Screening for lung cancer: we still need to know more

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The holy grail for a screening test is that it discovers more cancers in the screened arm than in the control; that those cancers are of an earlier stage and there is, as a consequence, a stage shift towards lower stage cancers compared with the control group; that the test is acceptable to, basically, healthy individuals with low risks of serious side effects resulting from tests following a positive screen; and that the cost of a life saved, or a quality-adjusted life-year (QALY) is acceptable to the economy of the day.

Published in *Thorax* there is an end-of-screening report on a Danish CT-based study.[1] They entered 4104 men and women, (of which 45% were women, unusually high) aged between 50 and 70 years, a 20 pack-year smoking history; lung function was recorded but was not used as an inclusion criterion. The screened group underwent five annual CTs and the control group nothing, but were seen every year. It was not stated why, or what was done to this latter group. At the end of the study period 69 cancers were found in the screened arm and 24 in the control. There were more early stage (stages I and IIB) cancers found in the screened arm than in the control arm: 48 versus 21. However, the number of advanced stage cases (IIIB and IV, and extensive disease small cell) were similar: 21 versus 16, ie, no stage shift effect. There was also a large preponderance of adenocarcinomas and bronchoalveolar cell tumours, typical of screened populations. Also, of 611 participants followed for 5 years, 1404 non-calcified nodules (NCN) were identified, another enduring problem in CT-based trials. Evaluating all deaths by the end of the study, there were 61 in the screen arm of which 15 were from lung cancer, compared with 42 deaths in total with 11 from lung cancer in the control group.

This study shows similar results to the other CT-based randomised screening trials currently in progress, with more early stage cancers found with CT compared with either nothing or a chest x-ray (CXR) in control groups. However, the overall numbers in this Danish study will be too small to show a conclusive stage shift, which could elevate screening to routine practice.

The other trials in progress, briefly, include the Italian DANTE study,[2] which recruited 2472 men aged between 60 and 74 years, and a 20 plus pack-year smoking history. They all had a CXR and sputum cytology at baseline and then were randomly assigned to an initial CT scan with four annual follow-ups, or, in the control group, annual clinical examinations. In the CT group, 28 cancers were found, of which 16 were stage I. In the control arm, eight cancers were seen at baseline—a prevalence of 0.67%, of which four were stage I. Adenocarcinoma and bronchoalveolar cell tumours accounted for 61% of cancers in the CT arm and 50% in the control arm. The effect on mortality is not yet available.

The French DEPISCAN study[3] enrolled 1000 men and women from general practice who were asymptomatic, aged between 50 and 75 years, and had smoked more than 15 cigarettes a day for 20 years. They were randomly assigned to low-dose CT or CXR with two annual screens. Eight lung cancers were found in the screened arm, but five of these were advanced stages IIIb or IV, and only one was stage IA, compared with just one in the CXR arm, but 45% in the CT arm had abnormal scans, compared with 7.6% in the control group.

The NELSON trial[4] is a Belgian–Dutch collaborative trial with 15 428 subjects (as of October 2005) randomly assigned to a CT scan at baseline and at 1, 2 and 4 years, versus a control arm with no tests. Subjects were mainly men aged 55–75 years, smokers of at least 15 cigarettes a day for 25 years, or 10 a day for 30 years. Selection was based on the degree of risk for lung cancer, and it was calculated that 28 000 participants would have been needed to detect a benefit of lung cancer mortality by 20%. Results after the screen period are expected soon.

The ITALUNG cohort contains 3206 subjects,[5] chosen from general practices in Italy, randomly assigned to 4 years of CT screening or nothing. They were aged between 55 and 69 years, with at least a 20 pack-year smoking history. In the screened arm 21 cancers were found in the prevalence screen (rate of 1.5%), with 10 being stage I.

Another study being piloted is a UK study,[6] which will enrol 4000 volunteers for randomisation between a single CT screen versus nothing, and will assess whether early diagnosis improves mortality and whether benefit exceeds harm in a cost-effective manner. If positive, another 28 000 will be enrolled. The design is based on selecting subjects who are at a high risk of getting lung cancer (5% over the 5 years of observation) using a validated risk-identifying model, the Liverpool lung project risk model. Only subjects with clearly defined abnormalities on their CT will be asked for further scans, depending on nodule volume analysis, based on the nodule analysis scheme being used in the NELSON trial.[7]

The first randomised study to report final results is the very much larger American National Lung Cancer Screening Trial (NLST),[8] which showed that lung cancer screening with low-dose CT reduced lung cancer mortality by 20% and all-cause mortality by 6.7% compared with CXR screening. The trial enrolled 53 454 persons between August 2002 and April 2004, all high-risk 30 pack-year smokers from 33 centres across the USA. Twenty-six thousand seven hundred and twenty-two participants were randomly assigned to low-dose CT and underwent three annual screens, or a single CXR for the 26 732 participants in the control arm. The rate of positive screens was high: 24.2% in the CT arm and 6.9% for the CXR. Of these, a total of 96.4% in the CT arm and 94.5% in the CXR arm were false-positive results, due mainly to the finding of benign NCN. The incidence of lung cancer was 645 cases per 100 000 person-years (a total of 1060 cancers) in the low-dose CT group, compared with 572 cases per 100 000 person-years (941 cancers) in the CXR group. There were 247 deaths from lung cancer per 100 000 years in the CT group and 309 in the CXR group, representing a relative reduction in the death rate from lung cancer of 20.0%.

The NLST is a hugely important trial but expensive and therefore the cost effectiveness of a screening intervention becomes very important. An assessment

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of the cost-effectiveness of NLST, based on an existing lung cancer policy model that simulates lung cancer development, disease progression, treatment and survival, was applied to each decade of the NLST population (the authors did not have access to individual data such as smoking habits). They compared estimated QALY for lung cancers based on the screening test, compared with either nothing in the control arm or the addition of a smoking cessation programme for both study arms.[9] They also took into account smoking history, ie, 20–40 or more than 40 pack-year histories. Their study concluded that the annual screening of current and former smokers aged between 50 and 74 years costs between US$126 000 and US$169 000/QALY for a minimum of 20 pack-years of smoking, and between US $110 000 and US$166 000/QALY for a 40 pack-year minimum. If, however, the screen was linked to a smoking cessation programme that doubled the quit rate in the screened arm (and reduced the number of smoking-related deaths) the cost fell to US$75 000 for a 50 years plus and minimum 20 pack-year smoker. If screening halved the quit rate from cessation programmes, which is possible due to the 'reassuring' effect of a negative screen, then the cost effectiveness of screening is erased. The authors compared their data with the cost of colorectal screening versus simple control of US$13 000 to US$32 000/QALY, and with breast cancer screening by mammography in women over 40 years of 47 700/QALY.[9] In an accompanying editorial to this study by McMahon *et al*,[9] Evans and Wolfson[10] emphasise the importance and cheaper costs of smoking cessation, which is far more cost effective than screening alone and also more cost effective than cessation plus CT screening. The model used by McMahon *et al*[9] predicted that if the cessation rate was doubled to 6% from its baseline 3%, it would cost US$17 000–20 000/QALY, but if combined with annual screening, it would still remain more cost effective at US$73 000 for men and US$40 000/QALY for women.[10]

Another feature of the NLST was the huge preponderance of 98% of NCN being benign (falsely positive CT), and this will need optimal assistance from radiologists to minimise subject anxiety. The volumetric approach to nodule growth as used in the NELSON and the UK Lung Screen (UKLS) trials may diminish the need for more than one follow-up CT.

The other unresolved issue for most trials is bias. This includes lead time bias, which explains the higher number of still clinically occult cancers found with CT compared with a control group; length time bias, which may also be relevant if the tumours identified are less aggressive than normal, with prolonged preclinical phases; and overdiagnosis bias, in which many of the cancers discovered may not result in that individual's death. Therefore, final mortality data, often accrued years after the study closes, will have to be collected to see if a screening test actually saved lives. Studies of growth rates of screen-detected cancers suggest that many have a volume doubling time (VDT) in excess of 400 days, making overdiagnosis bias relevant. A review of the 1520 high-risk subjects screened in the 5 year Mayo Clinic programme calculated the VDT of tumours that were imaged more than once. Sixty-one lung cancers were found in 59 individuals. VDT were calculated in 49 cases, with a mean value of 518±1049 days. Twenty-seven of these had a VDT of more than 400 days and most were adenocarcinomas. The mean VDT was longer in women (688 days) than for men (234 days), and this was consistent for tumours of all cell types. Perhaps, the authors conclude, overdiagnosis bias may occur, and especially in women.[11] In fact, the participants in the Danish Lung Cancer Screening Trial suggest that combining VDT analysis with assessment by positron emission tomography may further improve the sensitivity and specificity for the detection of malignant nodules found at screening.[12]

Another way to try to identify those who, if screened, would be more likely to have a high incidence of lung cancer would be to screen only target populations. The NLST and most other trials in progress target smokers, or ex-smokers, usually limited to 70 years of age. The UKLS trial uses the Liverpool lung project risk score to identify high-risk people, and the other current UK trial, lung SEARCH, which is based on initial sputum analysis in the screened arm is using forced expiratory volume in 1 s to include only heavy smokers with mild or moderate chronic obstructive pulmonary disease.

The lung cancer population is, in the main, elderly, of lower socioeconomic status, often with significant comorbidities, and still mainly male. It is not obviously a population that seems keen to be screened. Many individuals, by the risk taken by smoking, are risk averse and not interested in their longer-term health. There is thus the possibility of a national screening programme, should one be set up, not attracting appropriate or adequate numbers of individuals.

Silvestri *et al*[13] showed that smokers were less willing to pay for a screening test in the USA, and less willing to undergo treatment should disease be found. They were also less willing to undergo any screening test compared with ex-smokers and never smokers.

The NLST recruited widely across the USA, and subjects were sought through the press, local mailings, advertising and the internet. Care was taken to recruit from minorities, but there is no information on the relative success of the campaign, ie, how many individuals did not wish to join. The study population was, however, representative of the high-risk smoking USA population.[14] In the NELSON study a questionnaire was sent to 335 441 men aged 50–75 years from population registries[4]; 106 931 replied and subjects were chosen on their smoking habits and risk factors so as to minimise the number of recruits needed. Of these, 11 103 gave consent to the study. This represents 3.3% of all who were initially approached. There was a second round to the population in 2005, in which 250 000 questionnaires were sent and 44 509 persons replied. Of these, 4535 have been randomly selected, 1.8% of the initial population approached. In the ITALUNG trial a total of 3206 subjects was enrolled from 71 232 letters sent from 269 general practices[5]; again, a low uptake of 4.5% of all subjects approached. In the DEPISCAN trial 765 subjects were recruited from 205 general practices and by 25 occupational physicians, a median of six subjects by each active centre, and only 41% of centres became active and able to find subjects.[3] All these trials seemed to have difficulty in recruiting.

The Danish trial confirms that lead time and possibly length time bias will identify more early cancers if sought by a sensitive test, but it is too early to arrive at any conclusion about an effect on reducing mortality. This, and the other current trials, may have to be studied by a meta-analysis to see how they compare with the huge NLST, which for the present suggests that CT-based screening is worthwhile. However, cost pressures, especially with the high cost of QALY for CT screening, will drive us to a better identification of the population to screen. Even then there are challenges, both methodological, in persuading the 'right' people to accept a screen, in interpreting the true from false-positive results, and in driving the costs of these expensive methods down. Finally, one

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may have to wait several years to find whether discovering more cancers early means more lives saved.

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