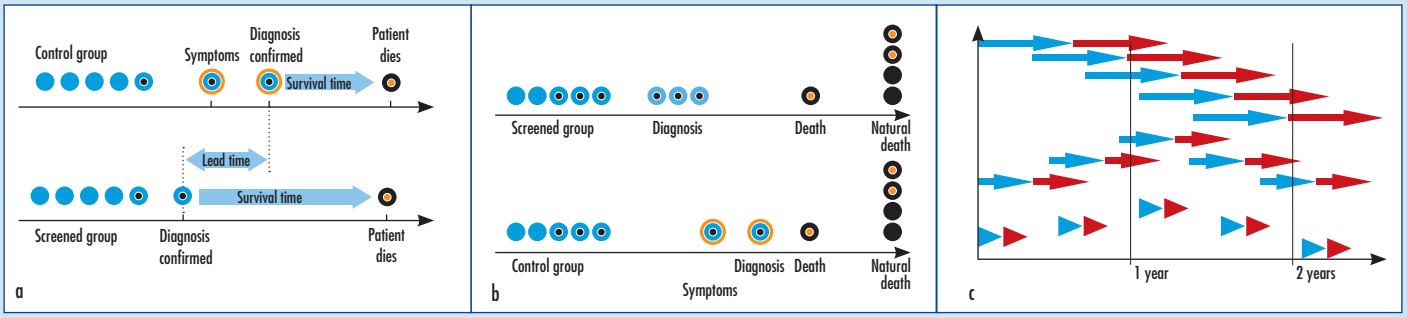

Table 1. Randomized controlled trials in lung cancer screening using computed tomography

Study	Country	Age range (years)	Years of recruitment	Completion or expected completion	Inclusion criteria	Participants (baseline) (*n*)				Screening schedule (years)	Total follow-up (years)
						LDCT arm	Control arm	Total	Control arm		
Lung Screening Study (pilot)	USA	55–74	2000	2001	Current or ex-smokers (>30 pack years, quit <10 years ago)	1660	1658	3318	Chest X-ray	0	1
DANTE	Italy	60–74 (men only)	2001–6	2010	Current or ex-smokers (>20 pack years)	1276	1196	2472	Annual clinic review (chest X-ray and sputum cytology at baseline)	0, 1, 2, 3, 4	4
National Lung Screening Trial (NLST)	USA	55–74	2002–4	2009	Current or ex-smokers (> 30 pack years, quit <15 years ago)	26722	26 732	53 454	Chest X-ray	0, 1, 2	5
NELSON	Netherlands and Belgium	50–74	2003–6	2015	Current or ex-smokers (> 15 pack years, quit <10 years ago)	7915	7907	15 822	Usual care	0, 1, 3	10
ITALUNG	Italy	55–69	2004–6	2006	Current or ex-smokers (> 20 pack years, quit <10 years ago)	1613	1593	3206	Usual care	0, 1, 2, 3	NA
DLCST	Denmark	50–70	2004–6	2014	Current or ex-smokers (> 20 pack years, quit <10 years ago)	2052	2052	4104	Usual care	0, 1, 2, 3, 4	10
Dépiscan (pilot)	France	50–75	2002–4	2004	Current or ex-smokers (> 15 pack years, quit <15 years ago)	336	285	765	Chest X-ray	0, 1, 2, 3	2
Multicentric Italian Lung Detection (MILD)	Italy	49–75	2005–11	NA	Current or ex-smokers (> 20 pack years, quit <10 years ago)	1190 (annual) 1186 (biennial)	1723	4099	Usual care	Annual or biennial for 10 years	NA
LUSI	Germany	50–69	2007	NA	Current or ex-smokers (> 15 pack years, quit <10 years ago)	2029	2023	4052	Usual care	0, 1, 2, 3, 4	5
UKLS (pilot)	UK	50–75	2011 onwards	Ongoing	5% risk of developing lung cancer in 5 years using Liverpool Lung Project risk model	2000	2000	4000 (aim)	Usual care	1	10

DLSCT = Danish Lung Cancer Screening Trial; LDCT = low-dose computed tomography; LUSI = Lung Cancer Screening Intervention Study; NA = not available; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; UKLS = UK Lung Cancer Screening Trial

Harms associated with lung cancer screening

The main harms to consider are radiation exposure from low dose computed tomography, adverse events from further invasive investigation of abnormal computed tomography findings, overdiagnosis, costs incurred by screening and additional diagnostic tests, and possible negative effects on smoking cessation rates.

Radiation exposure

The radiation dose in low dose computed tomography is around a fifth of that of standard thoracic computed tomography scanning, accounting for less than half of the annual background radiation dose of an individual. Annual screening using low dose computed tomography is estimated to cause one radiation-induced lung cancer for every 22 deaths prevented (de Koning et al, 2014).

Overdiagnosis and false positive results

It is estimated that around 25 benign lesions will be detected for every cancer (false positives). Harm can therefore arise from investigation of these non-cancerous abnormalities. In NLST, across the three screening rounds, 96.4% of the low dose computed tomography tests were false positive, with the vast majority of these being the result of detection of benign lymph nodes or granulomata. The majority of these false positive results were confirmed non-invasively using follow-up computed tomography scans. However, 0.2% (59/26 722) of those screened underwent computed tomography-guided lung biopsy for a benign lesion, with seven (0.03%) experiencing a major complication (National Lung Screening Trial Research Team et al, 2011).

Overdiagnosis can occur, as summarized in *Figure 1*, when an indolent tumour which would not kill the patient is detected during screening. Estimates from NLST suggested that 18.5% (95% confidence interval 5.4–30.6%) of cancers were overdiagnosed (Patz et al, 2014). These patients do not benefit from the diagnosis and, in addition to the psychological harm associated with a diagnosis of cancer, they are also subject to the harms associated with invasive diagnostic investigations and unnecessary treatment.

False negative results

A false negative result occurs when the test fails to demonstrate the malignancy in an affected individual. In NLST, of the group screened with low dose computed tomography, 44 of the 1060 (0.04%) participants with lung cancer had a negative screening test (National Lung Screening Trial Research Team et al, 2011).

Cost effectiveness

The cost effectiveness of a programme will be strongly influenced by the frequency of screening, duration of screening programme, risk profile of the screened population, uptake of screening in hard to reach groups and smoking cessation. Modelling has been performed, largely based on the results from NLST, with cost-effectiveness estimated at $23 000 (£13 786), reducing to $17 000 when smoking cessation interventions (varenicline and behavioural techniques) were included (Villanti et al, 2013).

In the UK, the National Institute for Health and Care Excellence uses a standard and internationally recognized method to compare treatments and measure their clinical effectiveness: quality-adjusted life years. A quality-adjusted life year gives an idea of how many extra months or years of life of a reasonable quality a person might gain as a result of treatment. Generally if a treatment costs more than £20 000–30 000 per quality-adjusted life year it is not considered cost-effective.

UK Lung Screen (UKLS) has modelled data obtained from the pilot study and has shown a cost per quality-adjusted life year of £12 300. By way of comparison, cost effectiveness estimates for breast cancer screening vary widely from £3000 per quality-adjusted life year (Advisory Committee on Breast Cancer Screening, 2006) up to £20 000 (Pharoah et al, 2013) with less conservative estimates. The best estimate probably comes from the Erasmus group who estimate €12 000 (£9700) per quality-adjusted life year for a breast screening programme (de Gelder et al, 2009).

Smoking cessation

There has been some concern that screening would offer false reassurance in those who smoke, leading to continued smoking, new or renewed uptake of the habit. There were somewhat reassuring smoking cessation results from the largest European study (NELSON), with rates of quitting of 14.5% in the screened arm and 19.1% in the control arm. These are substantially higher than the background rate of 6–7% (van der Aalst et al, 2010).

Hard to reach groups

An important consideration is uptake rates into a screening programme, as low uptake would render it non-viable (Spiro, 2007). Recruitment into UKLS showed that those who were deemed (using risk stratification tools) to be at highest risk of developing lung cancer were least likely to take up the offer of screening (McRonald et al, 2014). This same finding has been encountered with many other screening programmes (Hoare, 1996; Jepson et al, 2001; Ladabaum, 2007), with many cultural, social and other demographic reasons postulated as the cause. Data suggest that smokers view screening in a nihilistic way and perceive early detection to be of limited use and, as such, are less likely to consider screening participation (Silvestri et al, 2007). Work is ongoing to try to determine how best to target these hard to reach groups to both recruit and retain them in lung cancer screening programmes.

What is happening in the UK?

The UK National Screening Committee uses 22 internationally-recognized criteria to establish whether a national screening programme is warranted for a particular condition. These are summarized in relation to lung cancer in *Table 2*. Lung cancer screening with low dose computed tomography satisfies all of the applicable criteria, in total 19 of 22, and the Department of Health Science and Technology committee have received submissions regarding evidence for screening, alongside a proposal submitted to the UK National Screening Committee.

Who, how and when to screen

This is still under consideration in the UK, although the most likely initial implementation regimen will probably use risk stratification tools to identify those who have in excess of 1% per annum risk of lung cancer and offer them annual or biennial screening with low dose computed tomography from the age of 60 years, alongside a clear protocol for the investigation and manage-

ment of abnormal findings and in conjunction with ongoing research into the best methods for selection, recruitment and retention.

Conclusions

A large American randomized control trial has shown that lung cancer screening with low dose computed tomography reduces lung cancer mortality, with pooled results of European randomized controlled trials awaited to confirm this finding. It seems likely that lung cancer screening using low dose computed tomography will be introduced in the UK in the not too distant future. Future implementation must ensure cost effectiveness as well as conferring the minimum risk of harm to those screened, by accurate selection of those who are most likely to benefit and use of robust imaging and investigation protocols. **BJHM**

Table 2. UK National Screening Committee Criteria for appraising the effectiveness, appropriateness and viability of a screening programme in relation to lung cancer

		Lung cancer
The condition	An important health problem	✓
	The epidemiology and natural history should be understood, with a detectable risk factor	✓
	All cost-effective primary prevention should have been implemented	✓
	If carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood	NA
The test	A simple, precise, safe and validated screening test	✓
	The distribution of test values in the target population should be known, with a suitable cut-off level defined	✓
	The test should be acceptable to the population	✓
	An agreed policy exists on further diagnostic evaluation of individuals with a positive test result	✓
	If the test is for mutations, the criteria to select the subset of mutations, if all possible are not to be tested, should be clearly set out	NA
The treatment	There should be an effective treatment for patients identified through early diagnosis, with evidence of early treatment leading to better outcomes than late	✓
	There should be agreed evidence-based policies covering which individuals should be offered treatment	✓
	Clinical management of the condition and patient outcomes should be optimized in all health-care providers before screening programme participation	✓
The screening programme	Evidence exists from high-quality randomized controlled trials that the screening programme is effective in reducing mortality or morbidity	✓
	The complete screening programme is clinically, socially and ethically acceptable to health professionals and the public	✓
	The benefit of the programme should outweigh the physical and psychological harm	✓
	The cost of the screening programme should be balanced in relation to spending on medical care as a whole	✓
	A plan for managing and monitoring the screening programme and an agreed set of quality assurance standards	✓
	Adequate staffing and facilities to run the screening programme are available	✓
	All other options for managing the condition should have been considered to ensure there is no more cost-effective intervention that could be implemented	✓
	Evidence-based information explaining the consequences of testing, investigation and treatment should be available to potential participants	✓
	Public pressure for widening the eligibility criteria or reducing the screening interval or increasing the sensitivity of the test should be anticipated and decisions should be justifiable	✓
	If the screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members	NA

NA = not applicable

Conflict of interest: Dr E O'Dowd: none; Professor D Baldwin is a member of the UKLS study group.

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KEY POINTS

- Four categories of screening have been studied in lung cancer: imaging, bronchoscopy, sputum analysis and biomarkers in serum and other fluid, but only computed tomography screening is effective in reducing mortality.
- The United States National Lung Screening Trial showed a 20% reduction in lung cancer mortality in the computed tomography-screened arm compared to chest X-ray.
- None of the smaller European trials have shown a mortality advantage but the results of the largest one (NELSON) are expected in 2015/16.
- Key considerations before implementing lung cancer screening are minimization of harms, optimization to include better selection criteria and recruitment methods, improved work-up protocols and effective integrated smoking cessation, and cost effectiveness.
- In the UK screening is likely to target those with >1% annual risk of lung cancer above the age of 60 years with annual or biennial low-dose computed tomography but Department of Health Science and Technology committee and National Screening Committee appraisals are awaited.