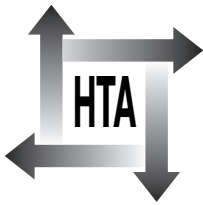# The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews

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The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews

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The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned by the HTA Programme as project number 04/41/01. The contractual start date was in September 2004. The draft report began editorial review in March 2005 and was accepted for publication in July 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Abstract

The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews

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Objectives: The aim of this review is to examine the clinical and cost-effectiveness of screening for lung cancer using computed tomography (CT) to assist policy making and to clarify research needs.

Data sources: Electronic databases and Internet resources.

Review methods: A systematic review was undertaken and selected studies were assessed using the checklists and methods described in NHS Centre for Reviews and Dissemination (CRD) Report 4. Separate narrative summaries were performed for clinical effectiveness and cost-effectiveness. Cost-effectiveness analysis resulting in a cost per quality-adjusted life-year was not feasible, therefore the main elements of such an appraisal were summarised and the key issues relating to the existing evidence base were discussed.

Results: Twelve studies of CT screening for lung cancer were identified, including two randomised controlled trials (RCTs) and ten studies of screening without comparator groups. The quality of reporting of these studies was variable, but the overall quality was adequate. The two RCTs were of short duration (1 year) and therefore there was currently no evidence that screening improves survival or reduces mortality. The proportion of people with abnormal CT findings varied widely between studies (5–51%). The prevalence of lung cancer detected was between 0.4% and 3.2% (number need to screen to detect one lung cancer = 31–249). Incidence rates of lung cancer were lower (0.1–1% per year). Detection of stage I and resectable tumours was high, 100% in some studies. Adverse events, as a result of investigation or surgery,

or the screening process per se were poorly reported. Incidental findings of other abnormalities requiring medical follow-up were reported to be as high as 49%. Six full economic evaluations of population CT screening programmes for lung cancer were included in the review. The magnitude of cost-effectiveness ratios reported varied widely. None was set in the UK and generalisation was complicated by wide variation in the data used in different countries and a paucity of UK data for comparison. All six made the fundamental assumption that screening with CT for lung cancer reduced mortality. At the current time, there is no evidence to support that assumption. In the absence of evidence of health gains from screening for lung cancer, in terms of either quantity or quality of life, and faced with a range of uncertainties, from the frequency of abnormal screening findings within a population to the natural history of screening detected lung cancers, it is not feasible at the current time to develop accurately and meaningfully an economic argument for CT screening for lung cancer in the UK. For subgroups, in particular certain occupational groups, there is evidence of increased risk of lung cancer, but the role of screening has not been demonstrated by the current studies.

Conclusions: The accepted National Screening Committee criteria are not currently met, with no RCTs, no evidence to support clinical effectiveness and no evidence of cost-effectiveness. RCTs are needed to examine the effect of CT screening on mortality, either with whole-population screening or for particular subgroups; to determine the rate of positive screening and detected lung cancers. Research is also needed to

understand better the natural history and epidemiology of screening-detected lung cancers, particularly small, well-differentiated adenocarcinomas; as well as the impacts on quality of life. Increased collection is needed of UK health service data regarding resource use and safety data for lung cancer management and services. Research is also needed into the feasibility and logistics of tracing people who have in the past worked in industry where there was exposure to lung carcinogens.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Baseline screening Sometimes also referred to as prevalence screening, describes the first time a population is screened.

Incidence screening All subsequent CT examinations conducted at a known time interval. New or altered nodules will be reported. Any detected tumours will have developed since the previous CT examination (i.e. new disease).

Lead-time bias Screen-detected patients are accorded extended survival times solely because cancer was detected earlier owing to screening, although death occurred at the same time as would have happened without screening (i.e. the intervention yields no benefit).

Length bias Screening introduces a bias in relation to expected survival by detecting more patients with less aggressive disease (who have longer survival) and fewer of those with more aggressive disease.

Non-calcified nodule Used in screening studies to denote any lesion in the lung in which malignancy cannot be ruled out and for which the study protocol indicates that further follow-up is required.

Over-diagnosis bias Small, slow-growing lesions are detected by screening for intervention that would never become symptomatic within a patient's lifetime in the absence of screening.

Pack-years The number of years that the individual has smoked an average of one pack of 20 cigarettes per day.

Screening test validity Assessed by considering the following four components of the test:

- sensitivity: proportion of individuals with the disease who are correctly identified by the test
- specificity: proportion of individuals without the disease who are correctly identified by the test
- positive predictive value: proportion of individuals with a positive test result who have the disease
- negative predictive value: proportion of individuals with a negative test result who do not have the disease.

Another aspect of assessment of the validity of the test is precision: this assesses the reproducibility of the results of the test.

Spiral (helical) computed tomography Rather than doing one slice at a time as in standard CT, the X-ray tube rotates around the patient at the same time as the patient is moved through the scanner. This reduces the time taken to scan.

List of abbreviations

AE	adverse event		LDCT	low-dose computed tomography
ALARA	as low as reasonably achievable		LYG	life-years gained
BL	baseline screening		NA	not applicable
CEA	cost-effectiveness analysis		NCI	National Cancer Institute
CHART	continuous hyperfractionated accelerated radiotherapy		NCN	non-calcified nodule
COPD	chronic obstructive pulmonary disease		NHS EED	NHS Economic Evaluation Database
CRD	Centre for Reviews and Dissemination		NICE	National Institute for Health and Clinical Excellence
CT	computed tomography		NNS	number needed to screen
CUA	cost–utility analysis		NPV	negative predictive value
CXR	chest X-ray		NR	not reported
DARE	Database of Abstracts of Reviews of Effectiveness		NSC	National Screening Committee
ELCAP	Early Lung Cancer Assessment Project		NSCLC	non-small cell lung cancer
FU	follow-up		PAH	polycyclic aromatic hydrocarbon
HRCT	high-resolution computed tomography		PET	positron emission tomography
HSE	Health and Safety Executive		PPV	positive predictive value
IARC	International Agency for Research in Cancer		QALY	quality-adjusted life-year
ICER	incremental cost-effectiveness ratio		QoL	quality of life
			RCT	randomised controlled trial
INAHTA	International Network of Agencies for Health Technology Assessment		RR	relative risk
			SCLC	small cell lung cancer
INC	incidence screening		SEER	Surveillance, Epidemiology and End Results
			SF-12	Short Form 12

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Screening for lung cancer has been the subject of debate for the past three decades. This has largely stemmed from the results of chest X-ray screening studies where improvements in survival were obtained but without reductions in disease-specific, or total, mortality. The debate raises two issues: the design of studies to evaluate screening for lung cancer, in particular the choice of comparator; and the potential role of over-diagnosis of well-differentiated, slow-growing tumours that would not have led to symptoms or death in the lifetime of the affected patient.

Lung cancer is the leading cause of death from cancer in the UK, killing approximately 34,000 people per year. By the time symptoms develop, the tumour is often at an advanced stage and the prognosis is bleak. Treatment at a less advanced stage of disease with surgical resection has been shown to substantially reduce mortality. Screening would be attractive if it could detect presymptomatic lung cancer at a stage when surgical intervention is feasible.

Objectives

The aim of this review is to examine the clinical and cost-effectiveness of screening for lung cancer using computed tomography (CT) to assist policy making and to clarify research needs.

Methods

Search strategy
Fifteen electronic databases and Internet resources were searched from 1994 until December 2004/January 2005. In addition, bibliographies of the retrieved articles were searched and the register of projects held by the International Network of Agencies for HTA (INAHTA) was also checked.

Inclusion/exclusion criteria
Studies were included where screening for lung cancer was the principal theme of the paper. The initial search was for randomised trials in which survival in a group receiving CT screening was compared with a group not screened, but because of the lack of such studies, no restriction was placed on study type. Studies were reviewed by two authors independently.

Data extraction
Data extraction included details of the screening protocol, follow-up, diagnosis and participants. Information was sought about test characteristics, including sensitivity and specificity. The checklists and methods described in NHS Centre for Reviews and Dissemination (CRD) Report 4 were used for the quality assessment of studies.

Analysis
Separate narrative summaries were performed for the clinical effectiveness and cost-effectiveness. Cost-effectiveness analysis resulting in a cost per quality-adjusted life-year was not feasible, therefore the main elements of such an appraisal were summarised and the key issues relating to the existing evidence base were discussed.

Results

Summary of clinical effectiveness
In total, 12 studies of CT screening for lung cancer were identified, including two randomised controlled trials (RCTs) and ten studies of screening without comparator groups. The quality of reporting of these studies was variable, but the overall quality was adequate. The two RCTs were of short duration (1 year) and therefore there was currently no evidence that screening improves survival or reduces mortality. The proportion of people with abnormal CT findings varied widely between studies (5–51%). The prevalence of lung cancer detected was between 0.4 and 3.2% (number need to screen to detect one lung cancer = 31–249). Incidence rates of lung cancer were lower (0.1–1% per year). Detection of stage I and resectable tumours was high, 100% in some studies. Adverse events, as a result of investigation or surgery, or the screening process per se were poorly reported. Incidental findings of other abnormalities requiring medical follow-up were reported to be as high as 49%.

Summary of cost-effectiveness

Six full economic evaluations of population CT screening programmes for lung cancer were included in the review. The magnitude of cost-effectiveness ratios reported vary widely. None was set in the UK and generalisation was complicated by wide variation in the data used in different countries and a paucity of UK data for comparison. All six made the fundamental assumption that screening with CT for lung cancer reduced mortality. At the current time, there is no evidence to support that assumption.

Economic appraisal

In the absence of evidence of health gains from screening for lung cancer, in terms of either quantity or quality of life, and faced with a range of uncertainties, from the frequency of abnormal screening findings within a population to the natural history of screening detected lung cancers, it is not feasible at the current time to develop accurately and meaningfully an economic argument for CT screening for lung cancer in the UK. For subgroups, in particular certain occupational groups, there is evidence of increased risk of lung cancer, but the role of screening has not been demonstrated by the current studies.

Conclusions

The accepted National Screening Committee criteria are not currently met, with no RCTs, no evidence to support clinical effectiveness and no evidence of cost-effectiveness.

Recommendations for research

In terms of what information is needed to assist decision-making about CT screening for lung cancer, the following research priorities were identified.

- RCT evidence is needed about the effect of CT screening on mortality, either with whole-population screening or for particular subgroups. One such trial is underway in the USA, recruiting 50,000 participants, and is due to end in 2009, although final follow-up will not complete until around 2014.
- UK data about the rate of positive screening with CT and detected lung cancers could be obtained from an RCT or a cohort study. Even relatively small-scale studies would provide valuable information when trying to assess the generalisability of RCT data currently being conducted elsewhere.
- There is a need to understand better the natural history and epidemiology of screening-detected lung cancers, particularly small, well-differentiated adenocarcinomas. This could be met, in part, by lung cancer screening RCTs or cohort studies, but a review of existing published epidemiological and pathological data, along with primary analysis of UK lung cancer epidemiology, would usefully inform current understanding.
- Information about the quality of life impact of CT screening, acceptability of screening, and uptake and retention rates in the UK would be valuable in any future assessment of the cost-effectiveness of screening in the UK.
- Increased collection is needed of UK health service data regarding resource use and safety data for lung cancer management and services.
- Research is needed into the feasibility and logistics of tracing people who have in the past worked in industry where there was exposure to lung carcinogens.

Chapter 1

Aim of the review

This review was commissioned by the UK HTA Programme on behalf of the National Screening Committee (NSC). The aim of this review is to examine the clinical effectiveness of screening for lung cancer using computed tomography (CT), taking into account the effect on mortality, detection of early disease and the impact on quality of life. An economic appraisal is also provided. One stimulus for the review has been publicity about the use of whole body CT screening. This review will not consider the effectiveness of screening for conditions other than lung cancer, but will report on incidental disease findings. A separate review will consider the case for screening for heart disease and, if appropriate, the economic case for dual screening will be addressed.

1

Chapter 2
Background

Introduction

Although smoking rates have fallen, and improvements in treatment have occurred, lung cancer remains the leading cause of death from cancer in the UK. The principal hope for curative treatment remains surgical resection, which requires tumours to be recognised early, before local invasion or remote spread of disease.[1] Improvements in CT technology, in particular the increased rapidity of imaging facilitated by spiral CT, make the detection of smaller lung abnormalities and mass screening feasible, at least in theory. There is currently no mass-screening programme for lung cancer in the UK.

This technology appraisal was undertaken to inform the NSC discussions about the feasibility of screening for lung cancer using CT. Following an introduction to lung cancer and issues surrounding screening in this chapter, the evidence regarding the clinical effectiveness (Chapter 3) and cost-effectiveness (Chapter 4) is reported. An economic appraisal is provided (Chapter 5). Compatibility with the NSC criteria for a screening test is then examined (Chapter 6). Finally, the weaknesses of the research evidence, recommendations for future research and the implications for clinical practice are discussed (Chapter 7).

Lung cancer: the burden of disease

Lung cancer is the leading cause of death from cancer in the UK. Over the past two decades there has been a reduction in incidence of lung cancer in men and a slowing in the rate of increase among women, related largely to the fall in smoking rates and reduction in tar content in cigarettes. Despite this, approximately 34,000 people die annually from lung cancer across the UK: 20,000 men and 14,000 women. Overall survival after diagnosis is poor (less than 10% at 5 years) with little improvement in the rates over the past 10 years despite advances in chemotherapy regimens for lung cancer.[2]

The classification of lung cancer divides the disease into three main types: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and mesothelioma. NSCLC accounts for about 83% of all lung cancers.[2] Overall survival is poor among patients with NSCLC, but surgical resection offers a potential cure for some. Survival varies substantially with clinical stage of tumour at diagnosis, with a 60–70% 5-year survival among those with stage IA disease but less than 10% for those with stage III disease or worse. Pathological staging, based on a tissue biopsy and therefore generally considered to be more accurate, shows a similar pattern.[2,3] More than 50% of people with lung cancer present with tumours at stage III or later.[2,4]

Histologically, the most common type of NSCLC presenting clinically is squamous cell carcinoma. In the UK, it accounts for 35–45% of all lung cancers, with adenocarcinoma and large cell accounting for 15% and 10%, respectively. Adenocarcinoma is the least strongly associated with smoking and generally occurs in periphery of the lungs.[2]

SCLC is typically aggressive, generally presenting with invasive disease and surgery is rarely, if ever, indicated. Mesothelioma is a rare cancer of the pleural lining of the lung accounting for less than 1% of all lung cancer.[4] It is strongly associated with asbestos exposure. Like SCLC, the outlook after diagnosis is bleak with little potential for curative therapy at present. Given current treatments, it is only people with NSCLC who have a potential to benefit from a screening programme that would enable disease to be identified before local or distant spread.

The risk of developing lung cancer varies across the population and a number of risk factors can be identified. The incidence of lung cancer rises with age and is rare below the age of 40 years. The highest incidence rate occurs among over 70-year-olds.[2]

In the UK, lung cancer remains more common in men than women, despite the incidence falling in men in recent years (*Figure 1*).[5]

The biggest single risk factor for lung cancer is smoking, with 85–90% of all people who present
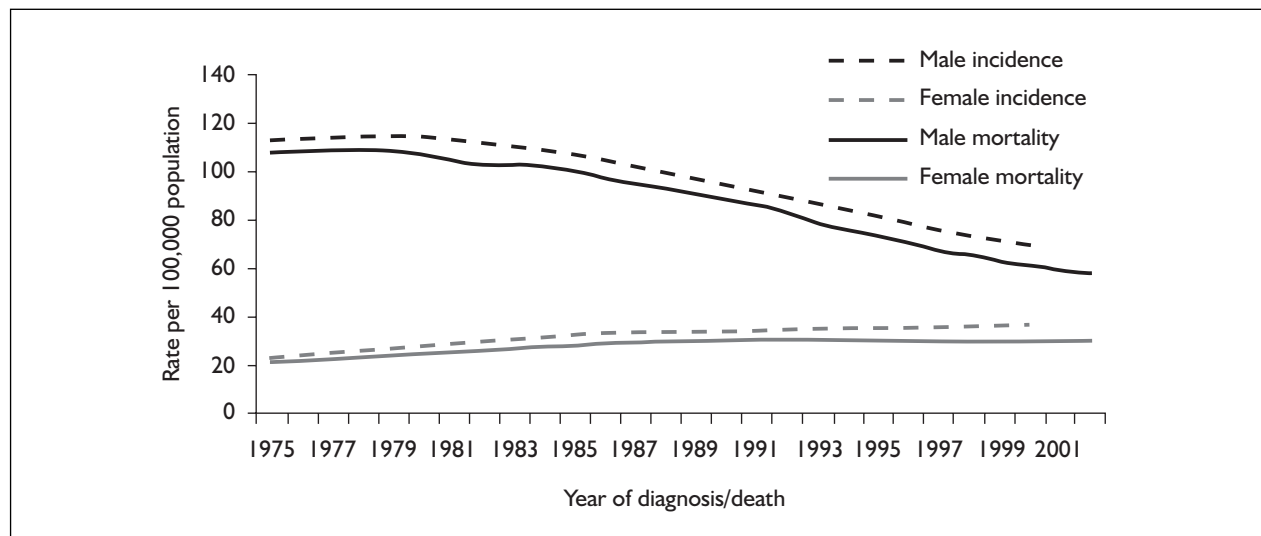
FIGURE 1 *Lung cancer incidence and mortality rates in the UK, 1975–2002. (Reproduced from Cancer Research UK.[5])*

with lung cancer having a history of smoking.[6] Both the number of cigarettes smoked per day and the duration of smoking are among the important factors that correlate with risk of lung cancer. The risk of lung cancer among lifelong heavy smokers is up to 50 times that of non-smokers of similar age.[6] Close temporal links can be seen between the fall over the past two decades in smoking frequency and cigarette tar yields, and male lung cancer mortality. Former smokers experience a substantial decline in risk of lung cancer as the time since last cigarette increases: a 34% reduction in the first 10 years, and reducing to close to the risk for a lifelong non-smoker by 30 years. Stopping smoking even up to the age of 60 years has been shown to reduce substantially the risk of developing lung cancer.[7,8]

Smoking is by no means the only risk factor for lung cancer and increased risks of lung cancer have been reported in association with a variety of occupational exposures. The estimated risk associated with various occupations and key reviews are summarised below and in Appendix 1.

Lung cancer and occupation

The occupational contribution to lung cancer is underestimated and tends to be appreciated only where a well-recognised potential cause is identified, notably asbestos exposure. From a number of studies of specific workforce populations the International Agency for Research in Cancer (IARC) has identified 16 specific occupations, exposures or processes that they class as having 'sufficient evidence' to say that they

cause lung cancer (IARC evidence grade 1)[9,10] (*Table 1*, with fuller review in Appendix 1).

The two main causes of occupational lung cancer are asbestos and silica, but there remains considerable discussion as to whether lung cancer can develop in the absence of associated lung fibrosis. For instance, the estimated relative risk (RR) for workers exposed to silica varies between no increased risk and a relative risk of approximately 1.3. However, patients with silicosis show a greater increased risk (estimated RR around 2.3). A similar situation exists with respect to asbestos. The relative risk of lung cancer in patients with asbestosis is around six-fold higher than in the non-exposed population, whereas asbestos exposure itself carries a smaller risk (RR varying between 1.2 and 2.0 in selected studies, but not increased in others).

In some occupations, carcinogenic exposures may be multiple (e.g. chemical workers). In addition, many workforces are increasingly exposed to diesel fumes, which are currently recognised to be a 'probable' (IARC class 2A) carcinogen. For workforces where diesel is the only exposure, the estimated relative risk for lung cancer lies between 1.3 and 1.5. A range of other occupations is associated with an increased risk for lung cancer, although the relative risks are smaller than those seen with asbestos (see Appendix 1). It may, therefore, be more important to consider occupation rather than specific exposures when determining whether a workforce may be considered for CT screening for lung cancer. It is also important to note that the interpretation of many of the studies contributing to the IARC

TABLE 1 *Agents with 'sufficient evidence' (IARC grade 1) to be classed as occupational lung carcinogens*[9]

Agent	Main industry/use
Arsenic (inorganic) and arsenic compounds	Glass, metals, pesticides
Asbestos	Insulation, filter material, textiles
Beryllium and beryllium compounds	Aerospace industry/metals
Bis chloromethyl ether	Chemical intermediate/by-product
Cadmium and cadmium compounds	Dye/pigment manufacture
Chloromethyl methyl ether (technical grade)	Chemical intermediate/by-product
Chromium (VI) compounds	Metal plating, dye/pigment manufacture
Coal-tar pitches	Building materials, electrodes
Coal tars	Fuel
Crystalline silica	Stone cutting, mining, glass and paper industries
Mustard gas	War gas
Nickel compounds	Metallurgy, alloys, catalyst
Radon decay products	Underground uranium and hard rock mining
Soots	Pigments
Talc-containing asbestiform fibres	Paper, paints
Tobacco smoke (personal and environmental)	All

evidence base are complicated by heavy co-exposure to cigarette smoke.

Certain workforce groups appear to be at greater risk of lung cancer than the general population and some may, therefore, merit special consideration when identifying a potential population for screening. When assessing the risk of developing lung cancer in a workforce, consideration needs to be given to the size of the workforce (at one site or in a specific group of industries) and to the change in exposure pattern over time, bearing in mind the latency of development of lung cancer and changes in work processes aimed at reducing specific exposures. For instance, while arsenic is recognised as a lung carcinogen, very few workers in the UK are now occupationally exposed and exposure levels in those exposed are very low. Consequently, current risk to those workers is essentially that of the normal population. In at-risk workers who are older and who experienced worse working conditions early in their working lives, risk will be higher whatever the current exposure. The workforce most exposed to asbestos is now ageing and often no longer in the employment of the industry that resulted in their exposure. As a result there are substantial logistical difficulties associated with trying to identify at-risk occupational groups for the purposes of a screening programme.

The increased risk of lung cancer associated with certain occupations and exposures, particularly asbestos, may warrant consideration of the feasibility of a screening programme for workers or ex-workers. A case would have to be made on

an occupation-by-occupation basis, with evidence not only of their risk of lung cancer, but also of the feasibility of running an effective screening programme in that population.

Despite reductions in smoking and a fall in the incidence of lung cancer, at least among males, lung cancer remains a serious public health issue, affecting large numbers of people and with a bleak prognosis when presenting after symptoms develop. Treatment of stage I and II disease with surgical resection has been shown to reduce mortality substantially. Screening for lung cancer is an attractive proposal, particularly since symptomatic disease is strongly associated with more advanced and inoperable cancer.

Current service provision

There is no screening service for lung cancer in the UK. The NSC reviewed the topic in March 2004 and concluded that the policy not to offer screening should continue.

Imaging technology for lung cancer screening

The chest radiograph (chest X-ray) remains the most commonly used imaging technique in the investigation of respiratory disease, but it is not a sensitive test for pulmonary nodules, with an estimated 50% of nodules measuring 6–10 mm being missed owing to superimposition of the chest wall, heart and mediastinal structures.[11] The past 30 years have brought revolutionary

developments in imaging techniques, including the development of CT.

The first generation of CT systems had an X-ray tube and a single row of detectors that were positioned on opposite sides of a ring that rotated around the patient lying on a mobile table. During each rotation of the ring, the X-ray tube produced a narrow beam of X-rays that passed through the patient to the row of detectors, acquiring a single axial image with a slice thickness of 1 cm. The table then moved the patient a set distance through the system, acquiring the next axial image. A physical link was required between the X-ray tube and a power supply and after each rotation the ring had to stop and rotate in the opposite direction. The first generation of CT systems was of limited value in the investigation of chest disease, as total examination times were long and the images were prone to artefact due to movement with respiration. In addition, small lesions could be missed if they were present between the thick axial slices.[12]

The incorporation of slip-ring technology into scanners in the late 1980s resulted in the development of spiral (helical) systems. The slip ring is an electromechanical device that allows the transmission of power and electrical signals from a stationary to a rotating structure. This allowed the X-ray tube to rotate continuously, while the table carrying the patient advanced. Data could be acquired rapidly with slices as thin as 1 mm and with image acquisition times as short as one breath-hold of 15–20 seconds.

Further advances with multiple rows of detectors have led to multislice CT. These systems have four to 64 detector rows that acquire multiple image slices during each rotation of the X-ray tube. Image acquisition times are, therefore, faster with less movement artefact as a result.[12] The type of system being used in studies for CT screening for lung cancer is generally spiral CT, but multislice CT systems could also be used.

The advances in CT mean greater sensitivity than plain chest X-ray in the detection of pulmonary nodules. CT has the potential to detect pulmonary nodules as small as 1–2 mm owing to the high contrast between nodules and aerated lung. A study assessing the sensitivity of spiral CT for pulmonary nodules, using surgical exploration and histological analysis as the gold standard, showed the sensitivity of spiral CT to be much higher than previous reports of standard sequential CT with a sensitivity of 100% for intrapulmonary nodules larger than

10 mm, 95% in nodules larger than 5 mm and 66% in nodules less than or equal to 5 mm.[11]

However, the newer generation scanners are expensive, with greater capital costs and increased running and maintenance costs for replacement components. Sophisticated data storage and management systems are required and, because of the volume of data produced, there are increased interpretation and reporting times. In the UK in 2002, a typical spiral scanner could be expect to have one tube replaced per year, at a cost of around £25,000.

In screening, the balance between image quality and radiation dose is particularly important and every effort should be made to minimise the radiation dose. There are differences between countries in how CT parameters are set, and different countries have different priorities in this balance between image quality and safety. It has been estimated that the lifetime risk of developing cancer attributable to all diagnostic X-rays is 0.6–1.8%. In the UK this equates to up to 700 cancers per year.[13] It is imperative to obtain a radiological diagnosis with the lowest radiation dose that is reasonably achievable (the ALARA principle).[14] Compared to chest X-ray, CT results in exposure to higher radiation doses. At present, the National Radiation Protection Board states that the average effective dose from a standard-dose spiral CT of the thorax is 8 millisieverts (mSv), whereas chest X-ray is around 0.1 mSv and mammography 0.4 mSv. The average background radiation dose in the UK is 2.2 mSv. The risk of a fatal cancer of any type is estimated to be 1 in 2500 for standard-dose CT of the thorax.[15] CT of the thorax imparts the highest radiation dose to the lungs and breast tissue and as a result the radiation dose is higher in women.

To minimise the radiation dose, low-dose schedules have been developed. It is possible to reduce the dose by decreasing the tube current from the standard 140–400 mA to 20–140 mA. The resulting effective radiation dose equivalent is much lower, 0.3–0.6 mSv.[16] Studies comparing spiral CT of the thorax obtained at standard tube current with those obtained at reduced tube current showed no reduction in the detection of pulmonary nodules in patients with known or suspected pulmonary nodules.[11,17] Most studies of CT screening for lung cancer incorporate the use of low-dose spiral CT regimens.

Therefore, CT technology now affords us with a mechanism to image the thorax rapidly and with

substantially more detail than using chest X-ray. However, these advances come at an increased cost and radiation dose.

CT-detected abnormalities

As discussed already, CT can detect very small abnormalities within the lung fields. Discrete pulmonary nodules are the most commonly reported abnormality that may be suggestive of malignancy, but abnormal scarring and ground-glass opacities are also recognised as potentially malignant changes. Unfortunately, CT abnormalities are not specific for malignancy and some series report more than 90% of CT nodules to be benign.[18] Radiologists report a number of features that assist in differentiating between benign and malignant lesions. Demonstration of fat within the nodule is a reliable feature of benign lesions, but is rarely seen. Benign patterns of calcification support the diagnosis of non-malignant lesions such as hamartomas and granulomas (associated with tuberculosis, histoplasmosis and other granulomatous diseases), but the evidence base is limited.[1] Nodules suspicious of malignancy are often referred to as non-calcified nodules (NCNs) in the screening literature. The term NCN refers to the fact that the nodule cannot be excluded from being malignant based on the pattern of calcification.[11,19]

Size is also important in determining the likelihood that an NCN is malignant, and large lesions are more likely to be malignant than small lesions. Analysis from one of the CT screening studies reports that, of 378 positive baseline screening CTs identifying NCNs of less than 5 mm, none proved to be malignant on further investigation. In contrast, 3.3% of those 5–9 mm and more than 50% of those greater than 9 mm were malignant.[18]

Screening programme requirements

Screening is not simply about the technology used, but the whole programme, including call and recall of the screening target population using primary care records to identify smokers, investigation of the positive screenees and all associated services. In terms of equipment and staff, access to a spiral CT and experienced CT personnel is essential, along with specialist radiologists to interpret the images. CT systems are generally available across the NHS (approximately seven per million population).[20] A current investment programme aims to replace all CT systems over 11 years old in the next 3 years. Despite recent investment, most are already heavily committed to a service workload. In addition, staffing in the existing radiology service, in particular with radiologists and radiographers, is already stretched. For some regions of the UK, distance to travel to a CT system is long and access may be an important issue in promoting screening uptake. Mobile screening units have been described and could potentially improve access.[21] Support services, including a mechanism to call and recall participants, personnel to counsel participants in making informed choices about screening, and the facilities and staff to deliver the required follow-up in a timely fashion, are all crucial to the screening programme. Follow-up is complex and includes detailed imaging plus, where necessary, interval CT examination for signs of growth. The principal aim of follow-up is to minimise the number of people being exposed to tissue biopsy and the associated risks (10% of people undergoing percutaneous transthoracic needle biopsy require a chest drain and 0.04% die as a result of biopsy complications).[1] The screening programme would aim to identify more people who could be offered surgical resection. The effect would be to increase demand on surgical services, but potentially to reduce the number requiring radiotherapy or chemotherapy.[4] Screening will also identify cancers at an advanced stage and non-surgical oncology services will be necessary to deliver the care these individuals need.

The attitudes of the public towards screening will be important in ensuring good participation in any screening programme and adherence to a screening protocol. The authors are not aware of any published studies evaluating patient attitudes to lung cancer screening in the UK. A small survey (62 participants) conducted by the Roy Castle Lung Cancer Foundation asked delegates at a conference (delegates were largely patients with lung cancer and their relatives) about their views on screening: 92% responded that the UK should take part in a study of CT screening for lung cancer. When offered the option to abandon further research into screening and just start a screening programme, 87% responded 'yes' (Baird J, Director of Patient Care, Roy Castle Lung Foundation: personal communication; 18 March 2005). In the USA, a survey of 172 smokers and former smokers found that 62% expressed an interest in CT screening for lung cancer.[22] There

has also been substantial demand for whole-body CT screening in the USA.

Other current issues

Screening for lung cancer has been the subject of debate for the past three decades. Several systematic reviews of screening for lung cancer using chest X-ray, alone or in combination with sputum, have concluded that there is insufficient evidence of benefit in terms of reduction in disease-specific mortality.[23–25] However, there has been much criticism in the literature of both the methods and interpretation of these studies.

First, several of the studies did not use placebo as the comparator and instead compared intensive screening with less frequent screening, or chest X-ray alone with chest X-ray plus sputum. These studies could not, therefore, assess whether screening was better than no screening. Second, the studies, despite consistently demonstrating improved survival, did not demonstrate improvements in disease-specific or total mortality. Without evidence that overall mortality is reduced, improvements in survival time may be subject to three types of bias: over-diagnosis, length bias and lead-time bias.

- over-diagnosis bias: small, slow-growing lesions are detected by screening for intervention that would never become symptomatic within a patient's lifetime in the absence of screening
- length bias: screening introduces a bias in relation to expected survival by detecting more patients with less aggressive disease (who have longer survival) and fewer of those with more aggressive disease, because the duration of asymptomatic disease is longer in less aggressive tumours.
- lead-time bias: screening-detected patients are accorded extended survival times solely because cancer was detected earlier owing to screening, although death occurred at the same time as would have happened without screening (i.e. the intervention yields no benefit).

Conclusion

CT is more sensitive than chest X-ray in detecting small pulmonary nodules but that raises additional issues for a screening programme in terms of both the clinical significance of these very small abnormalities and the potentially large number of false-positive screening CT examinations. Investigation, therefore, becomes a trade-off between the probability of the nodule being malignant and the risks associated with further investigation. Diagnostic tests are not without hazards and the challenge of obtaining tissue diagnosis is greater in very small nodules. There has been no consensus to date about how best to manage these small, screening-detected nodules. Given the lack of evidence of effectiveness for screening with chest X-ray, this review will only consider the effectiveness of CT screening in comparison to current practice; that is, no screening programme.

The main issues when considering screening for lung cancer using CT therefore include:

- Should there be screening with CT for lung cancer at all? Does it meet the UK NSC criteria for a screening test?
- If there is screening, should it be universal or selective?
- Which CT schedule should be used as a screening test?
- Which CT screening protocol should be used? Within a screening programme, the frequency of screening, call and recall processes, and management of those who test positive will all be important in determining clinical and cost-effectiveness.
- What cut-off should be used for defining a positive screening test? Small lung nodules are not an infrequent finding on CT, and not all are malignant. There is debate about how to best investigate and manage people with such findings.
- What is the gold-standard test if someone screens positive? A tissue diagnosis plus imaging is generally required to diagnose and stage lung cancer. Biopsy has associated risks, and there has been debate about the option to follow up small nodules with imaging to determine growth rate before committing to biopsy.
- What are the consequences if screening is positive for lung cancer but at an inoperable stage?
- Is universal or targeted screening for lung cancer cost-effective?

Chapter 3
Evidence of clinical effectiveness

Methods of the literature review

Literature search

Preliminary searches showed that very few randomised controlled trials (RCTs) had been conducted to evaluate screening for lung cancer using CT. The search was not, therefore, restricted by study design. All primary studies evaluating CT screening for lung cancer were included. Systematic reviews were also sought and assessed for quality. The conclusions of the systematic reviews are reported under a separate section in the discussion. A sensitive search strategy (described in full in Appendices 2 and 3), including the keywords of lung cancer, CT examination and mass screening, was constructed to search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Clinical Trials, NHS Economic Evaluation Database (NHS EED), HTA Database, Database of Abstracts of Reviews of Effectiveness (DARE), Bandolier, Health Management Information Consortium, American Society of Clinical Oncology, Research Findings Register, National Horizon Scanning Centre, Science Citation Index, Web of Science Proceedings and National Research Register. The register of projects held by the International Networks of Agencies for Health Technology Assessment (INAHTA) was also checked. For completeness, the search strategy was not restricted by language; where reports in a language other than English were identified, they were noted but translations were not sought. The searches were restricted to cover from 1994 to the present and the search was last updated on 5 January 2005 (unless otherwise stated in Appendix 3). The bibliographies of included studies were also searched, but authors of included studies were not contacted for further information.

Selection of papers

The sensitive search identified a large number of potential titles. Each title and abstract was reviewed by two of the authors (CB and RDV) to assess the relevance to this review. Two categories of titles were included for data extraction: (1) for inclusion in the clinical effectiveness review and (2) for inclusion in the cost-effectiveness review. The inclusion and exclusion criteria were:

- screening for lung cancer was the principal theme of the paper
- primary research (RCT, cohort or case–control, economic analysis) or systematic review
- CT screening compared with no screening (or, if a study included a comparison group that were screened using an alternative screening method, then only data from the CT screening arm of the study included).

There was no important disagreement between the two reviewers that was not resolved by discussion. Studies evaluating the use of methods for screening for lung cancer other than CT were not included, nor were those that evaluated the use of CT for other conditions (e.g. whole-body screening or screening for coronary artery calcification). Studies evaluating the use of CT for diagnostic or staging purposes in lung cancer were also excluded.

Relevant papers were retrieved and reviewed by two authors independently. Data extraction included details of the screening protocol, follow-up, diagnosis and participants. Information was sought about test characteristics, including sensitivity and specificity. The checklists and methods described in Centre for Reviewers and Dissemination (CRD) Report 4 were used for the quality assessment of studies.[26] A summary of the data extraction for each included study is provided in Appendix 4. Papers meeting the criteria for the review of cost-effectiveness studies are dealt with separately in Chapter 5.

Outcomes of interest

This review was not simply interested in the effectiveness of CT in detecting lung cancer, but in the effectiveness in the context of a mass population-screening programme. The principal outcome of interest, as discussed in Chapter 2, was the effect of the screening programme on disease-specific mortality (i.e. lung cancer mortality) and on total mortality. While studies with no comparator group could provide information about the screening process, the natural history of the detected nodules and survival, only RCTs could provide information about the effect of screening on mortality.

An improvement in disease-specific mortality requires not only that CT examination is effective, but also that the entire screening programme and management of those with positive screening tests is effective. In a population at increased risk of mortality from other causes (i.e. smoking and cardiovascular disease), total mortality is more important in judging effectiveness of screening.

Additional outcomes of interest in assessing the effectiveness of CT screening programmes were:

- What proportion of people were found to have abnormal CT examinations at screening?
- What proportion of those people had lung cancer?
- What proportion were stage I and resectable tumours?
- What was the survival among those with lung cancer detected by screening?

Outcomes were also sought that are likely to have a service impact; that is follow-up requirements, quality of life issues and adverse events.

Summary of included studies

Included studies

A total of 12 studies of CT screening for lung cancer was identified for inclusion in the review of clinical effectiveness. Several of these studies have been described in multiple publications. *Table 2* summarises the 12 studies, indicating the main reference used for each study and any additional publications. Two RCTs were identified, but one of these used a comparator group that received chest X-ray screening.[27,28] Therefore, only the experience from the CT-screened arm was included in the main analysis. A further nine studies without comparator groups were reported in the review of clinical effectiveness. In addition, one study describing a comparator group initially, but then failing to report details of this group any further, was included for the CT intervention arm details.[29] In all ten of these studies, participants who agreed to take part in the study all received CT screening and were followed up over time to assess outcomes. The limitation of this design is discussed in Chapter 2 (section 'Other current issues', p. 8).

Two components of the screening programmes are reported throughout this section:

baseline screening and incidence screening. These two terms are defined below.

Baseline screening, sometimes also referred to as prevalence screening, describes the first time a population is screened for lung cancer. In this situation, there will be a mixture of people with tumours that have begun to grow recently and tumours that have been developing for some time but have not yet caused symptoms. In addition, this may be the first time that the lungs have been imaged in an individual and, therefore, radiologists have nothing for comparison when interpreting the CT examination, with the effect of making it more difficult to determine the malignant potential of the NCN. Change in a lesion is a strong marker of malignant potential.[1]

Incidence screening refers to all subsequent CT examinations conducted at a known time interval. New or altered NCNs will be reported. Any detected tumours will have developed since the previous CT examination (i.e. new disease) and will, in theory, either be at an early stage or, if at an advanced stage, then will be aggressive, fast growing tumours. In having at least one previous CT examination for comparison, radiologists are often able to exclude an abnormality as representing possible malignancy on the basis of no change in size during the intervening period.

Unfortunately, there were no data from the UK. In total, 25,749 people have participated in baseline, one-off CT screening and, in all, 54,342 CT examinations for the purposes of screening for lung cancer have been reported. Five of the 12 studies were conducted in the USA and a further three in Japan. The remaining four took place in Germany, Italy, Ireland and Finland (*Table 2*).

All the studies included involved CT screening with five of the studies only reporting the findings after one round of CT screening. In Kaneko,[37] participants also received a chest X-ray and sputum examination. Swensen[46] included sputum examination. ELCAP included a baseline chest X-ray.[33] Gohagan randomised participants to be screened with chest X-ray or CT, but as chest X-ray has not been demonstrated to be an effective screening method for lung cancer the results of this arm of the study are reported in the table only and the comparison is not discussed in detail.[28] Sone reported identifying false-negative CT examinations on the basis of sputum, but did not detail in the methods whether sputum samples were routinely obtained in all screened participants.[29]

TABLE 2 *Summary of the 12 studies included in the review of clinical effectiveness*

No.	Study	Participants	Screen interval	No. screened	Positive screen (% of screened)	Biopsy (% of screened; % screen positive)[b]	Total lung cancer (% of screened; % screen positive); NNS[c]	No. of NSCLC	Stage I for NSCLC (% of NSCLC) NNS[d]	Resectable lesion (% of NSCLC)	Survival
RCTs											
1	Gohagan, 2004, USA[a] Main ref.: 28 Other ref.: NA	55–74 y, 30 pack-years, quit < 10 y	Single CT vs CXR	CT: 1586 CXR: 1550	CT: 325 (20.5%) CXR: 152 (9.8%)	CT: 53 (3%; 16%) CXR: 15	CT: 30 (1.9%; 9.2%) CXR: 7 NNS = 53	CT: 29 CXR: 7	CT: 16 (53%) CXR: 6 NNS = 99	NR	NR
2	Garg, 2002, USA Main ref.: 27 Other ref.: NA	50–80 y, atypical sputum cytology + COPD, or 30 pack-years	Single CT vs no screening	CT: 92 None: 98	CT: 30 (33%)	?? (2 reported but 3 cancers, 1 not discussed in text)	CT: 3 (3.2%; 10%) NNS = 31	CT: 2	NR	NR	NR
Studies without comparator groups (all participants screened with CT)											
3	ELCAP, 2001, USA Main ref.: 30 Other refs.: 31–36	60+ y, 10 pack-years' smoking	Annual	Baseline: 1000 Year 1: 841 Year 2: 343 (Incidence: 1184)	Baseline: 233 (23.3%) Incidence: 40 (3.4%)	Baseline: 30 (3%; 13%) Incidence: 8 (0.7%; 20%)	Baseline: 27 (2.7%; 11.6%) Incidence: 7 (0.6%; 17.5%) Interval: 2 NNS = 37 (BL); 169 (INC)	Baseline: 26 Incidence: 6 Interval: 1	Baseline: 23 (88%) Incidence: 5 (71%)	Baseline: 27 (100%) Incidence: 6 (100%) NNS = 37 (BL); 197 (INC)	Baseline: All with cancer alive at mean 2.5 y; 5 died of other causes
4	Kaneko, 2002, Japan Main ref.: 37 Other refs.: 38; 39	40+ y, 20 pack-years' smoking	Twice per year	Baseline: 1611 Incidence: 7891 (over 5 years)	Baseline: 186 (11.5%) Incidence: 721 (9.1%)	Baseline: 21 (1.3%; 11.3%) Incidence: 35 (0.4%; 4.9%)	Baseline: 13 (0.8%; 7.0%) Incidence: 19 (0.2%; 2.6%) NNS = 115 (BL); 420 (INC)	Baseline: 13 Incidence: 18	Baseline: 10 (77%) Incidence: 15 (83%)	Baseline: 12 (92%) Incidence: 17 (89%) NNS = 134 (BL); 464 (INC)	Baseline: 76.2% 5-y survival Incidence: 64.9% 5-y survival
5	Diederich, 2004, Germany Main ref.: 40 Other ref.: 41	40+ y, 20 pack-years' smoking	Annual	Baseline: 817 Year 1: 668 Year 2: 549 Year 3: 366 Year 4: 128 Year 5: 24 (Incidence: 1735)	Baseline: 350 (43%) Incidence: 89 (5.1%)	Baseline: 13 (1.6%; 3.7%) Incidence: 5 (0.3%; 6%)	Baseline: 17 (2.1%; 4.9%) Incidence: 3 (0.2%; 3.4%) Interval: 5 NNS = 48 (BL); 578 (INC)	Baseline: 16 Incidence: 3 Interval: 3	Baseline: 9 (56%) Incidence: 1 (33%)	Baseline: 16 (100%) Incidence: 3 (100%) NNS = 51 (BL); 578 (INC)	Baseline: 4 lung cancer deaths, 1 sudden death (at mean 27-month FU) Incidence: 2 lung cancer deaths

continued

12

TABLE 2 *Summary of the 12 studies included in the review of clinical effectiveness (cont'd)*

No.	Study	Participants	Screen interval	No. screened	Positive screen (% of screened)	Biopsy (% of screened; % screen positive)[b]	Total lung cancer (% of screened; % screen positive); NNS[c]	No. of NSCLC	Stage I for NSCLC (% of NSCLC) NNS[d]	Resectable lesion (% of NSCLC)	Survival
6	Sone, 2001, Japan Main ref.: 29 Other refs.: 42–45	40+ y, smokers and non-smokers (was a comparator group but not reported further)	Annual	Baseline: 5483 Year 1: 4425 Year 2: 3878 (Incidence 8303)	Baseline: 279 (5.1%) Incidence: 309 (3.7%)	Baseline: 29 (0.5%; 10%) Incidence: 43 (0.5%; 14%)	Baseline: 22 (0.4%; 7.9%) Incidence: 34 (0.4%; 11%) Interval: 4 NNS = 249 (BL); 755 (INC)	Baseline: 22 Incidence: NR	Baseline: 22 (100%) Incidence: NR	Baseline: 22 (100%) Incidence: 34 (100%) NNS = 249 (BL); 755 (INC)	2 lung cancer deaths, 3 died of other causes, 51 disease-free (1.2–3.7-y FU)
7	Swensen, 2003, USA Main ref.: 46 Other refs.: 47–49	50+ y, 20 pack-year, quit <10 y	Annual	Baseline: 1520 Year 1: 1478 Year 2: 1438 (Incidence: 2916)	Baseline: 782 (51%) Incidence: 336 (11.5%)	NR 8 resections of benign disease	Baseline: 26 (1.7%; 3.3%) Incidence: 9 (0.3%; 2.7%) Interval: 2 + 2 by sputum only NNS=58 (BL); 324 (INC)	Baseline: 24 Incidence: 9 Interval: 1	Baseline: 18 (69%) Incidence: 6 (63%)	31 of 40 tumours resected No surgical deaths	Deaths in 3 y: 2 SCLC, 3 NSCLC, 4 heart disease, 2 infection, 5 other cancer, 1 suicide, 2 unknown
8	Pastorino, 2003, Italy Main ref.: 50 Other refs.: NA	50-y, 20 pack-years	Annual	Baseline: 1035 Incidence: 996	Baseline: 61 (5.9%) Incidence: 34 (3.4%)	Baseline: 11 (1.1%; 18%) Incidence: 11 (1%; 33%) 6 benign lesions resected	Baseline: 11 (1.1%; 18%) Incidence: 11 (1.1%; 32%) Interval: 0 NNS = 94 (BL); 91 (INC)	Baseline: 11 Incidence: 11	Baseline: 6 (55%) Incidence: 11 (100%)	Baseline: 10 (91%) Incidence: 11 (100%) NNS = 104(BL); 91 (INC)	Lung cancer: 1 dead, 3 recurrence, 18 alive (at mean 2.5 y); No lung cancer: 7 deaths (3 vascular)
9	Nawa, 2002, Japan Main ref.: 51 Other refs.: NA	50+ y, smokers and non-smokers, employee health insurance group	Annual	Baseline: 7956 Incidence: 5568	Baseline: 541 (6.8%) Incidence:148 (2.7%)	Further investigation: Baseline: 64 (0.8%; 11.8%) Incidence: 7 (0.1%; 4.7%)	Baseline:36 (0.45%; 6.7%) Incidence:4 (0.07%; 2.7%) NNS = 221 (BL); 1392 (INC)	Baseline: 35 Incidence: 4	Baseline: 31 (86%) Incidence: 4 (100%)	NR	4 other cancers identified

TABLE 2 *Summary of the 12 studies included in the review of clinical effectiveness (cont'd)*

No.	Study	Participants	Screen interval	No. screened	Positive screen (% of screened)	Biopsy (% of screened; % screen positive)[b]	Total lung cancer (% of screened; % screen positive): NNS[c]	No. of NSCLC	Stage I for NSCLC (% of NSCLC) NNS[d]	Resectable lesion (% of NSCLC)	Survival
10	MacRedmond, 2004, Ireland Main ref.: 52 Other refs.: NA	50+ y, 10 pack-years, still smoking at 45 y	Annual	Baseline: 449	Baseline: 109 (24%)	Baseline: 9 (2%; 8%)	Baseline: 2 (0.4%; 1.8%) NNS = 225 (BL)	Baseline: 1	Baseline: NR	Baseline: 1 (100%) NNS = 449(BL)	Incidental findings: 61.5% 1 death from pancreatic cancer
11	Huuskonen, 2002, Finland Main ref.: 53 Other refs.: 54	<75 y, smoked 10 y, asbestos related occupational disease	Single scan	Baseline: 602	Baseline: 111 (18.4%)	Baseline: 30 (5%; 27%)	Baseline: 5 (0.8%; 4.5%) (1 missed on biopsy, diagnosed at 12-month FU) NNS = 120 (BL)	Baseline: 5	Baseline: 0	Baseline: 1 (20%) NNS = 602 (BL)	5 died <21 months Incidental: 1 peritoneal mesothelioma
12	Miller, 2004, USA Main ref.: 55 Other refs.: NA	Nuclear fuel workers	18-monthly	Baseline: 3598	Baseline: 1139 (32%)	NR	Baseline: 22 (0.64%; 1.9%) 1 'incidence' tumour reported, but no mention of incidence scans NNS = 163 (BL)	Baseline: 21	Not available for all	Too poorly reported	NR

[a] RCT comparing CT with chest X-ray. Chest X-ray arm reported in table but not included in any of the further analysis of the trials as chest X-ray not being considered by this review.
[b] Biopsy recommended (not necessarily conducted and some undergo biopsy against advice; these are not included).
[c] Number needed to screen to identify one lung cancer.
[d] Number needed to screen to identify one stage I lung cancer.
BL, baseline screening; COPD, chronic obstructive pulmonary disease; CXR, chest X-ray; ELCAP, Early Lung Cancer Action Project; FU, follow-up; INC, incidence screening; NA, not applicable; NNS, number needed to screen; NR, not reported.

Screening participants

Although all the studies clearly described their inclusion and exclusion criteria, they did not provide an evidence base for why certain cut-offs were selected. All studies based entry criteria for screening on three participant characteristics: age, smoking history and fitness for surgery.

Age

It is known from cancer registries that the incidence of lung cancer increases with age, so it is of little surprise to find lower age restrictions on screening. The youngest study participants were 40 years old (*Table 2*).

Smoking

Two of the studies in Japan included smokers and non-smokers.[29,51] The remaining studies restricted their screened populations to those with a history of at least 10 'pack years' (i.e. an average of one pack of 20 cigarettes per day for 10 years). 'Pack years' are widely used to summarise smoking history, but have limitations including translating from other forms of tobacco use, interpreting intensity of smoking and considering threshold exposure levels. The two RCTs limited the study populations to those who had a smoking history of more than 30-pack years.[27,28] Time since smoking cessation was incorporated into three of the studies by restricting screening to those who were smokers within the 10 years before recruitment.[28,46,52]

In the studies, participants were interviewed about smoking history after volunteering to participate. A screening programme in the UK could be mediated via GPs who could restrict invitation to those patients with a recorded history of smoking. Until recently, the recording of smoking data in primary care computer records has been variable.[56] However, the new GP contract includes incentives to record smoking status in all patients aged 15–75 years as well as additional contractual requirements to record smoking status in people with asthma, COPD, diabetes or cardiovascular disease.[57]

Fitness for surgery

Most studies reported some degree of assessment of fitness for surgery before proceeding to screening. There are three principal reasons for this: fitness to hold breath for the duration of the CT data acquisition, fitness for diagnostic procedures and fitness for surgical resection. While radical radiotherapy is an option for those not fit for surgical resection, adequate lung function is still a prerequisite for treatment. In addition, the survival gain from radical radiotherapy [including continuous hyperfractionated accelerated radiotherapy (CHART)] is nowhere near as good as surgical resection in stage I or stage II tumours (17% 5-year survival with radiotherapy versus 60–70% with surgery).[1]

None of the studies reported the proportion of people failing to meet the entry criteria based on fitness. Given the population at risk of lung cancer, co-morbidities may be significant, with other tumours, cardiovascular disease and COPD having the greatest impact on fitness for surgical resection. In a male population screened for abdominal aortic aneurysm in the north-west of Scotland and similar to potential lung cancer screenees in terms of age and smoking history, only 0.6% (62/9657) of the volunteers were considered not to be fit for elective surgical aneurysm repair by the GPs at initial assessment.[58] However, fitness for aortic aneurysm repair may be very different to fitness among smokers for pneumonectomy. It is, therefore, difficult to anticipate what proportion of the potential screening population in the UK would meet the criteria for screening based on fitness for surgery.

Subgroup at high risk of lung cancer

In addition to the population criteria identified above, a number of the studies included additional subgroups identified by the researchers to be at a potentially increased risk of lung cancer. These included the following.

COPD

COPD is strongly associated with heavy smoking and, as a result, lung cancer. One RCT[27] selected some of its participants based on the presence of obstructive airways disease confirmed by pulmonary function tests. Those with COPD were required to have sufficient lung capacity (and adequate general health) to undergo surgical resection, if required. In addition to having COPD, this group was further defined to be at high risk of lung cancer by having atypical sputum cytology.

Occupational exposure

Numerous types of workplace exposure have been associated with an increased risk of lung cancer and were summarised in Chapter 2. Workers exposed to asbestos, silica (especially patients with associated fibrosis), radiation and chrome (e.g. electroplaters, chemical workers) have been reported as having double the risk of

lung cancer compared with unexposed populations. Polycyclic aromatic hydrocarbon (PAH) exposure is high in coke-oven workers and there are, historically, high relative risks associated with asphalt workers and chimney sweeps (RR 17.5 and 16.2, respectively). These are important occupational risk factors for lung cancer in the UK setting.

The association between asbestos exposure and intrathoracic cancers has been recognised for many years. The Health and Safety Executive (HSE) estimates that around 6000 occupational cancers (all forms) occur each year, of which 3500 are due to asbestos (essentially all thoracic malignancies). Of these asbestos-related malignancies, in 2003, 1900 were mesotheliomas and most of the remaining 1600 were NSCLC.[59]

One study of CT screening included only workers who had been exposed to asbestos.[53] A further three of the studies included a subgroup (2–14% of the total study population) within the study who had a history of asbestos exposure.[30,40,52] None of these papers quantified the extent of asbestos exposure.

The only other study dealing with occupational exposure was by Miller and colleagues in the USA.[55] They report a screening programme in a workforce employed in the nuclear fuel industry with exposure to a number of risk factors including radiation, asbestos and beryllium.

No other occupational exposure groups were identified that have participated in studies for CT screening for lung cancer.

The screening process

CT technology
Ten of the studies reported using some form of spiral CT system and two used mobile systems that were not otherwise specified.[21,29,55] Effective radiation dose was poorly reported, but two studies estimated exposure to be 0.6 mSv for men and 1.1 mSv for women.[40,50] All but one of the studies reported using low-dose protocols and, where reported, the CT parameters included tube voltages of 120–140 kVp, tube currents of 25–60 mA and pitch of 2:1. Huuskonen and co-author reported using standard dose CT with tube currents of 125–200 mA.[53] The duration of CT data acquisition was not well reported, but varied between single and two breath-holds and 15 to 40 seconds.

Definition of a positive screening CT
For the most part, the definition of a positively screened image was based on the detection of an NCN (*Table 3*) In Diederich[40] and Swensen,[46] any image with one or more nodules of any size was treated as positive. Studies conducted by Pastorino[50] and Huuskonen[53] also used these criteria, but specified that any nodule must be greater than 5 mm to be significant. The RCT conducted by Gohagan[28] defined positive images as those with nodules greater than 3 mm in size and in addition included spiculated NCNs less than or equal to 3 mm. Gohagan also included focal ground-glass opacification and endobronchial lesions. Henschke,[30] Garg[27] and MacRedmond[52] all specified that CT examinations with one to six nodules of any size were classed as positives. The presence of more than six nodules was considered to represent diffuse disease. Further, MacRedmond also included ground-glass opacities and mediastinal masses. The study conducted by Nawa[51] included images with fewer than six nodules that were greater than 7 mm in size as positive.

Two Japanese studies, Kaneko[37] and Sone,[29] used a subjective rating system where radiologists determined the likelihood of cancer without specifying what features of the CT examination made cancer more likely.

Miller[55] did not specify the criteria used for defining a positive examination. Those images that were found to be indeterminate or suspicious were said to be positive.

Follow-up of positive screening examinations
Most studies used similar guidelines when following up positive screening CT examinations: small nodules were followed up with imaging to detect growth, and larger nodules and nodules demonstrating growth were biopsied or resected. Henschke[30] and MacRedmond,[52] for example, followed up with high-resolution CT (HRCT) for nodules 5 mm or smaller, performed at 3-, 6-, 12- and 24-month intervals for growth. HRCT was restricted to one or two slices to minimise radiation dose. For larger nodules immediate biopsy was considered. Miller[55] also followed up positive CT examinations by rescanning with an HRCT technique.

Garg[27] and Diederich[40] used repeat low-dose CT (LDCT) screens to detect growth in small lesions. In Garg[27] nodules larger than 10 mm were further evaluated with contrast-enhanced

TABLE 3 *Definition of positive CT screening examinations*

Study	Definition	Size	No. of nodules	Other features
Garg, 2002[27]	NCN	any	1–6	None
Gohagan, 2004[28]	NCN	>3 mm (any for spiculated NCN)	Unspecified	Ground-glass opacities + endobronchial lesions
ELCAP, 2001[30]	NCN	Any	1–6	Ground-glass opacities
Diederich, 2004[40]	NCN	Any	1 or more	None
Swensen, 2003[46]	NCN	Any	1 or more	None
Pastorino, 2003[50]	NCN	>5 mm	1 or more	None
Nawa, 2002[51]	NCN	>7 mm	1 to 6	None
MacRedmond, 2004[52]	NCN	any	1 to 6	Ground-glass opacities + mediastinal lesions
Miller, 2004[55]	Unspecified	Any	1 or more	None
Sone, 2001[29]	(A) Examination unsatisfactory (B) Normal (C) Lung abnormality of little clinical importance (D) Non-cancerous lung lesion (Ed) Non-cancerous but suspicious lung lesion (E) Suspicion of lung cancer (F) Small lung nodule (<3 mm in diameter) (Ed, E and F seem to be considered suspicious)			
Kaneko, 2002[37]	(A) Inadequate image (B) Normal (C) Scar lesion caused by a previous inflammatory episode (D) Benign tumour or an active inflammatory disease (E) Suspected lung cancer	Any	1 or more	None
Huuskonen, 2002[53]	NCN	>5 mm	1 or more	None

CT, positron emission tomography (PET) and/or biopsy.

Pastorino[50] followed up nodules 5 mm or larger with HRCT and contrast enhancement in selected cases. Nodules 7 mm or larger on HRCT were then followed by PET scans. Further, nodules were biopsied if there was positive enhancement or a positive PET scan.

Quality of included studies

There were three main issues of study quality that had implications for the interpretation of results

for the UK setting (details given in data extraction summaries, Appendix 4). First, none of the studies reported information about the representativeness of their samples. All samples were obtained on a volunteer basis. It is difficult to interpret how well these volunteers represented the general population to whom screening may be offered. Second, the duration of follow-up was limited in most studies, with few presenting data beyond 2 years. Given the outcomes of interest, survival and disease-specific mortality, this short duration is a problem. It was further complicated by the high attrition rates in the studies of longer duration, where compliance with the screening programme of annual CT scans appears to be poor. Finally, the

lack of comparator groups in most of the studies means that it was not possible to determine the impact of screening on lung cancer and total mortality rates in comparison with no screening.

Other general points about the quality of the studies relate largely to the quality of reporting in the papers. Many studies have reported annual interim results. In one study in particular it was not possible to reconcile either the details of the participants (i.e. age of included participants) or the number screened.[29,44,45] Where this occurred, the data extractors made a judgement as to which report was the most complete and this was used. In several studies the reporting of withdrawals from the screening programme was poor and similarly the following of screen-positive patients through their follow-up was not always complete or accurate. The details of the quality issues are provided in the data extraction summaries in Appendix 4

Outcomes of screening

The main outcomes of interest are summarised in *Table 2* and in the data extraction summaries in Appendix 4.

Positive CT examinations
As outlined above, the definition of a positive CT examination has not been universally agreed. It is not unsurprising, therefore, that there is some variation in the rate of positive CT examinations. What is more surprising is the extent of the range, from 5.1%[29] to 51%[46], at baseline. Seven studies report incidence CT examinations. The incidence rate for positive CT was substantially lower than baseline (3–11.5%). From the 12 studies, 4146 positive CT examinations were reported from baseline screening and a further 1677 from incidence screening in the seven studies in which more than one screening round had occurred.

Two of the three studies restricting the definition of positive to only those with NCNs greater than at least 5 mm in diameter[50,51] reported baseline screening to be positive in 5.9–7% of the population. In the third study,[53] baseline positive reporting was high (18.4%). Sone,[29] asking the radiologists to identify lesions suspicious of cancer or indeterminate, produced the lowest positive screening results (5.1%), but Kaneko,[37] using similar definitions, found 11.5% of baseline CT examinations to be positive.

Compared with chest X-ray, CT screening identified more people with positive screening

results. The one RCT study[28] comparing CT screening with chest X-ray identified almost double the number of people with NCNs at baseline by CT compared with chest X-ray (20.5% versus 9.8%). At baseline, ELCAP identified 23.3% of people as having positive CT examinations. Chest X-rays in the same study participants only detected NCNs in 6.8% (and more than half of these were considered not to be nodules on CT).[30] In Kaneko,[37] CT and chest X-rays were carried out in each study participant and approximately ten times more nodules were detected by CT than by chest X-rays.

Investigations and follow-up
Management of positive screening CT varied by study, but generally involved either follow-up by further CT to observe for change in size, or if very suspicious of cancer (because of size, other features or growth) then biopsy was recommended. In most of the studies the study coordinators managed the screening part of the programme and recommendations for further clinical management of the results were made to the attending physicians. Almost all of those with positive CT screening were recommended for follow-up with at least one further CT. Not all recommendations were followed, because of physician or participant choice. Biopsies were carried out in 3–27% of positive screenees. The studies report only a small number of cases where a biopsy was recommended but not carried out, or biopsies were undertaken when not recommended by the study protocol. After an incidence CT, 6–35% of positive screenees were biopsied. *Table 2* shows the range of biopsy rates obtained in the screened population. Insufficient information was reported to identify what proportion had CT-guided biopsy or bronchoscopy with biopsy or bronchoalveolar lavage to obtain tissue for diagnostic purposes.

Detection of lung cancer
Prevalence and incidence
A total of 215 patients with lung cancers was diagnosed as a result of 25,749 baseline screening CT examinations. The highest prevalence of lung cancer was reported in the five studies from the USA (0.6–3.2%). Prevalence rates in the studies from Europe and Japan were generally lower (<1.0%), except for the German study with a reported prevalence of 2.1%.[40] In the seven studies with incidence data, a further 87 cancers were identified. Incidence rates varied from 0.07%[51] to 1%.[50] Five studies[29,30,37,40,46] reported more than 1 year of annual CT screening data, but in all the compliance with follow-up was poor

(*Table 3*). Between 1.8 and 32% of people with positive screening CT examinations went on to receive a diagnosis of lung cancer confirmed, in most, by histology. Among the four studies with the lowest rates of positive screening CT examinations,[29,37,50,51] Pastorino had the highest positive predictive value for CT screening.[50]

Most lung cancers detected by baseline screening were NSCLC (206/215, 96%). Adenocarcinoma was the major histological type reported in nine of the 12 studies (range 33–94%). At incidence screening, SCLC still accounted for a small proportion of the total (2/87, 2.3%).

The numbers of interval cancers were reported in four studies using annual screening protocols. Reporting was not consistent, and the term 'interval cancer' included not only new lesions that developed for the first time between CT examinations, but also for tumours that were, in retrospect, visible on the previous screening CT examination. The one study with CT examinations twice per year did not report any interval tumours.[37]

Stage
Between 53 and 100% of prevalent tumours were identified as stage I disease (with the exception of the Huuskonen study,[53] where only one of the five tumours identified was stage 1). For incidence tumours, 71–100% (excluding Diederich, where only three incidence tumours were detected[40]) were reported to be stage I disease. Three studies did not report stage adequately. Only three studies reported a higher percentage of stage I tumours at incidence scanning than at prevalence scanning, although detection of stage I disease was high in both screening settings.[27,52,55]

Resectability
Where reported, the resectability of tumours found by screening was high, more than 80% in most studies (*Table 2*). Not all participants agreed to surgery. The resection rates reported in the screening studies are substantially higher than current clinical experience in the UK.[4,60] The CT screening studies did not clearly report what types of surgical resection were conducted. In the UK, the current National Institute for Health and Clinical Excellence (NICE) guidelines indicate that, where possible, lobectomy is the surgical procedure of choice when curative resection is the intention.[1] There will be situations where this is not feasible for clinical reasons and more limited resection may be appropriate. However, the NICE guidelines were not constructed to provide

evidence for the best management of very small lung cancers detected by mass-population CT screening, and the most effective surgical option for such tumours is not known.

Quality of life
None of the studies reported any data about quality of life in the screening participants. There were data about the impact of a positive test result (or negative result) on quality of life. Similarly, there were no data about the quality of life in those undergoing further investigation or surgery. Several did note the high positive rate from the initial screening CT and speculated on the impact that this, along with the subsequent follow-up regimen, may have on screening participants in terms of anxiety pending definitive diagnosis.

A subgroup of participants in the large Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) in the USA, using chest X-ray to screen for lung cancer, have completed health-related quality of life questionnaires [Short term 12 (SF-12) plus cancer-specific distress questions] at baseline and during the first year of follow-up. This study reports a significant increase in cancer-specific anxiety in the short term among those who receive abnormal screening results. Once abnormal tests were known to be false positives, anxiety fell back to that of the group with normal screening results. Ongoing participation with the screening programme was, however, influenced by previous false-positive results (93.7% adherence versus 78.7%).[61]

Test accuracy results
One of the difficulties in estimating test accuracy is the absence of a gold standard. Therefore, true cases of lung cancer were determined by tissue confirmation at biopsy or surgery or, in a few cases, on the basis of detailed CT enhanced by contrast medium (where tissue sample was not possible). Truly negative results could only be determined by the absence of presentation with disease over a period of time (or at subsequent screening). Interval tumours were reported in three of the studies and some authors commented on whether, in retrospect, these lesions had been visible at screening but missed. This was not generally reported in detail. Only one study[29] reported sensitivity and specificity results for CT screening. Where available data allowed, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the screening test were estimated (*Table 4*). Studies that did not report follow-up of the screened population for at least 12 months were excluded

TABLE 4 *CT test accuracy results*

Study	FU >12 months	Interval tumours	CT wrongly reported negative (in retrospect)	Detected by another test	Accuracy
Gohagan, 2004[28]	Insufficient FU				
Garg, 2002[27]	Insufficient FU				
ELCAP, 2001: Baseline[31]	Yes	2	4	None	Sens: 27/33 = 81.8% Spec: 763/969 = 78.7% PPV: 27/233 = 11.5% NPV: 763/767 = 99.5%
ELCAP, 2001: year 1+2[30]	Not reported by year Insufficient follow-up				
Kaneko, 2002[37]	Yes	None reported	None reported	1 (sputum)	PPV: 13/186 = 7.0%
Diederich, 2004: overall[40]	Yes	5	2 (of the 5 interval tumours)	NA	Sens: 20/22 = 90.9% Spec: 2111/2530 = 83.4% PPV: 20/439 = 4.6% NPV: 2111/2113 = 99.9%
Sone, 2001: Baseline[29]	Yes	None reported	17	1 (sputum)	Sens: 22/40 =55% Spec: 5186/5443 = 95.3% PPV: 22/279 =7.9% NPV: 5186/5204 = 99.7%
Sone, 2001: year 1[29]	Yes	None reported	3	2 (administrative error)	Sens: 25/30 = 83.3% Spec: 4247/4395 = 96.6% PPV: 25/173 = 14.5% NPV:4247/4252 = 99.9%
Swensen, 2003: overall[46]	Yes	2	4 (but information not given by year)	2 (sputum)	PPV: 35/1118 = 3.1% Unable to estimate as details by screening round not presented
Pastorino, 2003: baseline[50]	Yes	None reported	6 (all visible but correctly classified as negative)	NA	Sens: 11/17 = 64.7% Spec: 968/1018 = 95.1% PPV: 11/61 = 18% NPV: 968/974 = 99.4%
Pastorino, 2003: year 1[50]	Insufficient FU				
Nawa, 2002: baseline[51]	Yes	Not reported	3	None	Sens: 36/39 = 92.3% Spec: 7412/7917 = 93.6% PPV: 36/541 = 6.7% NPV: 7412/7415 = 99.9%
Nawa, 2002: incidence[51]	Yes	None reported	Not reported	None	PPV: 4/148 = 2.7%
MacRedmond, 2004[52]	Insufficient FU				
Huuskonen, 2002[53]	Insufficient information				
Miller, 2004[55]	Insufficient information				

Sens, sensitivity; Spec, specificity.

from these estimates as insufficient time had elapsed for missed lung cancers to have presented. Where interval cancers were not described, or no discussion was made of reviewing the previous year's CT examinations, only PPV was estimated.

Reflecting the high false-positive rate from CT screening, the PPV was universally poor (<20%), regardless of the protocol adopted for defining a positive CT. Where positive screening CT was based on subjective radiologist assessment of risk of malignancy, the PPV tended to be slightly higher (7–14% versus 2–5%). The predictive value of a negative CT was high (>95% where it could be estimated). Despite the high NPV, people with abnormalities were missed. Two studies reported detecting positive baseline CT examinations when reviewing the previous annual CT (i.e. missed NCNs): Swensen found 25% of the first year's CT examinations to be positive in retrospect,[46] and Diederich found 5% to be positive in retrospect.[40] The most rigorously reported review of annual CT examinations was by Sone and colleagues.[29] When reviewing the CT examinations of those with cancer, they identified a high proportion that could, in retrospect, be seen in the baseline CT screening. This appeared to relate to radiologist experience and was not repeated in the subsequent year's results. In the remaining studies, where it was possible to make some estimate of false negatives, the sensitivity was around 80–90%. CT screening for lung cancer performed well in terms of specificity and a negative CT examination result was highly predictive of no lung cancer. It should be noted that not all interval tumours are evidence of false-negative screening CT, but may also include new disease that has truly developed in the interval (i.e. is not visible in retrospect on the baseline CT). In addition, some could be seen in retrospect on the original CT, but were correctly classified as negative at that time because they were very small (only an issue for the studies using a bottom cut-off for size). This was true of the Pastorino study, where six tumours, identified in year 2 CT examinations, were visible but very small in year 1; all were considered resectable and were stage IA disease at the year 2 CT examination.[50]

Survival
The information available regarding survival is summarised in *Table 2*. Only one study[37] reported 5-year survival, with 76.2% of the people with cancer detected at baseline CT (n =14) surviving for 5 years and 64.9% of the incident CT-detected cancers surviving for 5 years (n = 22). In ELCAP, after 2 years of follow-up for tumours diagnosed at the baseline screening CT, none had died

(n = 27).[30] Sone reports two deaths among the 50 people diagnosed and surgically treated in the first 2 years of their screening programme (follow-up period estimated to be approximately 2–3 years, but not reported).[29] In one of the occupation screening group studies, survival was particularly poor, with no patients surviving for more than 2 years (n =5).[53] Follow-up in the remaining studies was short and the duration of individuals' follow-up was not adequately reported in these studies to allow comment on survival. Within the screened populations, death due to other causes, in particular cardiovascular disease, was not infrequent.

Mortality rates
None of the studies reported total or disease-specific mortality rates. In the most part, follow-up was too short. Where several years of screening had occurred, follow-up was limited to those still participating in the screening programme. The two randomised trials were effectively pilot studies and did not continue long enough to determine effect on mortality. None of the other studies had comparator groups; therefore, change in disease-specific mortality between those screened with CT and those not screened could not be assessed.

Other outcomes

Impact on smoking behaviour
A small subgroup of 134 smokers at one of the centres participating in the ELCAP was surveyed about smoking attitudes and behaviour after baseline CT screening.[36] Quitting was associated with younger age, perception of risk and fear of cancer, and having had an abnormal CT examination. Long-term follow-up of smoking behaviour was not available. Seventy-four per cent said that it increased their motivation to quit smoking, and 23% reported having quit. A further 26% reported a reduction in smoking. Unfortunately, the timing of the follow-up interviews in relation to the CT examination was not reported. Similarly, a subset of the Swensen study was randomised to different smoking cessation interventions in conjunction with CT screening.[47] Swensen and co-authors reported that higher attempt rates of smoking cessation were achieved with the provision of Internet-based resources. The rates of cessation are similar to those reported with other types of smoking cessation programmes such as nicotine replacement. None of the studies reported whether any participants felt 'exempt' after receiving a normal CT examination and therefore

TABLE 5 *Outcome trends by age group*

	Study (prevalence screening)				
	Kaneko, 2002[37]		Diederich, 2004[40]		Sone, 2000[29]
Age (years)	CT +ve (%)	Lung cancer (%)	CT +ve (%)	Lung cancer (%)	Lung cancer (%)
40–49	8.9	0	16.4	0	0.8
50–59	11.1	0.38	19	0.96	0.6
60–69	11.6	1.43	11.6	4.2	0.6
70–79	15.8	1.49	3.1	0	1.5

felt a reduced interest or desire to give up smoking. Positive CT examinations were associated with a higher motivation to quit.[36]

At-risk subgroups

Age
Three of the studies[29,37,40] presented results by age band, and separated baseline and incidence screening (*Table 5*). Kaneko showed a gradient in both positive screening CT examinations and lung cancers with increasing age.[37] At incidence screening, this trend was not as apparent. Diederich did not report a gradient with age, but included very small numbers of participants in the older age bands.[40] All were consistent in identifying no cases of lung cancers in those aged less than 45 years. Similarly, in the studies with higher minimum age restrictions, the proportion with detected cancers tended to be higher.

Smoking
Two of the Japanese studies[29,51] included smokers and non-smokers in the screening programme. Only one of these,[29] however, reported results in sufficient detail to allow comparisons between smokers and non-smokers. Of the 5483 screening participants, 54% were people who had never smoked. Although 44% of the study population were female, among the women less than 6% smoked, whereas 93% of the men were smokers. The proportion of people at baseline screening with lung cancer who were never smokers was 0.44%, similar to that of smokers (0.40%). In the non-smokers, the lung cancer was statistically significantly more likely to be a well-differentiated adenocarcinoma (90% of tumours in non-smokers versus 48% in smokers).

COPD
Of the 55 COPD participants with atypical sputum in the US study by Garg, 22 (40%) had NCNs on CT screening and underwent further investigation.[27] In two patients NSCLCs were diagnosed (3.6% of COPD participants). Completed follow-up of those with smaller nodules

has not as yet been reported. In comparison, the 37 smokers with no history of COPD had eight (22%) NCNs detected by CT with only one NSCLC on biopsy (2.7%).

Unfortunately, there was no follow-up information on the management or survival of those with COPD and lung cancer. Survival among people with COPD is generally reported to be poor, with age, continued smoking and forced expiratory volume in 1 second (FEV_1) being strong predictors.[62] Screening for lung cancer may not achieve the same benefits because of mortality from other causes. Among those with moderate respiratory failure and advanced airflow limitation [arterial oxygen tension (PaO_2) 7.4–8.7 kPa and FEV_1/forced vital capacity (FVC) postbronchodilator <70%] 3-year survival has been reported to be around 66%.[63]

Asbestos
Huuskonen and co-authors reported a workforce-screening programme for 602 participants with asbestos-related disease identified in an earlier study of asbestos-exposed workers in Finland.[53] Of the workers screened, 65 (11%) required follow-up of some sort after the screening CT and five were found to have lung cancer (plus one who was diagnosed late after symptoms and a false-negative screening test) (1% lung cancer prevalence). Only one underwent resection and all died within 21 months of diagnosis.

Miller and colleagues also studied workforce screening, but this time in a nuclear fuel industry workforce in the USA.[55] Thirty-two per cent of these workers had positive CT examinations on screening, but only 0.6% were diagnosed with lung cancer.

The low prevalence of cancer in the workforce screening studies may reflect the age of the screened population, restricted to working age. The two studies do not report the age of the screened population in any detail. Neither

workforce study reported the extent of exposure to potential carcinogens among the workforce.

The other four studies with subpopulations exposed to asbestos did not report separate data for their outcomes.

Adverse events

General

Adverse events, as a result of any part of the screening programme, were poorly reported. Only Gohagan reported fully adverse events potentially associated with investigation for positive screening CT.[64] Six patients experienced adverse events (a total of eight complications: three pneumothorax, two infections/fever requiring antibiotics, one atelectasis, one stroke and one acute respiratory failure). In addition, one person died 5 months after screening, but this was not attributed to screening. Kaneko reported two deaths in the 6 months after surgery from infection in the absence of tumour recurrence.[38]

Surgical deaths and morbidity were not reported in these studies. NICE guidelines for lung cancer report the mortality from all thoracic surgery with curative intent for NSCLC to be 3.5% (range 1–7.6%), with a further 30% experiencing morbidity.[1]

Radiation exposure

None of the studies provided information about the risk of cancer induced by radiation exposure as a result of screening. The follow-up period was too short in most, if not all, of the studies. As none of the RCT studies reported more than preliminary findings, again no comment could be made about incidence rates of tumours in those exposed to radiation versus those not exposed.

The International Commission on Radiological Protection predicts that CT examination with LDCT, using the type of regimens described in the screening studies (~1 mSv estimated effective radiation dose), would induce five cancers per 100,000 CT examinations.[11] Additional radiological exposure occurs with each repeat annual CT and any additional imaging investigations.

Incidental findings

Reporting of incidental findings (i.e. other than lung cancer) was variable and related to the specified screening protocol. One study[37] restricted the radiologists to only examining the lung fields for pathology, while the others allowed full chest images.[30,40] Two studies reported in detail the findings other than NCNs. Fourteen per cent[46] and 49.2%[52] had findings other than NCNs that merited further investigation. Swensen reported 17 other cancers, 35 adrenal masses and 33 renal masses among the 817 screened individuals.[46] In MacRedmond, COPD (29%) and coronary artery calcification (14.3%) were the most commonly reported findings.[52] Kaneko, who only reported other malignancies, identified 14 additional malignancies of the chest wall and mediastinum among the 7891 screening CT examinations conducted.[37] Garg reported one patient with metastatic laryngeal tumour and one with multiple granulomatous disease.[27]

Service implications of screening

Although a number of the studies recognised the substantial costs to the health service in terms of screening per se and the follow-up of large numbers of positive screening CT examinations, none reported the costs beyond the cost of conducting the screening CT (including the examination itself, staff and reporting costs). The costs reported varied from US$50 to 200 per CT and tended to be lower in Japan than in the other study countries. No discussion of quality control criteria or mechanisms, administration requirements, or impact on oncology or surgical services was reported.

In all of the studies with greater than 1 year of screening experience, the number of participants in the screening programme fell dramatically with each successive year (*Table 2*). Only one study had reasonable participant retention,[46] with less than 5% loss after 2 years. At 2 years, ELCAP had lost 65% of study participants.[30] Diederich experienced similar losses at 2 years (33%) and reported on only 24 people who had undergone 5 years of annual screening.[40] Losses included people who had died, developed lung cancer and failed to return for annual screening on time (although some may have been screened at intervals of greater than 1 year, but these were reported separately, or excluded, by most authors).

Summary of other systematic reviews

Several reviews of this topic have been published. Twenty-five reviews were identified from

TABLE 6 *Summary of systematic reviews of screening for lung cancer*

Study	Search methods described?	Search comprehensive	Inclusion criteria stated	Quality assessment described	Meta-analysis done	Main conclusions
Bepler, 2003[25]	Yes	Yes	Yes	Yes	No	Evidence for lung cancer screening by CT showed that it detects 'earlier stage' and smaller lung cancers with greater frequency than other screening modalities. Best suited to populations with low probability of benign pulmonary abnormalities. In such a population, the highest PPV for lung cancer would be in people above 60 years of age. Until mortality studies are completed, low-dose spiral CT screening should be considered an investigative tool rather than standard care
Manser, 2001[65]	Yes	Yes	Yes	Yes	Yes	Current evidence did not support screening for lung cancer with chest X-ray or sputum cytology. No controlled studies of spiral CT reported. Recommended need for a standardised and reproducible approach to the performance and reporting of CT examinations and the evaluation and follow-up of results. Impact of false positives needed to be systematically assessed.
Humphrey, 2004[24]	Yes	Yes	Yes	Yes	No	Lung cancer could be diagnosed at a significantly 'earlier stage' than currently occurs in clinical practice. Unclear whether this will translate to a mortality benefit.

examining the titles and abstracts. Of these, three were considered to be systematic reviews and are summarised in *Table 6*. One only considered chest X-ray screening.[65] The other two concluded, as have the present authors, that while there is evidence of a higher detection rate than with chest X-ray and small, resectable lesions are found, it is not yet possible to assess what effect this will have on mortality.[24,25]

Summary

In the absence of RCT evidence to examine the relative effectiveness of CT screening on disease-specific mortality and total mortality, other study evidence was considered. None of the 12 studies reported disease-specific or total mortality. Only one study reported survival data. It is not, therefore, possible at present to assess whether CT screening for lung cancer is clinically effective.

There is evidence that CT detects a greater number of NCNs and other suspicious chest abnormalities than chest X-ray. There is also evidence that smaller NCNs are detected by CT than by chest X-ray.

Substantial variation was seen between studies in terms of the proportion of screenees with positive CT examinations and the rate of cancer detected. The difference in results is to some extent explained by the different definitions of a positive CT examination. Despite this, where similar definitions were used, variation still existed. The difference in rates of detection of lung cancer between studies highlights the need for caution in generalising findings from other countries to the UK setting.

Baseline screening identified more stage I disease than the literature reports for series of lung cancer in the absence of screening. Incidence screening

also identified a high proportion of stage I disease. Resection rates were high, substantially higher than the current UK resection rates of below 10%.[4,60]

Is the increase in resection rates sufficient to imply a reduction in disease-specific mortality? There is evidence from the studies that substantial numbers of participants in screening will die from other causes, particularly cardiovascular disease. Similarly, the Japanese studies including non-smokers[29,51] identified a rate of cancer similar among smokers and non-smokers. In the non-smokers, the tumours identified were pathologically well-differentiated adenocarcinomas or bronchoalveolar carcinomas and grew at a substantially slower rate than tumours in smokers, with mean doubling times in excess of 800 days.[43] The frequency of these tumours decreased in subsequent screening rounds. This may support the notion of baseline screening detecting a substantial number of slow-growing tumours. The natural history of these well-differentiated small, screening-detected cancers is not yet well understood.

Large numbers of positive CT examinations were reported, particularly at baseline screening. As a result, a high proportion of screening participants underwent further follow-up, either by further CT or even by biopsy. All studies reported some biopsies conducted for what transpired to be benign disease. The rate of biopsy for benign disease varied with different follow-up protocols. Intensive follow-up with CT appears to reduce the number of biopsies. PET and CT enhanced by intravenous contrast medium enabled further classification of risk to reduce biopsy rates. However, only one study reported the systematic use of PET[50] and identified a number of cases where the use of PET led to biopsy of benign disease.

Adverse event reporting was universally poor in the studies. None of the studies explored the psychological or quality of life impact of the high false-positive rates of screening CT, in particular the potentially long periods of uncertainty while follow-up was undertaken. Only one study reported the adverse events associated with diagnostic investigation. Surgical outcomes were poorly reported. None of the studies was of sufficient duration to assess the risk associated with radiation exposure.

In conclusion, the current evidence base for CT screening for lung cancer is insufficient to demonstrate clinical effectiveness in terms of a reduction in mortality. The ongoing uncontrolled studies may provide a better understanding of the natural history of CT screening detected NCNs and lung cancer. To demonstrate a reduction in mortality, RCT evidence will be necessary.

Chapter 4
Economic literature review of CT screening for lung cancer

Lung cancer screening with CT

The aim of this chapter is to consider critically published evidence relating to the relative cost-effectiveness of population screening programmes for lung cancer using CT. The results of a systematic review of the published literature focusing on the identification of studies that consider the cost-effectiveness of different population screening programmes are reported. Six studies are included in the review and are limited to the comparison between low-dose helical CT (screening) and usual care (no screening). Their conclusions depend on whether it is accepted that screening for lung cancer in high-risk populations can lead to improved survival and a reduction in mortality.

Review of economic literature

The aim of this section is to summarise published cost-effectiveness analyses of population lung cancer screening programmes. Two reviewers (CB and RDV) searched the literature as outlined in Chapter 3 and Appendix 2 to identify relevant cost-effectiveness evidence. Two reviewers (ABol and CM) then independently assessed the studies to be included in the review.

Identification of studies

Two reviewers examined all the titles and abstracts of the 1041 articles identified by the electronic search, and 23 were considered potentially relevant to the cost-effectiveness review. A search of the references cited in the included papers did not identify any further articles for review. These articles were then assessed for inclusion in the review using the criteria below.

- *inclusion criteria:*
  - full economic evaluation
  - explicit synthesis of costs and outcomes in a cost-effectiveness ratio
  - CT (intervention)
- *exclusion criteria:*
  - no attempt to synthesise costs and benefits
  - reports, letters, editorials, reviews, commentaries or methodological papers
  - non-English language.

Data relating to economic study design, findings and quality were extracted by one reviewer and independently checked for accuracy by a second reviewer. All details were extracted on pretested data extraction forms. All of the studies were quality assessed using criteria updated from the checklist developed by Drummond and colleagues.[66]

Quantity and quality of research available

Only six of the studies assessed for inclusion met the criteria and were considered further below.[67–72] Seventeen studies were excluded from the review for the following reasons: published in Japanese language (2); discussion papers only (3); reviews of previously published studies (4); letters to the editor (3); inappropriate comparators (3) and technology assessment reports (2). For further details, see *Table* 7. Several of the 17 excluded papers discuss the findings from the six studies included in the review.

The six studies included in the review were full economic evaluations of population screening programmes for lung cancer using CT. Overall the quality of the published papers was difficult to judge for two reasons. First, reporting of the economic and mathematical models used in these studies was poor; this means that replication and verification by the reader is not possible, as the inner workings of the models are not disclosed. Second, lack of clinical effectiveness data means that there is no 'right' way to answer the research question of interest. As a result, it is difficult to judge which of the papers contained the most valid assumptions or used the most appropriate analytical methods.

In summary, all of the authors adequately described the research question and comprehensively described the relevant comparators. However, few papers included full and explicit discussion of the identification, measurement and valuation of the range of costs and benefits included in the analyses. Economic and mathematical models were used in all of the papers to produce cost-effectiveness ratios.

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TABLE 7 *Summary of included/excluded studies*

Study	Included/ excluded	Reason
Institute for Clinical Systems Improvement, 2001[73]	Excluded	Report
Gambhir, 1998[74]	Excluded	Not screening
Wisnivesky, 2003[72]	Included	Full economic evaluation
Marshall, 2001[71]	Included	Full economic evaluation
Caro, 2000[75]	Excluded	No CT examination as comparator
Okamoto, 2000[67]	Included	Full economic evaluation
Klittich, 2002[76]	Excluded	Review of published studies
Hunink, 2003[77]	Excluded	Review of published studies
Chirikos, 2003[78]	Excluded	Letter
Petty, 2003[79]	Excluded	Letter
Reich, 2003[80]	Excluded	Letter
Mahadevia, 2003[69]	Included	Full economic evaluation
Chirikos, 2002[68]	Included	Full economic evaluation
Marshall, 2001[70]	Included	Full economic evaluation
Iinuma, 1994[81]	Excluded	Japanese language
Anon, 2003[82]	Excluded	Review of published study
Bechtel, 2003[83]	Excluded	Discussion
Trow, 2003[84]	Excluded	Review of published economic evaluation
Asakura, 1999[85]	Excluded	Japanese language
Baba, 1998[86]	Excluded	No CT examination as comparator
Swedish Council on Technology Assessment in Health Care, 2003[87]	Excluded	Report
Grannis, 2002[88]	Excluded	Discussion
Grann, 2003[89]	Excluded	Discussion

Unfortunately, the majority of authors did not provide sufficient details of structural assumptions, definitions of variables, parameter estimates or equations relating variables to one another to permit intelligent peer review to be undertaken. Appropriate use of discounting, sensitivity analysis and incremental analysis was conducted in all but one study. Surprisingly, few of the authors included references to previously published cost-effectiveness results.

Clearly, the quality of the cost-effectiveness studies included in the review was less than satisfactory. See *Table 8* for details of study quality.

Characteristics of economic papers (*Table 9*)

The majority of the included economic evaluations were incremental cost-effectiveness analyses and reported outcomes in terms of incremental cost per life-year gained. One study presented results in terms of both incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained.[71] One study reported only incremental cost–utility analysis results,[69] and one study[67] reported only "total cost for one life saved" and "total cost per mean life expectancy of

a patient saved". One study was set in Japan[67] and the others were carried out in the USA. The frequency of CT screening ranged from a one-off CT examination[71] to an annual CT examination over a 20-year period.[69] Correspondingly, patient follow-up varied from a 12-month period[72] to a 40-year period.[69] CT was an intervention in all of the evaluations and no screening was a comparator. The study population was not uniform across the studies. Four out of six studies[69–72] evaluated CT screening for lung cancer in a population of high-risk individuals.

Economic evaluation models (*Table 10*)

All of the papers were based on mathematical[67] or economic models. The economic models were primarily decision-analytic models. The perspectives used in the models, and therefore in the economic analyses, varied from study to study. One study[69] described its viewpoint as societal, yet failed to estimate the costs of lost productivity and disability associated with screening and included informal care costs. The majority of authors outlined the major assumptions of their models. However, on closer inspection, much of the important detail was lacking. Only two studies[69,72] incorporated some form of bias assessment into their models. Two studies addressed bias in the sensitivity analysis,[70,71] while the remainder did

TABLE 8 *Quality of economic evaluations*

	Okamoto, 2000[67]	Marshall, 2001[71]	Marshall, 2001[70]	Wisnivesky, 2003[72]	Chirikos, 2002[68]	Mahadevia, 2003[69]
Well-defined question	✓	✓	✓	✓	✓	✓
Comprehensive description of competing alternatives	✓	✓	✓	✓	✓	✓
Effectiveness evidence	? Sources are unclear	– Single source	– Single source	– Single source	– Single source	✓ Pooled source
Relevant costs and consequences identified	? Perspective not stated; few cost categories	– Perspective not stated	– Perspective not stated	? Insufficient detail	– No biases included	✓
Costs and consequences measured accurately	? Sources are unclear. No price year	✓	✓	? Insufficient detail	– Costs per lung cancer detected only	✓
Costs and consequences valued credibly	? No aggregate costs presented	✓	– Error in ICERs	– No aggregate costs presented	– Valuation of treatment costs in both arms is vague	– No LYG presented
Costs and consequences adjusted for differential timing	X Not stated	✓	✓	– Costs only (3%)	– Costs only (7.5%)	✓
Incremental cost-effectiveness analysis	X Ratios only	✓	✓	✓	✓	✓
Sensitivity analysis performed	X None	✓	✓	✓	✓	✓
Inclusive discussion of study results	– Only two references	✓	✓	– Does not discuss Marshall (2000)	– Does not discuss relevant previous cost-effectiveness reports	– Does not discuss relevant previous cost-effectiveness reports

✓, appropriately discussed; –, partially/maybe discussed; ?, cannot tell; X, not stated; ICER, incremental cost-effectiveness ratio; LYG, life-years gained.

TABLE 9 *Characteristics of economic studies*

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Period of study
Okamoto, 2000[67]	CEA; total cost for one life saved; total cost for mean life expectancy saved	Mass screening (indirect chest X-ray for all screened and sputum cytology for high-risk individuals) in 1983 and in 1993 and CT option	Individuals aged 40–84 years	Japan	5 years
Marshall, 2001[71]	Incremental CEA; incremental cost per LYG	Baseline scan with spiral CT vs no screening	Hypothetical cohort of 100,000 high-risk individuals (60–74 years)	USA	5 years
Marshall, 2001[70]	Incremental CEA and CUA; incremental cost per life-year saved and cost per QALY saved	Annual scan for 5 years with spiral CT vs no screening	Hypothetical cohort of 100,000 high-risk individuals (60–74 years)	USA	5 years
Wisnivesky, 2003[72]	Incremental CEA; incremental cost per life-year saved	Single scan with spiral CT vs no screening	High-risk individuals (aged ≥ 60 years, at least 10 patient-years and no other malignancies)	USA	Costs were restricted to 1 year; benefits unclear
Chirikos, 2002[68]	Incremental CEA; incremental cost per LYG; cost per cancer case detected	Five annual screens with spiral CT vs no screening	Hypothetical cohort of screened and unscreened patients (general population ≥ 45–74 years)	USA	15 years
Mahadevia, 2003[69]	Incremental CUA; incremental cost per QALY gained	Annual screen (20 years) with spiral CT vs no screening	Hypothetical cohorts of 100,000 current, quitting and former heavy smokers (aged ≥ 60 years, 55% male)	USA	40 years

CEA, cost-effectiveness analysis; CUA, cost–utility analysis; QALY, quality-adjusted life-year.

not appear to consider the effect of bias on the cost-effectiveness results. Estimates of life expectancy are integral to the calculation of the cost-effectiveness analysis, yet two studies[67,69] did not explicitly state what method was used in their analyses.

Cost data and cost data sources (*Table 11*)

All of the studies explicitly reported the price year and the currency used, except for one[67] which failed to state the price year. Overall, for the majority of studies, the costs should have been comparable as the price years were within a 3-year band (1999–2001). The key categories of costs were similar across the studies and can be divided into screening costs and treatment costs. Some

studies were very inclusive and included the cost of managing non-cancer patients over the age of 65[70,71] and monitoring of indeterminate nodules.[69] Examples of costs included in the studies are presented in *Tables 12* and *13*. Most of the studies relied on the published literature (including Medicare reimbursement rates) for sources of cost data. One study[72] used registry data to identify newly diagnosed patients and then used the hospital finance database to allocate costs. Individual patient costing was not reported by any of the authors. Four studies used a 3% discount rate and one study[68] used a 7.5% rate. The majority of the studies presented total and incremental costs. However, one study[68] only presented screening and treatment costs per lung cancer detected.

TABLE 10 Economic evaluation models

Study	Type of model	Perspective	Model assumptions	Biases included	Life expectancy method
Okamoto, 2000[67]	Deterministic mathematical model	Not stated	Unclear	None	Not explicitly stated
Marshall, 2001[71]	Decision analysis model	Not stated: healthcare system	(1) Same cancer detection rate and false-positive rate as ELCAP. (2) Stage shift at diagnosis based on the observed distribution as reported by ELCAP. (3) Same total number of cancers in screened and unscreened populations. (4) Age- and gender-adjusted survival experience of individuals diagnosed at early stages through screening, same as those diagnosed at the same stage without screening	1-year lead-time bias addressed in SA	Life-years estimated from annual cumulative survival rates for lung cancer cases for gender, age group, stage and tumour size. Life-years for NSCLC cases estimated from annual survival rates for the US population for gender and age group
Marshall, 2001[70]	Decision analysis model	Not stated: healthcare system	(1) Capital equipment and resources are already in place to perform screening. (2) Same model assumptions as Marshall, above.[71] (3) 1-year decrease in survival benefit that may occur as a result of lead-time bias	Lead-time and over-diagnosis biases addressed in SA	See Marshall, above[71]
Wisnivesky, 2003[72]	Decision analysis model	Healthcare system	(1) Patients with stage I or II will be cured OR progress and die. (2) Patients with stage III–V will die. (3) Baseline assumption of similar aggressiveness for screen detected and incidentally discovered lung cancers	Lead-time bias incorporated into model; over-diagnosis addressed in SA	NSCLC LE estimated based on the US age-specific death rates. LE of cured person = LE of person without cancer. Otherwise DEALE method used
Chirikos, 2002[68]	Not stated: decision analysis model	US national payer groups	(1) Screening for lung cancers with CT under a defined diagnostic protocol is effective. (2) Screening results in downstaging of detected results. (3) Downstaging results in a corresponding survival benefit. (4) Survival benefits from downstaging translate to mortality benefits	None	ELYs are sum of conditional survival probabilities by single years of age for men and women in three age groupings over the 15 years. Relative survival rates for cancer patients and abridged life-table values for the general population
Mahadevia, 2003[69]	Computer-simulated Markov model	Society (excludes costs of disability and lost productivity)	(1) Only NSCLC had a stage shift. (2) Within histological and clinical stages, treatments and costs similar for all patients. (3) Safe screens. (4) Partial adherence screening not modelled. (5) Lung cancer cases due to length and over-diagnosis bias had the same costs as other lung cancer cases, but had mortality pairs similar to smokers without lung cancer. (6) Quality of life with screening-detected local used NSCLC greater than in same non-smoking patients	Length, over-diagnosis and lead time biases incorporated in model	Not explicitly stated

DEALE, declining exponential approximation of life expectancy; ELY, estimated life-years; LE, life expectancy; SA, sensitivity analysis.

TABLE 11 Cost data and cost data sources

Study	Cost items	Cost data sources	Cost of CT scan	Discount rate	Date and currency
Okamoto, 2000[67]	Primary screening of all participants, detailed CT examination of patients, cost of cancer therapy for screened and unscreened patients	Published literature	$11; ¥15,000	Not stated	Price year not reported; US dollars; Japanese yen
Marshall, 2001[71]	Screening programme testing costs, treatment of lung cancer by stage, managing non-cancer patients >65 years	Medicare reimbursement rates; published literature (Riley and Taplin)	$150	3% (costs and benefits)	1999; US dollars
Marshall, 2001[70]	Screening programme testing costs, treatment of lung cancer by stage, managing non-cancer patients >65 years. Authors explicitly state that the analysis does not deal with the setting up of a new programme, only with a steady state	Medicare reimbursement rates; published literature (Riley and Taplin)	$150	3% (costs and benefits)	1999; US dollars
Wisnivesky, 2003[72]	Physician-based and hospital-based direct medical costs; stage-specific treatment costs. Costs were restricted to the first year, although for advanced patients the costs of terminal care were added to initial costs	Scans, etc. (hospital's financial system database); stage-specific treatment costs (review of registry data to identify newly diagnosed patients then used hospital financial system costs); physician charges (Faculty Practice Plan database)	$165	3% (costs only)	2000; US dollars
Chirikos, 2002[68]	Costs of screening, initial treatment and continuing care	Diagnostic tests and physician visits (2001 National Physician Fee Schedules Relative Value Scale); informal care, treatment and its complications (published literature/Riley); Medicare reimbursement rates	$291	7.5% (costs only) 5% annual inflation rate	2000; US dollars
Mahadevia, 2003[69]	Facility and professional fees associated with screening, monitoring of indeterminate nodules, opportunity costs to get to screening	Screening and diagnostic CT procedures (reimbursement methodology of the federal Medicare programme); informal care, treatment and complications (published literature)	$300	3% (costs and benefits)	2001; US dollars

TABLE 12 *Examples of included screening and diagnostic cost items*

Study	Screening and diagnostic items	Cost (US$)
Wisnivesky, 2003[72]	LDCT examination	165
	HRCT examination	300
	Limited CT examination	65
	Fine-needle aspiration	500
Marshall, 2001[71]	LDCT examination	180
	HRCT examination	311
	Follow-up (3, 6, 9, 12 months)	311
	Biopsy	460
Okamoto, 2000[67]	Primary CT screening	30
	Detailed CT examination	107
Mahadevia, 2003[69]	Helical CT examination	300
	Follow-up diagnostic CT examination	429
	Antibiotic course	158
	Opportunity cost for cost of travel time	14
Marshall, 2001[70]	Low-dose helical CT examination	150
	HRCT examination	280
	Thoracoscopy with biopsy	430
	Office visit	30
Chirikos, 2002[68]	Screening CT examination	291
	Diagnostic CT examination	340
	CT thorax without contrast material	291
	CT thorax with contrast material	340
	CT thorax without and with contrast material	416
	CT guidance for needle biopsy	382
	Biopsy, lung of mediastinum, percutaneous needle	126
	CT-guided biopsy procedure, total	507

TABLE 13 *Examples of included cancer care cost items*

Study	Cancer care items	Cost (US$)
Wisnivesky, 2003[72]	NSCLC stage I	20,100
	NSCLC stage II	23,300
	NSCLC stage III	31,800
	NSCLC stage IV	32,700
	NSCLC stage V	25,900
Okamoto, 2000[67]	Average cost of therapy for CT screen-detected patients	7,200
	Average cost of therapy for outpatients (CT screened)	21,500
Mahadevia, 2003[69]	Localised NSCLC, surviving 1 year	43,900
	Localised NSCLC, dying 1 year	66,500
	Localised NSCLC, ongoing year	4,500
	Localised NSCLC, terminal year	30,400
Marshall, 2001[70]	Annual cost of management, stage I	16,242
	Annual cost of management, stage II	28,731
	Annual cost of management, stage III	28,731
	Annual cost of management, stage IV	56,527
	Annual cost of management without LC	6,146

Health outcome data and data sources (*Table 14*)

Only two short-duration RCTs of screening for lung cancer using CT exist. The majority of the published studies were, therefore, based on prospective, uncontrolled cohort studies. Five out of six studies, excluding Okamoto,[67] appear to use the Surveillance, Epidemiology and End Results (SEER) registry, a public-use database, to estimate lung cancer incidence and mortality probabilities

TABLE 14 Health outcome data and data sources

Study	Range of health outcomes	Utility values and data sources	Probabilities		Probability data sources
			Variable	**Value**	
Okamoto, 2000[67]	Lives saved, life-years saved	No QoL data		X-ray 1993/CT	Unclear
			Sensitivity of primary methods	70%/90%	
			Rate of participation	80%/80%	
			Sensitivity of detailed examination	100%/100%	
			5-year survival of screen detected patients	30%/60%	
			5-year survival rate of outpatients	10%/10%	
			% requiring detailed examination	2%/5%	
Marshall, 2001[71]	Life-years saved	No QoL data	Lung cancer prevalence	2.7%	Efficacy data from SEER registry public-use database; published results of ELCAP
			Cancer detection rate	100%	
			False-positive rate	21%	
			Stage I screened/unscreened	85%/21%	
			Stage II screened/unscreened	4%/4%	
			Stage IIIA screened/unscreened	7%/9%	
			Stage IIIB screened/unscreened	4%/20%	
			Stage IV screened/unscreened	0%/46%	
			<10 mm tumour size screened/unscreened	56.5%/5.3%	
			11–45 mm tumour size screened/unscreened	43.5%/77.7%	
			>45 mm tumour size screened/unscreened	0%/17%	
Marshall, 2001[70]	Life-years saved, QALYs saved	Utility values were obtained from the published literature (local: 0.88; regional: 0.8; distant: 0.69)	Lung cancer prevalence	2.7%	Efficacy data from SEER registry public-use database; published results of ELCAP
			Cancer detection rate	100%	
			False-positive rate	21%	
			Stage I screened/unscreened	85%/21%	
			Proportion LDCT examination	1.00	
			Proportion of follow-up high resolution	0.17	
			Proportion of subsequent high resolution	0.08	
			Proportion of biopsy	0.03	
			Lead-time bias	1 year	

TABLE 14 *Health outcome data and data sources (cont'd)*

Study	Range of health outcomes	Utility values and data sources	Probabilities			
			Variable	Value		Probability data sources
Wisnivesky, 2003[72]	Life-years saved	No QoL data	Incidence of NCN HRCT/1000	23% 178		Efficacy data from SEER registry public-use database; published results of ELCAP
			Lung cancer prevalence	2.7%		
			Cure at stage I	70%		
			Cure at stage II	30%		
			Cure at stage IIIA–IV	0%		
			Stage I screened/unscreened/5-year survival	85%/20%/67%		
			Stage II screened/unscreened/5-year survival	4%/6%/55%		
			Stage IIIA screened/unscreened/5-year survival	7%/16%/23%		
			Stage IIIB screened/unscreened/5-year survival	4%/17%/5%		
			Stage IV screened/unscreened /5-year survival	0%/41%/1%		
Chirikos, 2002[68]	Life-years saved	No QoL data	Abnormal prevalence screen	25–50%		Utilisation and cancer yield rates from SEER, Cancer Registry, ELCAP study and earlier lung cancer screening studies
			Abnormal incidence screen	5–15%		
			Lung cancer prevalence	1.2–2.7%		
			Lung cancer incidence	0.7–1.2%		
			Adherence	100%		
Mahadevia, 2003[69]	Absolute and relative differences in lung cancer deaths, harm (false-positive invasive test or surgeries per 100,000), QALYs saved	(1) From a study of NSCLC patients using the EuroQol multiattribute utility scale (median utility scores). (2) Systematic review of CUA in oncology (decrements and disutilities) Utility rates range from 0.73 to 0.88	% NSCLC	85%		Probabilities and utilities published literature and SEER registry public-use database
			Mortality NSCLC localised	10%		
			Mortality NSCLC advanced	63%		
			Lung cancer incidence in smokers	0.43%		
			Length bias (% of incidence)[a]	200		
			Lead time	1 year		
			Sensitivity[a]	93%		
			Specificity[a]	81%		
			False negative[a]	0.24%		
			False positive[a]	18.4%		
			Rate of lung cancers detected[a]	9/1000		
			Rate of benign biopsies/surgeries > CT[a]	2.3/1000		
			Annual non-adherence	6.5%		

[a] After baseline screen.
QoL, quality of life.

for the unscreened population. Three studies[70–72] used data from ELCAP to estimate probabilities for the screened population (e.g. distribution of tumours detected in screened population). Mahadevia and colleagues[69] used data from four previously published cohort studies to derive weighted probabilities for the screened population. One study[68] used data from a range of previously published studies including ELCAP for the screened population, whereas the remaining study[67] does not state the source of probabilities for any population. A list of probability data used in the studies can be found in *Table 14*. Where stated, estimates of life-years gained were taken from national survival rates for the US population. Only two studies[69,70] used quality of life data to describe the impact of lung cancer screening on patients and both studies used quality of life data from previously published sources. Only one study[69] did not report outcomes in terms of life-years saved, yet it reported absolute and relative reductions in deaths and cost per QALY gained.

Cost-effectiveness ratios (*Table 15*)

The ICERs varied considerably across all of the papers. Incremental life-years gained varied from US$2500[72] to $90,022[68] and incremental cost per QALY ranged from US$19,500[70] to $2,322,700.[69] All but one[67] of the studies used extensive sensitivity analysis to determine the robustness of the cost-effectiveness results. Specific variables that may lead to higher cost-effectiveness ratios included low prevalence rate, reduced survival (e.g. introduction of 1-year lead-time bias), increased cost of diagnostic tests, increase in the number of patients overdiagnosed and a less than 100% adherence to the screening programme. Of the six papers included in the review, four of the authors concluded that screening for lung cancer with CT could be a cost-effective approach. One author[71] was more cautious and stated that although at the time of the study there was insufficient evidence of costs and benefits, there was the possibility that lung cancer screening with CT could be cost-effective. Finally, Mahadevia and colleagues[69] argued against the introduction of a mass-screening programme for lung cancer using CT. It could be argued that the studies varied too much to allow a valid comparison of their results.

Summary of evidence

From the literature review presented above, it was very difficult to draw any conclusions on whether

or not screening for lung cancer using CT, compared with usual care, is a cost-effective option. All of the papers in the review approached the research question from different starting points. To illustrate, frequency of screening and definitions of high-risk groups varied across the studies. None of the papers in the review was set in the UK, and this means that their relevance to the NHS was somewhat limited. Given the paucity of UK data available, it was difficult to compare patterns of healthcare and possible differences in tumour behaviour between the UK and other countries.

More importantly, there was wide variation in the magnitude of the cost-effectiveness ratios. This disparity in cost-effectiveness ratios was not surprising as the authors described markedly different logistical approaches to screening and often incorporated quite different assumptions about survival and mortality. None of the economic evaluations discussed the costs of setting up (e.g. recruitment costs) or administering (e.g. purchase of new diagnostic equipment) a population screening programme, and it was assumed that the costs and benefits reported were those associated with a fully established programme. The actual size of the population to be screened was not explored in any of the papers, nor was the impact on healthcare budgets discussed. In addition, none of the papers estimated the benefits, harms and significant costs of incidental diagnoses obtained through screening.

There is currently a resurgence of interest in screening for lung cancer.[90] Previously, screening for lung cancer focused on the use of radiography and sputum cytology analyses.[73] However, none of these studies was able to demonstrate a decrease in disease-specific mortality.[87] Recently, there has been a worldwide call for the re-evaluation of screening programmes for lung cancer. There are three important reasons for this. First, it is argued that these previous studies were flawed in both methodology and interpretation.[91] Second, new technologies have been developed that may improve the effectiveness of screening for lung cancer,[90] and third, there is increased public demand for these technologies, particularly in the USA, as a result of aggressive consumer advertising.[92]

Lack of clinical evidence
Advising patients on the merits of lung cancer screening is difficult given the current lack of evidence,[93] both clinical and economic. According

TABLE 15 *Cost-effectiveness results*

Study	Cost-effectiveness ratios	Sensitivity analysis	Conclusion	Industry author affiliation
Okamoto, 2000[67]	Only reported graphically. Cost per life-year saved for CT screening was slightly lower than for mass screening in 1983 and in 1993 for men and women and all age groups	No explicit sensitivity analysis conducted. ≥ 60 years, cost for women was approximately double that for men (owing to lower prevalence)	Cost of screening with CT is high, but it is much more effective. CT screening should become the most appropriate screening method with respect to cost-effectiveness	
Marshall, 2001[71]	Incremental benefit = 4417 LYG Incremental cost = $26m. ICER = $5941 (discounted) or $6512 (undiscounted) per LYG	Lead-time bias of 1 year + high prevalence scenarios = $15,274; lead-time bias of 1 year + low-prevalence scenarios = $58,183 (discounted); 1 year leadtime bias + false-positive rate (50–99%) = $11,500–20,400 (discounted); CT scan ($500) and HRCT scan ($1000) = $17,100; high prices + length time biases = $44,000	As yet, insufficient evidence to recommend routine population screening for lung cancer with CT. Should reconsider the possibility that lung cancer screening with CT could be an effective and cost-effectiveness approach to cancer control	Bayer Diagnostics
Marshall, 2001[70]	Base model: incremental costs of screening = $96m, incremental LYG = 5036. ICER = $19,000 per LYG (incremental cost per QALY = $19,500)	1-year decrease in survival benefit: incremental costs of screening = $96m, incremental LYG = 1548. ICER = $62,000 (incremental cost per QALY = $50,000). A two-fold increase in the incidence rate = $14,449 per LYG; incidence rate halved = $21,677; CT ($50) = $10,809; CT ($300) = $31,205; CT ($400) = $39,364	Annual lung cancer screening with helical CT could be a cost-effective approach to cancer control in high-risk populations and is worth investigating further	Bayer Diagnostics
Wisnivesky, 2003[72]	Incremental benefit = 0.1 year. Incremental cost = $230. ICER = $2500 per LYG	CT scan ($300) = <$4000 per LYG; over-diagnosed cases >50% = >$50,000; prevalence (1%) = <$20,000; stage-specific lead times (50–150%) = <$6,000; other parameter variations did not lead to ICER >$50,000	Preliminary findings suggest that screening would be economically efficient	
Chirikos, 2002[68]	Least favourable assumptions: ICER ranges from $33,557 to $90,022 per LYG. Most favourable assumptions: ICER ranges from $33,884 to $45,822 per LYG Cost per cancer case detected (discounted) = $76,405	ICER is sensitive to the fraction of screened cohort that is detected with early stage disease. More favourable assumptions about age and gender of the cohort and the likelihood of more versus less extensive therapy reduce ICER by approximately $14,000 per LYG. Raising the discount rate lowers the ICER	If screening for lung cancer is effective, it is likely to be cost-effective if the screening process can detect >50% of cancers at localised stage	

TABLE 15 *Cost-effectiveness results (cont'd)*

Study	Cost effectiveness ratios	Sensitivity analysis	Conclusion	Industry author affiliation
Mahadevia, 2003[69]	Current smokers: ICER = $116,300 per QALY Quitters: ICER = $558,600 per QALY Former smokers: ICER = approximately $2m per QALY Incremental cost for all groups ranges between $4300 and $4600	For lung cancer screening <$50,000 then stage shift must be 91% for current smokers; screening dominated by no screening if stage shift was <23%; for quitting and former smokers, a 100% stage shift was insufficient. Parameters that changed incremental cost per QALY by ≥ 50% included: non-adherence, QoL for screening-detected localised NSCLC, cost of scan and anxiety about management of indeterminate nodules	Given current uncertainty of benefits and harms and the high costs of screening, direct to consumer marketing of CT is not advisable	

to Patz and colleagues,[90] a successful screening programme must be able to offer patients effective treatments that can reduce mortality. To date, there is no published evidence to support the assumption that screening for lung cancer leads to reduced mortality rates. However, there is evidence to suggest that screening for lung cancer can improve the stage distribution of tumours identified.[94] This means that more early-stage disease can be detected. However, whether or not a stage shift occurs[90] and whether or not detecting lung cancer early alters the natural history of the disease[25] are very much subjects of intense debate. In addition, the majority of peripherally located tumours are visible by CT, but the majority of centrally located tumours are radiologically occult.[95] The focus of screening programmes therefore appears to be the detection of peripheral cancers, although detection of centrally located lung cancers is still important.[96] The implications of this for the screened and unscreened populations were not discussed in any of the included studies.

Stage distribution
The studies included in the literature review assumed that the improved stage distribution did take place and there was an implicit assumption that this translated into a mortality benefit. However, only Mahadevia and colleagues[69] explicitly quantified the effect of varying this stage shift. Chirikos and colleagues[68] simply mentioned that the cost-effectiveness ratio was sensitive to the number of early-stage cancers detected.

Quality of life
Only two of the included studies[69,70] addressed quality of life issues and conducted cost–utility analyses. Both papers reported utility values from a previously published paper.[97] Neither of the studies explicitly mentioned that these utility values were not elicited directly from patients suffering from lung cancer, but were compiled for two hypothetical NSCLC patients. Consideration of quality of life issues in cancer studies is important; however, the methodological rigour with which utilities are measured must be maintained.[98]

Bias
It is reported that mortality is the true test of the effectiveness of screening for lung cancer,[99] as changes in mortality rates are unconfounded by bias. Survival rates are often reported in screening studies and used in cost-effectiveness reports. However, survival rates are said to be subject to lead-time bias, length bias and over-diagnosis bias,

as defined in Chapter 2 (p. 8).[90] Whether or not these biases are incorporated into the cost-effectiveness analysis, and the analytical methods chosen, can markedly affect the cost-effectiveness ratios produced, as demonstrated by the results of the included studies. If these biases are omitted from the analysis, then the survival (and mortality) benefit may be overestimated and vice versa. The methods used for dealing with bias in the included studies were not transparent enough to allow verification by the reader.

Harm must be included in the economic decision-making framework. Economic evaluation is often labelled as a systematic and objective framework for decision-making as it allows a full investigation of the costs and benefits of the healthcare technologies under scrutiny. Assessing the costs and benefits of population screening for lung cancer, therefore, requires careful consideration of the harms associated with screening, including the mortality and morbidity associated with the verification of indeterminate or falsely positive nodules, radiological risk and reduced participation in future screening programmes.

False positives
One of the major criticisms of screening programmes for lung cancer is the relatively high false-positive rate.[77] Only Mahadevia and colleagues[69] reported the number of unnecessary biopsies and surgeries associated with their screening programme. The false-positive rate of screening may be very high[93] and this is possibly one of the overwhelming arguments for not adopting a national screening programme in the UK.

Radiological risk
No incorporation of radiological risk was performed by any of the authors of the included studies. This was an important omission as radiation exposure (including follow-up CT examinations) may account for more deaths than lives saved by the screening programme.[93] Indeed, a recent report reveals that the radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer are substantial.[100]

Adherence
Finally, some argue that high-risk individuals who have a negative screen may perceive this as reinforcing their belief that their lifestyle does not require modification and that this will lead to reduced participation in screening programmes in the future. Linked to this is the explicit consideration of adherence in screening

programmes. Often described as a combination of compliance and persistence,[101] adherence is another factor that can influence the size of the cost-effectiveness ratio and was not explained in depth by any of the authors.

Generalisability

The generalisability of the results of the cost-effectiveness analyses included in this review must be explored. From a clinical perspective, as MacRedmond and colleagues[52] point out, it is very difficult to transfer the results of screening programmes from one country to another. For example, most of the included studies in the review used prevalence data from the US ELCAP study; this study reports a prevalence of CT-detected lung cancer of 2.7%.[94] In contrast, a study set in Ireland[52] found the prevalence of lung cancer detected in a population of asymptomatic high-risk smokers to be only 0.46%.

In terms of cost-effectiveness, the country of origin of the study is also very important. For example, one country may have a very aggressive follow-up policy after screening and this will be more expensive than a less aggressive policy. Year of the study is also central to the cost-effectiveness debate, especially where the technology of interest is rapidly evolving. All of the studies in the review will therefore need to be updated and their results reconsidered in the near future.[89]

Finally, each screening programme needs to be evaluated in terms of clinical and cost-effectiveness on its own merits. Generalisability will be limited when even slightly different screening programmes are being compared. For example, it has been suggested that patients should undergo individual counselling from their GP before screening for lung cancer to discuss possible outcomes.[102] Whether or not these costs are included in or excluded from a cost-effectiveness analysis would influence the size of the cost-effectiveness ratio.

Conclusion

In conclusion, there are many issues that remain unresolved in the debate over the true cost-effectiveness of lung cancer screening programmes. Before any definitive screening recommendations can be proposed, careful analysis of current and ongoing CT studies must be conducted; in addition, more complete and transparent cost-effectiveness analyses are required.[90] The introduction of a population-screening programme should depend on confirmation that screening for lung cancer using CT does lead to a reduction in mortality.

Chapter 5
Economic evaluation of lung cancer screening

Introduction

The central concern of this chapter is to explore how our current understanding and the corpus of reliable evidence might support a meaningful economic evaluation of lung cancer screening. Through assessment of the published economic studies already described and the modelling methods used, it has been concluded that it is not currently possible to perform a rigorous analysis that could yield useful information to inform decision-making in this important area of public policy.

The principal factors leading to this conclusion are:

- the lack of high-quality direct evidence of benefit (i.e. extension of life)
- the high risk of harm through large numbers of false-positive detections
- the currently weak understanding of processes involved in the origin and development of cancerous lesions amenable to screening, which prevents modelling of screening interventions with any confidence.

The following subsections describe and discuss various problems encountered in attempting to construct a mathematical and economic model of screening for NSCLC to demonstrate why the authors believe that attempting a full economic assessment is premature. An indication of the type of evidence that would be required to redress the perceived shortcomings is also given.

Lung cancer disease modelling

The economic evaluation of a screening programme for any disease or condition involves a careful comparison of the anticipated health-related costs and outcomes associated with two or more alternative possible 'futures', governed by the presence or absence of a defined screening programme. Regardless of the availability of high-quality RCT evidence of efficacy (but particularly when this is lacking), it is important to have a good understanding of how the disease originates, develops and progresses. Where such knowledge is available, it is best represented in the form of a mathematical model that allows the impact of a screening programme to be projected and quantified over extended periods (ideally the remaining lifetime of the individuals affected). However, the process of formulating such a model imposes a discipline on the researcher and exposes deficiencies in both evidence and logic which, if not rectified, render the whole exercise ineffectual.

The disease process

It is generally understood that any cancer originates from a single anomalous cell that begins to grow and replicate in an uncontrolled manner. In the early stages of growth (for solid tumours) the colony of affected cells is localised within a single organ and is not detectable clinically or by imaging technologies. In the absence of active screening (whether opportunistic or systematic) most cases are not identified until patients present with suggestive clinical symptoms. Current thinking assumes that tumours grow at an exponential rate, often measured in terms of a 'doubling time'. However, it is not clear whether this is a realistic reflection of the normal process of cell replication, or is merely a convenient mode of description.

The wide range of disease severity observed in patients with newly diagnosed lung cancer suggests strongly that the development of symptoms (and therefore the stage of disease progression at which the cancer is normally diagnosed) is related to, but not determined by, tumour size.

The present case is concerned solely with NSCLC (which constitutes around 83% of lung cancer cases), since early detection of NSCLC is associated with better treatment outcomes from surgical intervention, whereas the same is not true for SCLC.[103] However, the proposed screening technology only applies to cancers developing in the areas of the lung distant from the bronchi (where tumours are largely undetectable by CT). These generally appear as of any size from 1 mm to over 40 mm. Screening for such nodules is expected to be effective by allowing them to be removed surgically before they are able to grow and metastasise to adjoining or distant organs.
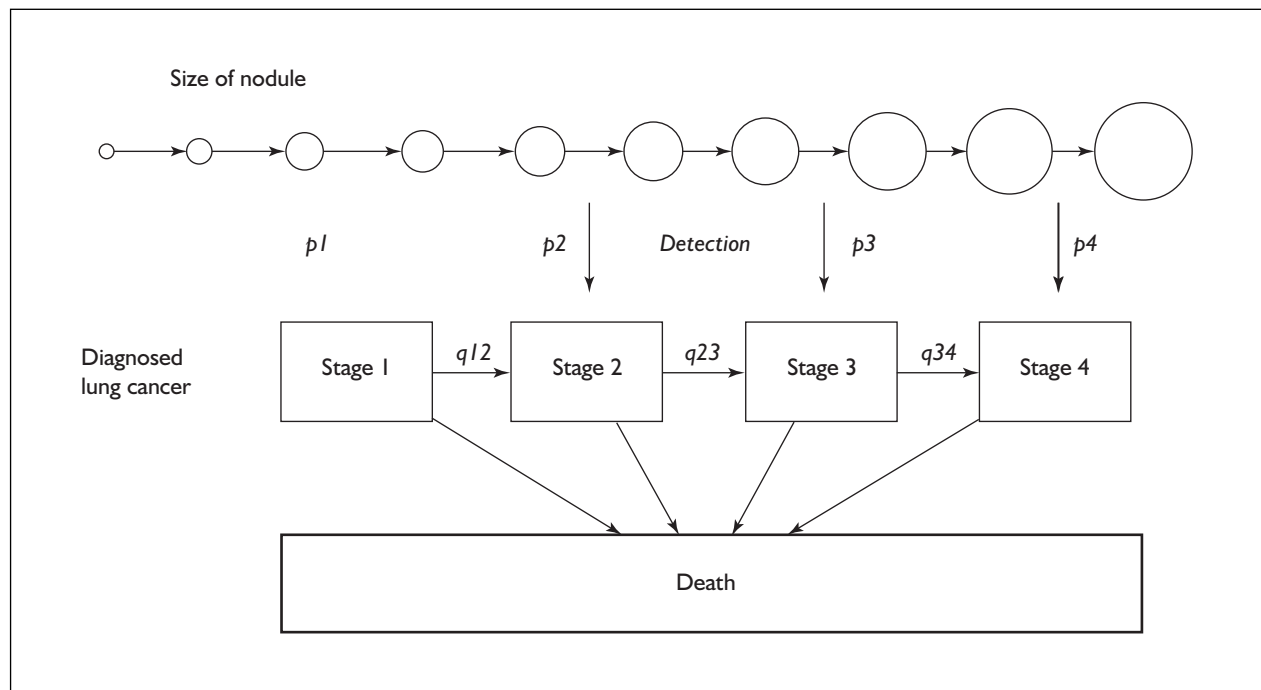
FIGURE 2 *Stylised representation of tumour growth, symptomatic detection and disease progression in an unscreened population*

A stylised representation of the natural development, progression and detection of NSCLC is shown in *Figure 2*. As a potentially cancerous nodule grows it moves along the scale of disease staging (left to right), and in parallel the probability of emergent symptoms resulting in detection (p1–p4) also increases. The balance of symptomatic disease detection rates, subsequent disease (i.e. stage) progression rates (q12–q34) and stage-related mortality rates governs the relative proportions of diagnosed patients in the various disease stages at any time after detection.

However, in this schema only the stage-specific mortality rates are directly measurable, and human studies to obtain the missing transition rate information would be unethical, since this would require treatment to be withheld from patients with known disease.

In addition, this conceptual model is based on assumptions that may be vulnerable to challenge. In particular, it is assumed that malignant NCNs will continue to develop steadily unless they are surgically removed. Yet it may be the case that some will stabilise, shrink or grow so slowly, if left *in situ*, that not all will develop into lethal lesions. This suggests that a more complex model structure would be needed, requiring additional parameter values to be estimated for which no evidence currently exists.

Patient diversity and bias

NSCLC is not a single disease, but a mixture of related types of cancer affecting different lung cells in a variety of ways. In addition, there is clear evidence of wide variations in the aggression of lesions affecting different patients, so that doubling times for tumours have been reported of under 80 days and more than 400 days.[43] Under the simple model of lung cancer development, doubling time is necessarily a positive number of days, and therefore its probability distribution is likely to be heavily skewed. Non-homogeneity to this degree calls into question the reliability of any disease modelling based on simple average parameter values. It also gives rise to the three types of bias often associated with studies of screening programmes and described in Chapter 2 (p. 8): over-diagnosis, length bias and lead-time bias.

A well-formulated disease progression model that fully reflected this essential lack of homogeneity would be automatically free of these biases, and indeed could be used to estimate the magnitude of bias observable in clinical studies. However, none of the models so far published for economic evaluation of screening is of this type. Therefore, authors have been obliged to introduce artificial adjustment factors in an attempt to correct for these biases. Yet the absence of reliable evidence to support calibration of a disease progression

model applies equally to estimation of the three types of bias, and the literature includes considerable debate and controversy concerning the importance of bias in relation to lung cancer screening.[99,104–107]

Stage shift and estimated survival

As noted in the review of clinical studies, there is currently no evidence that screening for lung cancer results in extended life expectancy in any population. Until such evidence is presented, the only way that a case can be made for screening is through indirect inference, assuming that intermediate outcomes (cases detected) can be converted with confidence into true outcome gains. Fundamental to all the published models is the notion of 'stage shift', which is used as the primary basis for estimating the expected gain in average survival and life-years. Since screening studies frequently show a preponderance of patients in the early stages of disease, compared with patients identified clinically, it is assumed that this alteration in the distribution of disease stage can be converted directly into improved survival using standard disease and treatment-specific register statistics.

Although plausible, this assumption is by no means free of suspicion. At a practical level, the survival estimates obtained from disease registers are invariably dominated by data from unscreened symptomatic patients. The biases noted above virtually guarantee that the prognosis of the latter patients at diagnosis is significantly different to that of asymptomatic screening-detected patients, even if all other factors are similar. This problem has been recognised by one author,[69] who invoked the idea of 'pseudo-stage shift' to moderate the size of simple stage shift in a sensitivity analysis.

Summary

The processes by which cancerous lesions arise, develop and progress into symptomatic lung cancer are not well understood or described. Missing information prevents design of a reliable disease model for unscreened disease. Modelling the effects of screening involves making further uncorroborated assumptions about disease progression and screening efficacy.

Screening and treatment protocol

The published studies of lung cancer screening and related economic evaluations have used a variety of protocols for screening people for disease, investigating suspicious screening results

and treating detected disease. The screening protocol that the present authors consider to be most appropriate in the UK is shown in *Figure 3*, which can be compared to the equivalent patient pathways for patients developing lung cancer in the absence of screening (*Figure 4*). These diagrams would form the basis for any future detailed modelling. However, important choices must be made before modelling and assessment in a number of areas, as follows.

Selection of screened population

It is generally recognised that any screening programme is most effective and cost-effective if targeted on those individuals for whom there are pre-existing risk factors present predisposing them to significantly higher risk of developing the disease. This means identifying relevant high-risk demographic subgroups (age, gender and ethnicity), as well as those whose lifestyle or occupation involves exposure to carcinogenic agents (e.g. tobacco smoke, asbestos). Only in Japan has unselected screening for lung cancer in the adult population been introduced. Elsewhere, some prescreening selection process is undertaken, generally involving medical or related professionals assessing patient records or questionnaires, or performing a clinical CT examination. This has the effect of reducing the number of unproductive screens carried out, but also of increasing administration costs per screened person.

A history of smoking is the most widely recognised predisposing factor for lung cancer, with risks increasing for both intensity of smoking [up to a three-fold difference between heavy smokers (>30 per day) and light smokers (<10 per day)] and duration of smoking.[108] The latter shows the strongest effect, with relative risks of 15 or more between lifelong smokers and non-smokers. In combination, these factors may increase cancer risks for smokers nearly 50-fold over non-smokers. Smoking cessation leads to a progressive reduction in lung cancer risks,[7] but probably never to the level experienced by non-smokers. Certain occupational exposure appears to be associated with increased risk of lung cancer, in particular asbestos exposure. Other co-morbidities may also be implicated, especially COPD.

In planning a screening programme it is important to define the target population clearly according to criteria easily implementable by those charged with prescreening selection. The number of eligible invitees and their risk of developing lung cancer are crucial components in the
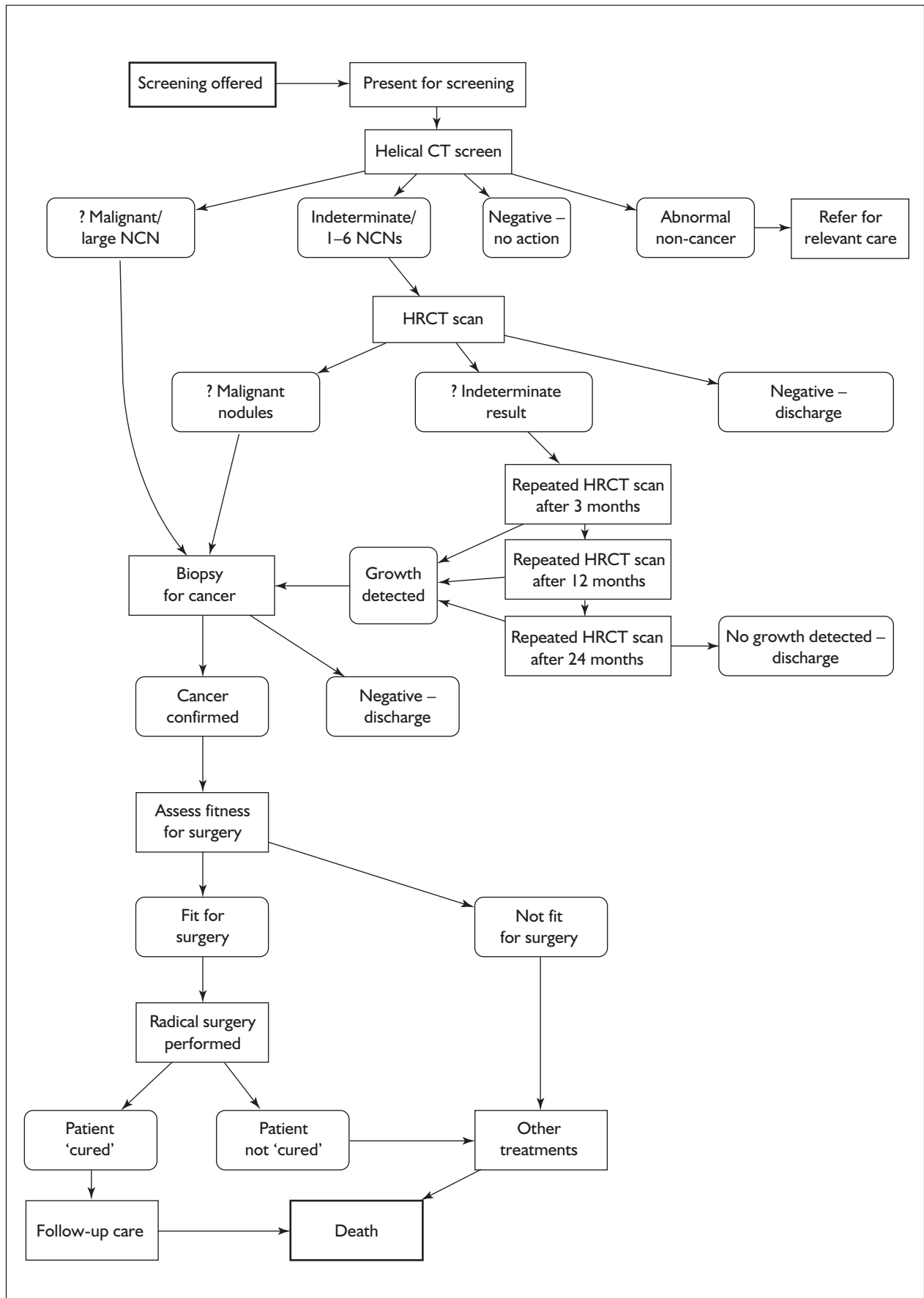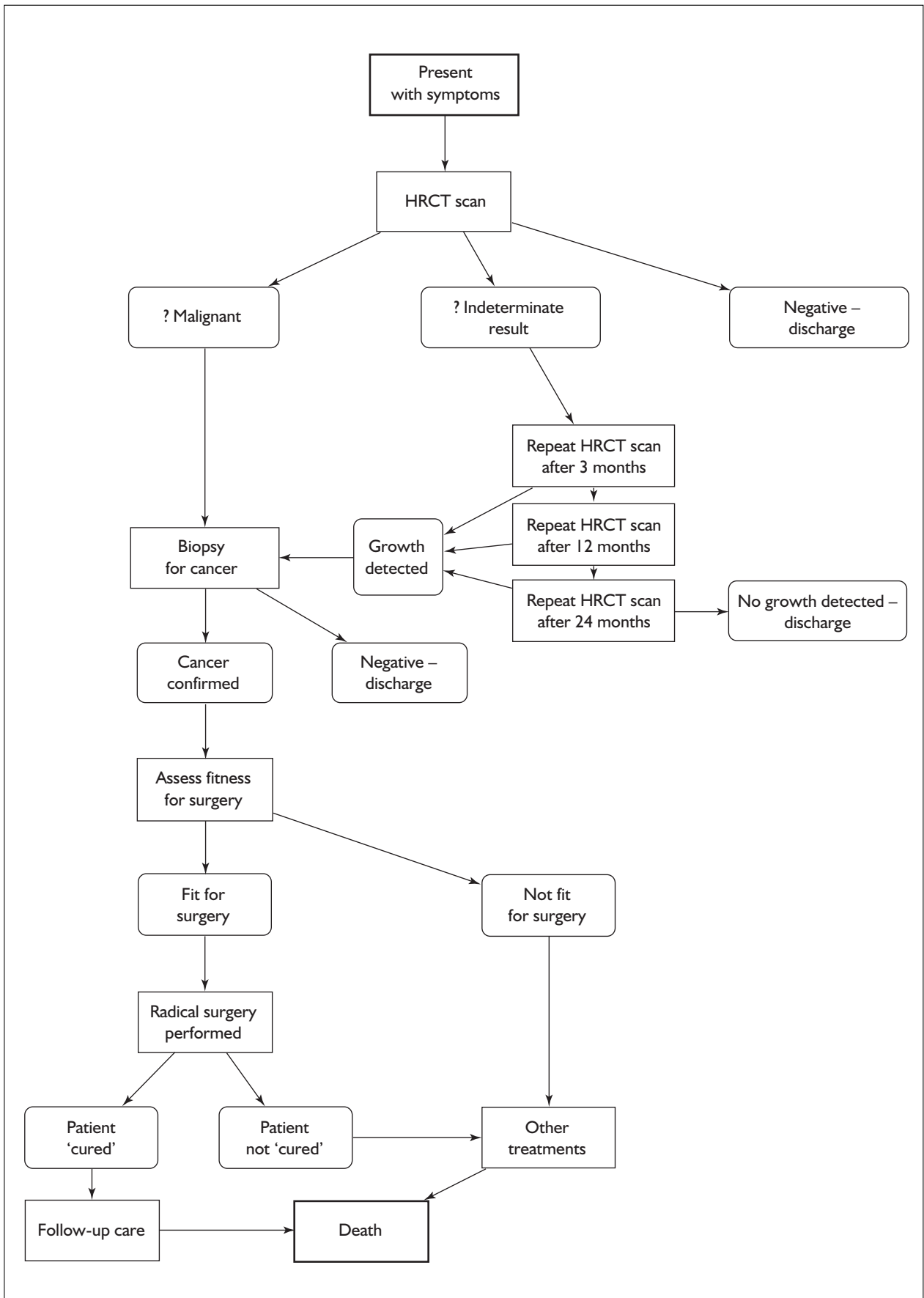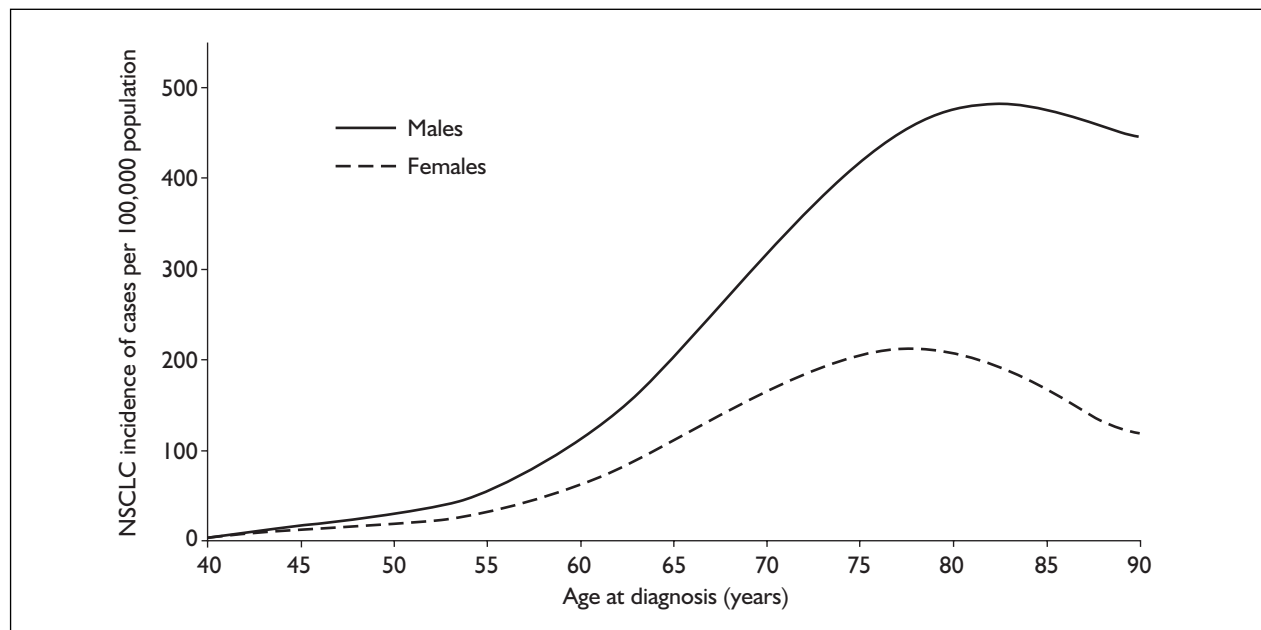
FIGURE 3 *Detection, confirmation and treatment protocol for screened NSCLC*

FIGURE 4 *Detection, confirmation and treatment protocol for unscreened NSCLC*

FIGURE 5 *Age-specific UK incidence rates of NSCLC in 2000. Sources: Lung cancer incidence statistics for 2000 (from www.cancerresearchuk.org),[2] combined with NSCLC:SCLC proportion from Clinical Outcomes Indicators 2002, CRAG Scottish Executive[103] and Office of Population Censuses and Surveys UK population estimates for 2001 (base-year 1994).*

estimation of both costs and cost-effectiveness. It may be necessary to carry out pilot surveys to determine the former (especially where routine data sources are incomplete or inaccurate) and historic case series analyses may be used to estimate the latter for a local area.

Summary
Selection of a high-risk subpopulation offers the greatest chance of good public health and economic outcomes for a lung cancer screening programme. Smoking is the main risk factor for selecting patients. However, performance of the screening programme is dependent on good local systems for identifying the highest risk individuals, and pilot studies may be appropriate to confirm feasibility.

## Frequency and timing of screening
The first screen offered to a population (usually referred to as a 'baseline' screen) is of a different character to subsequent repeat screens. A baseline screen detects prevalent asymptomatic cases of lung cancer, some of which may have been present and potentially detectable for several years. Further screens (called 'incidence' screens) are designed to detect new instances of lung cancer that have arisen in the period since the last screen. The yield from a baseline screen is bound to be considerably greater than that obtained with other screens, leading to better effectiveness and cost-effectiveness results (assuming that true survival

benefit is established). The relationship between baseline and interval screening yields is dependent on all the unquantified disease parameters referred to above, and is therefore difficult to estimate consistently. In the ELCAP study[94] the rate of cancers detected at baseline was 2.7%, whereas early results of repeat screening[30] suggested a yield of 0.7%, i.e. a ratio of about 1:4. Although it cannot be assumed that this figure is generally valid, it may provide a useful basis for illustrating the consequences of the distinction between screen types.

Analysis of UK cancer incidence data combined with life-table projections offers insights into the age at which screening should start and the frequency of subsequent interval screens. *Figure 5* shows that the peak incidence rate of NSCLC in the UK occurs at the age of 82 years for men and 78 for women. However, when converted into annual numbers of new cases diagnosed (*Figure 6*), the peak ages both occur at the age of 77 or 78 years, although the volume of disease in women is only 65% of that experienced by men.

The potential for benefit from early detection and treatment of NSCLC depends on the remaining expected lifetime of individuals if they do not have lung cancer. Individuals who receive curative surgery as a result of screening detection could expect to gain a substantial proportion of those projected years (assuming again genuine survival
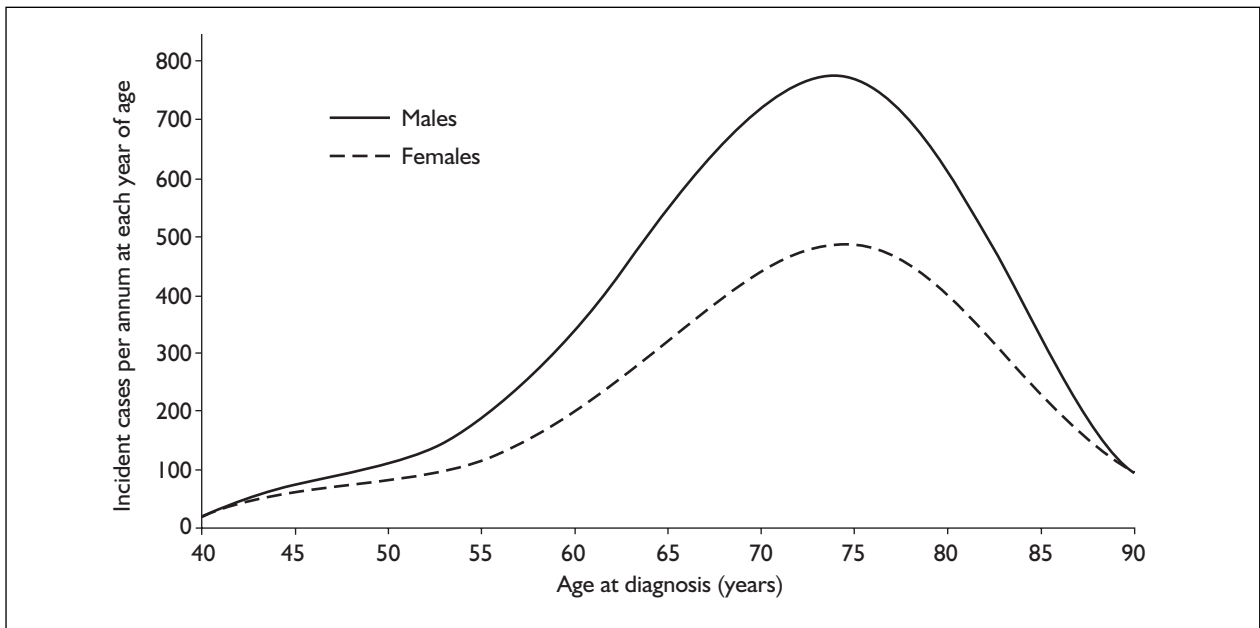
FIGURE 6 *Age-specific UK incident cases of NSCLC in 2000. Sources: Lung cancer incidence statistics for 2000 (from www.cancerresearchuk.org),[2] combined with NSCLC:SCLC proportion from Clinical Outcomes Indicators 2002, CRAG Scottish Executive[103] and Office of Population Censuses and Surveys UK population estimates for 2001 (base-year 1994).*

gain from screening). Although there will be a number of co-morbidities and other factors moderating this effect, especially among smokers, it is instructive to use the notion of 'life-years at risk' to explore questions of the age at which screening should start and how many screens should take place at what intervals.

Figure 7 shows a similar pattern for life-years at risk to *Figure 6* (new cases), except that the peak age has moved to 68 or 69 years and the potential to benefit among women is now 76% of that of men (owing to greater life expectancy of women). This pattern is broadly proportionate to the gains that may be expected from annual interval screening about 1 year earlier.

If one wishes to consider the optimal timing of a single baseline screen without any subsequent rescreening, this effect can be approximated by accumulating the annual risk over several previous years. Using the ELCAP result, and accumulating 4 previous years' incidence, it is found that the greatest potential benefit occurs with a single screen at the age of 70 for both men and women (although any age between 66 and 74 ensures that at least 90% of the maximum benefit is achieved).[30] However, best economic results are likely when the life-years gained per person screened are maximised. Owing to the reducing number of people in the population at older ages, the peak for this measure occurs rather later, at 73 years of age.

Equivalent results for other screening programme designs can be obtained by combining results from baseline screens with (say) annual interval screens over several years. This has the effect of moving the starting age forward; thus, following a baseline screen with five annual interval screens advances the starting age by 2–3 years. However, because the yield for interval screens is lower than for the baseline screen, and each additional screen includes screening times more distant from the optimal-yield age, the incremental gain from each extension of the programme diminishes.

These results have been confirmed by repeating the analysis substituting NSCLC mean survival times by stage, age and treatment derived from analysis of the US SEER database for patients with NSCLC, in place of UK life expectancy.[109] The conclusions are virtually identical, although it may be appropriate to vary the optimum ages by 1 years (or 2 years at most) to allow for possible lead-time bias.

Summary
If screening does lead to survival gains, then a single screen at about 70 years of age can be expected to provide the greatest gain in life-years across the population. However, the best cost-effectiveness of a single screen is likely at about the age of 73. Adding further interval screens to a baseline screen will incrementally increase overall outcome gains, but steadily erode the cost-effectiveness of the programme.

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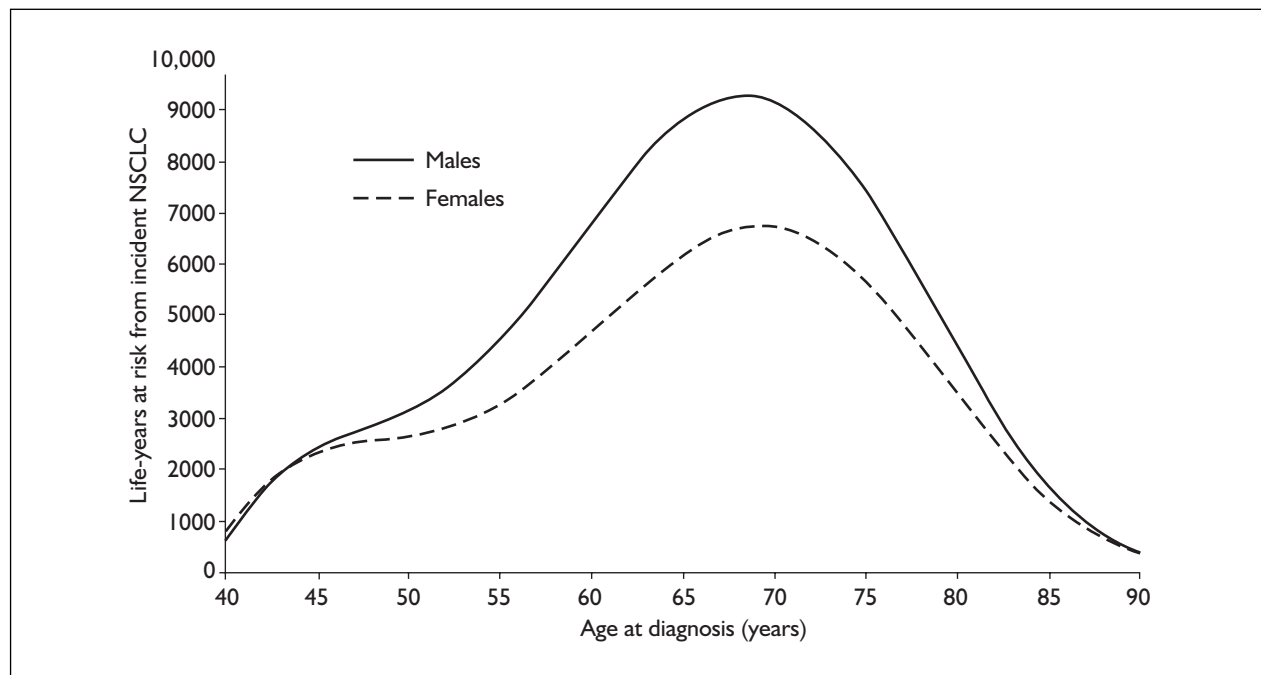
FIGURE 7 *Total years of expected remaining life at risk from newly diagnosed NSCLC by gender and single ages 40–90. Source: Interim Life Tables for UK based on 2001–2003, Government Actuary's Department.*

Criteria for positive screen

Although screening test criteria vary between published studies, the reviewers have assumed use of the ELCAP scheme[30] on the grounds that ELCAP has furnished the data most widely used in economic studies to date. A positive result involves the identification of one to six NCNs suggestive of possible lung cancer and requiring confirmatory investigation. Patients with evident malignancy or large nodules are referred directly for biopsy. Those with diffuse disease (more than six NCNs, diffuse bronchiectasis and/or ground-glass opacities) are also referred for confirmation. Any non-cancerous abnormalities are referred to the appropriate specialist for follow-up and treatment.

Confirmation and diagnosis

Confirmation of screening-positive or suspicious findings is by HRCT as soon as possible after the screening test. Any confirmed probable malignancy is referred for biopsy for a definitive histological diagnosis and staging. If HRCT clearly negates the initial screen suspicion, the patient is discharged and re-entered into any ongoing future screens defined by the screening programme.

Follow-up of suspicious screens

For any patient undergoing a confirmatory HRCT in whom suspicion remains, further HRCT examinations are scheduled for 3, 12 and 24 months to look for evidence of nodule growth suggestive of malignancy. If growth is found at any stage, the patient is referred for biopsy; otherwise, the patient is discharged to the normal screening schedule.

Treatment and follow-up of detected disease

Where biopsy fails to show any evidence of malignancy the patient is discharged. For confirmed cases of lung cancer, patients are clinically assessed as to their fitness for surgery appropriate to the stage and location of the malignancy. Those deemed fit receive curative surgery with conventional follow-up care, whereas those unfit receive conventional modes of supportive care appropriate to their needs.

Comment

Although the main screening protocol may be defined quite clearly, the specification of other aspects of care is more problematic. Ideally, a realistic economic evaluation should reflect 'normal' or 'average' practice in UK hospitals, but there is little reliable contemporary evidence describing the balance between different types of investigation or treatment and therefore the resources used. Thus, the degree to which bronchoscopy, thoracoscopy or guided

transthoracic percutaneous needle biopsies are used to confirm the diagnosis is unclear, as is the use made of various other imaging techniques when biopsy is not feasible or is unsuccessful (e.g. PET). The techniques used are likely to vary with the tumour location (central versus peripheral) and patient tolerance of the procedure. Little is also known of current UK practice in terms of the various types of surgical intervention. The nature and cost of 'supportive care' in lung cancer are particularly poorly researched. Although professional guidelines are of some interest, they may be more indicative of future aspirations than of the current state of clinical practice, which should be the baseline from which any decision is made.

Estimation of long-term survival

In the absence of direct evidence of survival gains, the case for lung cancer screening depends on the assumption that stage shift at detection and the consequent change in mode of intervention (i.e. increased use of curative surgery) lead to a better prognosis for most patients. To quantify this effect in the context of an economic evaluation it is necessary to use statistics derived from observational databases. Unfortunately the values routinely reported in clinical or epidemiological journals (median survival, survival at 1, 2 or 5 years) do not correspond to the measure required for economic evaluation, the mean estimated survival time. In particular, unless the survival time distribution is symmetric, it is probable that the median survival time will be a biased and unreliable basis for estimating life expectancy.

A further problem arises when analysing data with incomplete follow-up: although Kaplan–Meier estimation with censoring yields mean survival estimates, these often underestimate the true value of the population mean owing to the absence of sufficient data for extended follow-up. This problem must be addressed by fitting parametric models to the available data as a basis for projecting all patients forward to the time of their anticipated death. This procedure has been applied to individual patient data available in the SEER public-access database to derive mean survival times for each combination of age, gender, disease stage at diagnosis and principal mode of treatment (i.e. surgery or not surgery). The estimated mean survival in each case (for 5-year age bands) was calculated using the Kaplan–Meier technique, and then ordinary least squares regression was used to fit a two-part model involving one population component subject to high mortality risk (simple exponential function based on constant hazard), and a second subpopulation exposed to lower risk and represented by a Weibull distribution. Comparing differences between the Kaplan–Meier and parametric estimates (*Figure 8*) shows that for estimates up to about 6 years the two approaches yield very similar results, but beyond 6 years the parametric method produces larger values as expected, and is therefore to be preferred.

The SEER database is very widely used by published authors as the basis for survival calculations, partly because it is probably unique in the size, range and quality of its data, and partly because it is US specific and most evaluations of lung cancer screening have been US based.[1] Unfortunately, there is no comparable data source in the UK that would permit survival estimates to be generated that are consistent with UK case-mix profiles and treatment practices. In the regional cancer registries staging information is only available for a minority of patients, so it would be impossible to estimate the consequences of stage shift with any confidence. It is known from summary statistics that the proportion of UK lung cancer patients undergoing curative surgery has been much lower than in the USA or Europe,[60,110,111] so that there are strong reasons to believe that statistics derived from SEER will not be transferable to a UK setting, since the case-mix of patients benefiting from any stage shift would be quite different from those benefiting in the USA.

Summary
Estimation of survival gains indirectly through assumptions about stage shift requires access to an appropriate and reliable source of data in the UK, but this is not currently available. Use of the SEER database for this purpose is subject to serious and unquantifiable bias and so cannot be justified.

Utility values for lung cancer

Whether survival gains are obtained directly from an RCT or indirectly through stage shift assumptions, it is necessary to convert these to QALYs when performing a cost–utility analysis, using a set of utility values obtained through a validated generic methodology. As noted in the previous section, there is no mention in the published economic evaluations of an evidence-
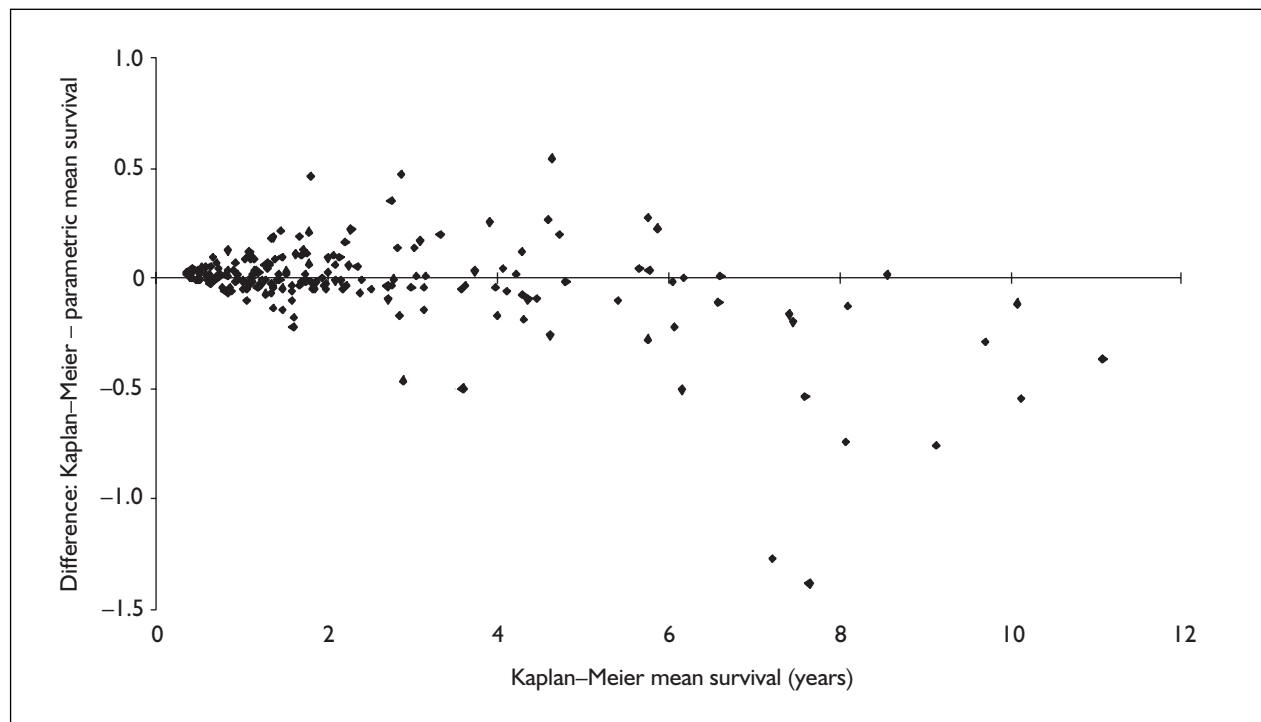
FIGURE 8 *Comparison of Kaplan–Meier and parametric mean survival estimates for age, gender and treatment subgroups*

based source for utility values; all the referenced sources ultimately derive values from a crude hypothetical exercise in which no patient data were used.[97] However, a more recent Italian study[112] collected quality of life and utility data (SF-36 and EuroQol) from 95 NSCLC patients in 15 hospitals. The authors quote mean EuroQol values of 0.58 for lung cancer, and report univariate binary variations for gender, age, time from diagnosis, the presence of metastases and three treatment modalities. Unfortunately, they did not report any multivariate analysis to facilitate estimation of utility by stage of disease, which would be required for evaluation of any benefits of lung cancer screening. Until comprehensive patient studies are carried out to estimate utilities for all the relevant lung cancer patient states using an appropriate generic instrument, utilities have to be 'guessed' or inferred by parallels with other patient types. Under these circumstances any cost–utility results will need to be subject to wide-ranging sensitivity analysis, and may therefore fail to command great confidence.

Summary
The lack of an evidence-based source for patient utilities means that any cost–utility analysis of lung cancer screening is likely to be subject to substantial uncertainty.

Potential for harm

False-positive results
The false-positive rate of CT screening (i.e. the complement of the test specificity) has an important bearing both on the impact of screening on the participating population and on the costs associated with the programme. A meta-analysis of test characteristics from published studies[69] shows a test sensitivity of 93% and specificity of 83%. The relationship between the number of cases of lung cancer correctly identified and the number of participants with a test result suggestive of cancer depends on the underlying prevalence of the disease in the population. For example, if the prevalence is similar to that experienced in the baseline ELCAP screen (where cancer was confirmed in 2.7% of screens), then one should expect 14–16 false-positive results for every case of lung cancer found.[30] However, if the prevalence was at the level reported in Ireland[52] (0.46%), then each case of lung cancer occurs alongside 83–93 false positives.

There are no definitive studies describing the impact on screenees of a 'suspicious' result, but it can be expected to involve considerable anxiety for the individual and their family until further

investigations provide full reassurance (which may take as long as 1 or even 2 years, depending on the protocol used), and this may represent an important (albeit limited) loss of quality of life and personal utility. In addition, false-positive results will lead to people affected undergoing several additional HRCT examinations and perhaps extra low-dose screening tests before doctors can be confident that the patient is not suffering from a clinically important lesion. These procedures add substantially to the total cost of the screening programme.

Adverse events

For a minority of false-positive detections, the patient may undergo invasive diagnostic procedures and even radical surgery for suspected malignancy, and these procedures all carry the risk of serious adverse events or even death. These risks, although small, may have importance to economic analysis, particularly as a single premature death (and the life-years lost thereby) may have a marked impact on ICERs. In ELCAP,[32] only one biopsy was taken from a patient with benign disease, and no patients had other invasive surgery. By contrast, in Ireland,[52] a total of eight procedures was carried out on seven patients with benign disease (1.6%). It appears that the probability of unnecessary thoracic surgery varies widely between locations, and hence the risk of serious adverse events leading to morbidity or mortality may be significant, but is difficult to predict.

Summary

A lung cancer screening programme is likely to produce large numbers of suspicious cases that, after further investigation, are found to be false positives. These will incur additional costs for diagnostic tests, and may involve many people in periods of unwarranted anxiety. Furthermore, a minority may undergo futile invasive procedures with attendant risks of morbidity or mortality.

Radiological exposure

Brenner[100] estimated the increased lifetime risk of lung cancer attributable to the additional radiation exposure involved in LDCT screening. He concluded that a single CT examination would result in a negligible extra risk, but that annual screening from the age of 50–75 is likely to increase the lifetime incidence of lung cancer by about 5% in women and about 1.5% in men. He also remarks that delaying screening until the age of 60 sharply reduces the excess risk (by about 80%), and offering screening twice a year rather than annually cuts the extra risk by half.

Summary

A model used to evaluate and compare screening schemes using multiple interval screens should include a risk adjustment to reflect the increased incidence rates associated with cumulative radiological exposure.

Incidental findings

MacRedmond and colleagues[52] highlighted the importance of other morbidities identified in the course of screening for lung cancer: in the Irish study, incidental findings occurred in 61.5% of patients, leading to many referrals to specialists in respiratory medicine, cardiology and gastroenterology. He reported that additional healthcare costs were incurred for 49% of those screened. It should not be any surprise to find such co-morbidities where individuals are selected for screening on account of their risk-factor profile, even if the large number of incidental cases reported may be exceptional. MacRedmond notes that two-thirds of such disease was related to cigarette smoking.

It is a matter for debate whether these incidental discoveries contribute important additional health benefits to the screening programme, or merely increase anxiety for many people and their families. What is not in dispute is that substantial additional healthcare resources are required to respond to these findings, some of which constitute 'new money' and some are merely incurred somewhat earlier than would otherwise have been the case.

Summary

The selection of high-risk individuals for invitation to screening increases the likelihood of incidental findings of treatable disease in many people. The extra costs and (dis)benefits of treating these conditions should be included in an economic evaluation of lung cancer screening.

Participation

The level of response to an invitation for a first screening test is important in restricting the quantity of prevalent disease that could be detected, and is also important in assessing the viability of a screening programme. However, it should not affect the cost-effectiveness of the programme greatly, unless response is biased in relation to risk factors for lung cancer. By contrast, the probability that individuals will drop out of

subsequent interval screens can adversely affect the economic assessment of programmes based on continuing surveillance. The ELCAP experience of repeat screening[30] achieved a participation rate of 84% in the first round of annual repeat screens, which increased to 88% after protocol exclusions. Mahadevia and colleagues[69] used 93.5% (a weighted average of ELCAP and another US study reported by Swensen[49]) for annual cumulative participation rate. Regardless of the value used, progressive erosion of the screened population over several years can dramatically reduce the likely yield of new detections in later years. After 10 years of annual repeat screens with a 10% annual attrition rate, less than 35% of the original cohort will still be participating, and only about 60% of the expected cancers will have been detected. Since each extra year of screening reduces the cost-effectiveness of the overall programme, loss of participation can threaten the economic case for multiyear screening. Experience in Japan,[37,44] where population-wide screening has a longer history, suggests that attrition rates may be considerably higher outside a study setting.

Summary

Participation rates in single-observation screening are important for the viability of a programme, but should not normally threaten its cost-effectiveness. However, progressive loss of participation in a series of repeat screenings can impact adversely on both viability and cost-effectiveness. Participation rates in studies may overestimate what is achievable in more routine use.

Costs and resources

The ten main classes of healthcare resources and costs required in a comprehensive economic evaluation of lung cancer screening are detailed in *Table 16*. None of the published economic studies encompasses all elements. There are important gaps in the availability of information applicable to a UK context, and new data would need to be collected via clinical studies or surveys in at least six areas. Cost models that are based on phases of patient experience have been developed for the US health system,[72,113,114] but cannot be used directly in the UK without recalibration to NHS-linked individual patient data.

Summary

There are serious shortcomings in the economic data currently available in the UK concerning treatment of lung cancer patients. New research is required to provide information needed for a comprehensive economic assessment of lung cancer screening in the UK.

Conclusions

This chapter has considered several issues of importance to researchers attempting an economic evaluation of screening for lung cancer using LDCT scanning. It has focused especially on the evidential and data requirements for constructing a suitable disease, screening and treatment model for such an evaluation. In the process, serious deficiencies in the type and quality of information from UK sources were identified. One or two such problems may sometimes be addressed through targeted scenario analysis, but the broad range of deficiencies in this instance renders such an approach infeasible.

The most severe problem is the lack of high-quality RCTs demonstrating directly that the screening programme is effective in reducing mortality or morbidity. Claims to efficacy have to be based on inference from intermediate outcomes, and the required logic, although convincing to some, is vulnerable to challenge. The weaknesses in this argument are directly related to gaps in our understanding of the early natural history of NSCLC, concerning the growth dynamics of NCNs and their development into clinical lesions. These weaknesses become apparent when attempting to structure and populate a mathematical model.

Efficacy is at the heart of any economic assessment of a health technology: if the evidence does not support health gains in either the quantity or quality of life, and there are net additional costs incurred (as is very likely with lung cancer screening), then it is highly improbable that screening can ever be shown to be cost-effective. Conversely, if lung cancer screening can be shown to generate significant extension of life with only modest additional cost per patient, then cost-effectiveness will very probably be demonstrable in most circumstances. Thus, the need for unambiguous RCT evidence of screening efficacy in a UK setting is paramount. Closely related to efficacy is reliable information concerning the prevalence and incidence of potentially identifiable NSCLC in selected populations. The disparity in prevalence findings between the Irish study and USA ELCAP studies raises serious doubts about the extent of detectable disease that may be expected in the UK. This is important since the cost-

TABLE 16 *Elements of health-related cost required for evaluation of lung cancer screening*

Cost element	Description	Comment	Resource and cost data	Sources
Screening programme administration	Staff, premises and computer systems to identify potential screenees, issue invitations, record results and manage follow-up. Also costs/fees reimbursed to GPs and other practitioners involved in patient selection and management	Some administrative costs are unrelated to the size of the population or the number selected for screening (i.e. fixed costs). Other costs are proportionate to service volumes	Variety of costs involved	May be best estimated by extrapolation from existing population screening services
Screening CT examination	Direct cost of LDCT examination	Although ideally cost of travel and loss of earnings should also be considered, most of those at risk are likely to be close to or beyond retirement age, so that omitting these costs is unlikely to be important	The use of dedicated facilities (fixed or mobile) for screening may increase the use of expensive facilities, thus reducing the unit cost	National tariff charges for outpatient CT examination or detailed costing of special facilities
Confirmation and diagnosis	Bronchoscopy, biopsy, sputum cytology and/or radiologically guided fine-needle aspiration	Preferred practice varies between centres	Use of each resource in screened patients in local area, or averaged for UK needs to be established	National tariff charges for unit costs. Sampling surveys required for resource use
Adverse events of diagnostic procedures	Additional hospital episodes related to diagnostic and invasive procedures (e.g. pneumothorax)		Adverse event rates required for each procedure used	National tariff charges for unit costs. Analysis of national hospital episode statistics to establish event rates
Follow-up of suspicious and inconclusive screening results	Expected number of further HRCTs per patient, consistent with follow-up detection probabilities			National tariff charges for outpatient HRCT examination. Detection probabilities from study results or observational studies
Curative surgery	Average cost of surgical episode to remove affected tissue	The case-mix of procedures carried out can be expected to vary with stage of disease as well as the characteristics of each patient. Routine hospital statistics may not record sufficient detail to permit this analysis to be carried out	Special surveys may be necessary to relate types of surgery to disease stage. HRG costing system costs will need to be modified to reflect the influence of disease stage on costs	National tariff charges for unit costs, modified for stage of disease. Local/national surveys of surgical case-mix
Follow-up following surgery	Number and speciality of outpatient follow-up care, including planned investigations	Outpatient visits and investigations are not routinely coded against the original diagnosis and surgical procedure	Patient surveys may be necessary to establish normal patterns of follow-up resource use	Average national tariff charges for speciality visit costs and investigations

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TABLE 16 *Elements of health-related cost required for evaluation of lung cancer screening (cont'd)*

Cost element	Description	Comment	Resource and cost data	Sources
Supportive and continuing care	A wide range of health needs may occur throughout a patient's remaining life. The intensity of resource use increases in the last 6–9 months of life, although there are large variations between individuals	Health resource use in late stage cancers is very poorly researched in the UK, although the amount of care provided is often much less than that provided in other developed countries	A consistent and comprehensive UK cost model of supportive care needs to be developed, which can be calibrated for each type of cancer from patient surveys	Resource-use data are scarce and largely unreliable. By contrast, unit costs can be obtained from national sources
Care for incidental findings	Evidence suggests that there is a wide range of potential conditions that would incur healthcare costs immediately, and in some cases over long periods	Each significant co-morbidity will require a separate economic submodel to be developed, and assumptions must be made about the extent to which this healthcare is additional expenditure	Detailed patient data will be required from studies to estimate likely resource use. Published sources may furnish cost models for some co-morbidities	Study data for resource use. National tariff charges for inpatient and outpatient care
Healthcare during extended survival	A patient who is 'cured' following successful surgery will gain extra life-years, during which time they suffer other unrelated health problems that incur costs to the NHS. Estimating these costs is necessary for a budget impact analysis, and (arguably) may be included in a cost-effectiveness analysis	It is not appropriate to use a population average resource-use profile, since screenees are generally selected for their high risk of disease	A large, comprehensive population database of linked NHS resource use is required. Patients would be selected who had curative surgery for lung cancer, and their subsequent resource use analysed	An integrated population database of NHS resource use

HRG, health resource group.

effectiveness of a screening programme is directly related to the prevalence of disease: if few cases are found the cost per detection is much higher.

Next to efficacy, the question most in need of further research is the possible harm arising from screening. Current estimates suggest that a large number of people screened will be falsely identified by LDCT as probably or possibly suffering from NSCLC. No attempt has yet been made to assess the psychological consequences on those affected (including their families), and the evidence on the physical risks associated with confirmatory testing is limited.

None of the published economic studies has adequately considered the implications of incidental findings from screening. The Irish study[52] suggests that as many as half of those screened will have such findings, resulting in considerable increases in costs and administrative workload. Any UK-based RCTs of screening should include comprehensive recording of all incidental findings and follow-up investigations and treatments.

Serious shortcomings are apparent in the evidence available on healthcare resource use associated with lung cancer and its treatment in the UK, partly related to the lack of a high-quality cancer register database similar to SEER in the USA. The failure of regional cancer registries to achieve the completeness of coverage of all types of relevant patient data suggests that there may be a case for new investment and/or greater priority for this function.

Although it has not been possible to develop a meaningful economic model to assess the cost-effectiveness of lung cancer screening, some conclusions may be drawn about the optimal organisation of a screening programme (assuming that real health benefits have been demonstrated):

- Survival gains from a single screen would be greatest at the age of 70 years.
- Each subsequent repeat screening yields progressively smaller incremental gains.
- There is no basis for setting different screening ages for men and women.
- Cost-effectiveness is greatest for a single screen at the age of about 73 years.
- Cost-effectiveness is improved by targeting the highest risk subpopulations.

So far, the cost-effectiveness of screening compared with conventional practices (i.e. symptomatic case finding and current treatment patterns) has been discussed. However, it may be argued that other options should also be introduced into an economic assessment. First, increased expenditure on preventive measures to encourage smoking cessation, or to prevent young people taking up smoking, may offer viable alternatives, with long-term public health benefits and potential economic gains. Second, lung cancer treatment in UK is characterised by a generally less aggressive approach to surgical intervention, but also worse survival outcomes than many European or North American countries. Increasing services and funds to allow more lung cancer patients to be actively managed can be expected to yield important gains, which may also be competitive in economic terms.

It appears that the evidence available on the efficacy of CT screening is not yet strong enough to permit a judgement to be made on whether it should be implemented in the UK. The primary requirement is for UK-based RCTs to be carried out. However, it is also important that enabling research be undertaken on the range of related questions detailed in this section in the meantime. Only then will researchers be adequately equipped to undertake a robust assessment of alternative approaches to reducing the burden of lung cancer.

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Chapter 6

Does screening for lung cancer using computed tomography meet the National Screening Committee criteria?

The UK NSC criteria for evaluating screening programmes were adapted from the WHO criteria published in 1966. The criteria are published by the NSC on their website.

This chapter applies the 22 criteria to lung cancer screening and summarises the evidence presented in the previous chapters. The authors' view on the extent to which the criteria are satisfied is appended after each criterion.

The condition

1. The condition should be an important health problem

By any definition of important, including frequency of the disease, severity of the consequences and economic burden, lung cancer is as an important health problem in the UK. Lung cancer heads the cancer league tables in the UK for deaths, with around 34,000 people dying each year. Prognosis is bleak and presentation as a result of symptoms is generally late. Less than 10% of people survive for more than 5 years after diagnosis in the UK. Survival, while better in some other countries and variable even within the UK, does not surpass 20% at 5 years. At the time of writing this report, NICE was in the process of issuing guidance for the diagnosis and management of lung cancer.[1] This guidance was issued in 2005. Although this may improve survival to some extent, the best way of improving survival is by surgical resection of tumours before they have spread. Most lung cancers are detected either as incidental findings on chest imaging or because of symptoms. For most, symptoms reflect the advance of the disease and 80% of lung cancer in the UK presents with stage III or above. Less than 10% of patients proceed to surgical resection.

Authors' summary opinion: Fully satisfied.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately

understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Screening studies have identified important gaps in our understanding of lung cancer epidemiology. The wide variation in prevalence found, for example, when comparing ELCAP to the MacRedmond study indicates that assumptions of equivalence in disease detection rates cannot be made.[30,52] There is evidence that stage I and II disease is associated with better survival with surgery, but progresses to cause death if surgery is not undertaken, but this comes solely from unscreened populations. There are few data on long-term follow-up of those with lung cancer detected by screening. Some of those data from screening programmes, particularly if non-smokers are included, suggest that screening may include the detection of some well-differentiated tumours that grow more slowly, with a high proportion of atypical adenomatous hyperplasia/bronchioloalveolar adenoma. There is evidence of debate among histopathologists about the nature of this pathological finding, but it is visible on CT as an NCN. One of the screening studies has reported information about tumour growth and indicates that some of the well-differentiated small cancers detected by screening grow very slowly.[43] At present, there is insufficient understanding to quantify the relationship between NCNs, screening-detected lung cancer and outcome.

Authors' summary opinion: Not satisfied.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

As smoking remains the predominant risk factor for lung cancer, one could argue as to whether everything practicable has been done by way of primary prevention. Certainly smoking rates are falling in most subgroups of the population. However, further preventive measures remain to be taken, including cessation of advertising, measures to prevent the sale of cigarettes to

underage people, the banning of smoking in enclosed public places, better recording of smoking in GP records, and systematic intervention using nicotine replacement therapy and other methods.

Regardless of successful implementation of preventive action, smoking leaves with it a legacy lasting for decades, and as Peto and colleagues described, the increased risk of cancer associated with smoking does not fall to close to background level for decades after an individual ceases smoking.[7] As a result, despite the increasing effort to promote smoking cessation, the benefits in terms of lung cancer will not be seen for several decades.

Authors' summary opinion: Partially satisfied.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications
Authors' summary opinion: Not applicable.

The test

5. There should be a simple, safe, precise and validated screening test
CT is a relatively simple investigation, at least from the patients' perspective. It involves the use of a technology that has wide penetration throughout the NHS. The safety of CT is good in terms of acute adverse events. However, it does involve a radiation dose that, while substantially reduced in comparison to standard-dose CT, is higher than that of a chest X-ray. The evidence of long-term safety in terms of radiation-induced cancers is not currently available. LDCT has been compared with standard dose and has been demonstrated to lose little in terms of precision for the identification of NCN in the lung. In the setting of screening, there is no gold standard for assessing validity other than long-term follow-up and investigation of those with abnormal screening CT examinations. LDCT is a sensitive tool, identifying large numbers of abnormalities in the lung. However, among the studies reported here, the specificity was poor. Many people had to undergo further investigation, often involving further radiation exposure.

Authors' summary opinion: Partially satisfied.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed
The international studies that have been included

in this review demonstrate a variation in the prevalence of positive CT examinations among the different studies. This occurs even where similar definitions of a positive CT have been used. The differences may reflect differences between the populations and as a result, make it difficult to generalise from studies conducted outside the UK.

Although there is evidence that the risk of cancer increases with increased NCN size, there is no consensus about what constitutes a size that is too small to cause significant risk of unresectable cancer before the subsequent round of screening. Of course, it is not the size per se that is of importance, but rather the growth rate. In very small nodules it should be noted that detecting an important change in diameter can be challenging.

Authors' summary opinion: Not satisfied for the UK population.

7. The test should be acceptable to the population
The studies reported here provide little if any information about the acceptability of CT in the setting of a screening programme, which may be reduced by full explanation of the possible harms of radiation.

Authors' summary opinion: Not satisfied.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals
In 2005, NICE issued on guidelines for the diagnosis and management of lung cancer presenting symptomatically or incidentally. These guidelines were not constructed for the management of screening-detected lung cancer and modifications would be required if CT screening were to be adopted in the future. From the current evidence, there is no consensus on the definition of a positive CT examination or how individuals with a single small nodule should be followed up in terms of either repeat imaging or biopsy. Similarly, the subsequent surgical management of screening-detected tumours has not been agreed.

Authors' summary opinion: Not satisfied.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out
Authors' summary opinion: Not relevant.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

There is evidence to support the effectiveness of surgical resection for stage I and II NSCLC. More advanced stage disease is associated with poor survival. For those not fit enough for surgery, there is also evidence of better survival among early-stage disease for those treated with radiotherapy. However, their survival is substantially worse than after surgical resection. What is absent currently is RCT evidence that screening will achieve a reduction in disease-specific mortality or total mortality and as a result lead to extension of life expectancy.

Authors' summary opinion: Partially satisfied.

11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

NICE guidelines cover this, but it has not been demonstrated that screening-detected lesions should be managed in the same way as those presenting as incidental findings or with symptoms. As discussed above, there is no consensus on what constitutes a positive screening test and how best to follow up such individuals.

Authors' summary opinion: Partially satisfied.

12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme

Variation in survival from lung cancer is seen when comparing lung cancer survival both within the UK and to other European countries that do not screen. Evidence from the 'best supportive care' arms of studies in the UK is comparable to Europe, so does not support the notion that the disease is more aggressive or diagnosed later in the UK. The rate of surgical intervention varies widely both within the UK and compared with other European countries. Similarly, variations in the use of other treatment options for lung cancer can be seen. At the time of writing the report, NICE guidelines that aimed to improve this situation were in the process of being delivered. These were issued in 2005.[1]

Authors' summary opinion: Not satisfied.

The screening programme

13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity

There is evidence from RCTs to date.

Authors' summary opinion: Not satisfied.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public

Participation and recruitment into screening studies is reported by most authors to be good. However, none of the studies reviewed presented data about uptake of participation into the study or reasons for refusal to participate. Excluding Swensen and Sone, the other studies that had run several years of follow-up all reported poor compliance either with timing (e.g. attending on time for annual review) or with subsequent participation. In the only study[115] that had run screening for up to 5 years, participation was extremely poor. No reasons for poor compliance were presented in the reports. None of the reports included any measures of quality of life or patient perceptions associated with the screening programmes. None reported any acceptability data for participating physicians.

Authors' summary opinion: Not satisfied.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

To date, the screening studies cannot provide an answer to this. Very little information about harm has been published. None of the studies identified has yet published any information about the impact on quality of life from screening. A large number of screened people will have a positive screening test and require some sort of further investigation. Algorithms to reduce the inappropriate biopsy and surgical resection of benign lesions minimised the number of people undergoing the most high-risk procedures. The studies to date do not report well the adverse events from investigation of a positive screening CT or management of lung cancer.

Authors' summary opinion: Not satisfied.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

In view of the lack of evidence of effectiveness to date, it is not possible to estimate the economic impact of a screening programme for lung cancer at present.

Authors' summary opinion: Not satisfied.

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

In the absence of evidence of clinical or cost-effectiveness for CT screening for lung cancer, this criterion is not applicable at this time.

Authors' summary opinion: Not applicable.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Although CT is a widely available technology, the staff and facilities are already under heavy demand within the service. Additional CT systems and staff are likely to be required if a screening programme is to be established in the UK.

Authors' summary opinion: Not satisfied.

19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available

There is evidence of regional variation in the survival from lung cancer, and the survival data from the UK are poorer than those from other European countries. Although there are difficulties in comparing the data between countries, there is evidence to support the fact that there is room for improvement in the management of lung cancer in the UK both surgically and with chemotherapy. The NICE 2005 guidelines address this. Nonetheless, maximising all other management options is not anticipated to provide improvements in survival, because chemotherapy and radiotherapy seldom effect cure.[1,4,116]

Authors' summary opinion: Partially satisfied.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

In the absence of evidence of clinical or cost-effectiveness for CT screening for lung cancer, this criterion is not applicable at this time.

Authors' summary opinion: Not applicable.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

The evidence for ideal screening intervals, cost and clinical effectiveness, and eligibility criteria cannot be acquired from the existing evidence base. Long-term follow up from the current screening programmes will provide information about tumour doubling times and inform the choice of eligibility criteria by providing a better understanding of the risk of cancer versus the risk of investigation in the population. International data may not be generalisable to the UK, because of the variation in risk of both lung cancer and positive screening CT.

Authors' summary opinion: Not applicable.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Authors' summary opinion: Not relevant.

Chapter 7
Discussion

Summary of findings

From the review of clinical effectiveness, it can be concluded that screening for lung cancer with CT is technically feasible and identifies more people with stage I cancer, compared with not screening. At present there is, however, no evidence about the impact of screening with CT on mortality. Published economic analyses are therefore based on the assumption that detecting more stage I disease will translate into both a survival advantage and improved mortality. Although this assumption may be attractive, it is fraught with problems, particularly for a condition that reaches a peak incidence among the over 70-year-olds and is associated with heavy and prolonged smoking. In addition, there is currently no consensus on what definition should be used for a positive screening test or how best to follow up those with positive screening tests. Finally, certain groups are at an increased risk of lung cancer based on age and exposure to cigarette smoke or as a result of occupational exposures, current or past. To date, there is insufficient evidence to support the recommendation of screening for lung cancer in any of these 'high-risk' groups. However, they should be considered in the designing of any future screening studies, when gathering epidemiological data about lung cancer and in the economic evaluation of screening should future studies conclude that there is an improvement in mortality as a result of CT screening.

In considering the economic argument for CT screening for lung cancer, this study has systematically considered the elements that would be fundamental to any economic analysis. In doing so, the conclusion was reached that it is not currently possible to produce a meaningful economic analysis. The lack of evidence of clinical effectiveness is clearly fundamental but, in addition, uncertainty around the understanding of the natural history of screening-detected NCN and lung cancer, and the poorly understood risk of harm associated with high proportions of false-positive screening results are among the problems identified.

Occupational at-risk groups

As noted previously, the increased risk of NSCLC lung cancer associated with certain occupations and exposures, particularly asbestos, may warrant consideration of the feasibility of a screening programme for workers or ex-workers. At present, no RCTs have been conducted to assess effectiveness of screening in such occupational groups. As the lead time for development of lung cancer in asbestos- and silica-exposed workers is long, screening should focus on workers exposed in the past. A case for screening would, therefore, have to be made on an occupation-by-occupation basis with evidence of the feasibility of running an effective screening programme in that specific population. Given the distribution of exposure to substances such as asbestos, with highest exposure in the UK among workers in shipbuilding areas such as Glasgow, Newcastle and Portsmouth, it may be feasible to use employee work records or other means (such as local support groups and trade unions) to identify at-risk individuals for screening in these areas, although appropriate approaches would depend on local circumstances. The logistics of identifying people who were at risk in the past would have to be investigated. The HSE would be an important collaborator and source of information under these circumstances.

Specific weakness of the evidence base

To date, most of the clinical effectiveness data have come from clinical studies with no comparator group. While this design will help our understanding of issues of feasibility, protocols and to an extent the natural history of the lesions detected, they do not answer the fundamental question: does screening reduce mortality? That cannot be answered without control groups.

All the current studies are of relatively short duration when considering the long-term survival of patients with lung cancer. The studies have also been restricted in terms of number of participants, and hence have limitations in terms of power when considering population screening for a condition that has a prevalence of around 2% in the participants screened.

TABLE 17 *Summary of NSC criteria*

Criterion	Authors' summary opinion	Comments
Disease		
I	Fully satisfied	Despite other preventive initiatives being feasible, they would
2	Not satisfied	not affect the population proposed for screening for several
3	Partially satisfied	decades
4	NA	
Test		
5	Partially satisfied	
6	Not satisfied	
7	Not satisfied	
8	Not satisfied	
9	NA	
Treatment		
10	Partially satisfied	
11	Partially satisfied	
12	Not satisfied	
Programme		
13	Not satisfied	Some of the later criteria are less relevant until screening has
14	Not satisfied	been approved in principle
15	Not satisfied	
16	Not satisfied	
17	Not applicable	
18	Not satisfied	
19	Partially satisfied	
20	Not yet applicable	
21	Not satisfied	
22	NA	

In terms of developing an economic case for screening, there are problems in generalisability of results to the UK from other countries, in terms of both the number of screen-positive participants and false-positive rates. The detection of incidental disease other than lung cancer also varied substantially between studies. The lack of robust and detailed UK data on stage from lung cancer registries has been identified in previous lung cancer-related technology appraisal reports and remains an issue when trying to model survival. There is also a lack of data about the current costs and utilisation of lung cancer services, which makes meaningful extrapolation of costs difficult.

Conclusions for NHS and NHS policy

In the authors' view, CT screening for lung cancer does not currently meet the accepted NSC criteria.

Table 17 summarises the current evidence, but most criteria are not satisfied, with no RCTs, no evidence of clinical effectiveness against mortality and no evidence of cost-effectiveness. Even if all the other criteria were satisfied, a screening programme would have to pass the cost per QALY hurdle; the threshold range generally followed by NICE is £20,000–30,000 per QALY, although it is far from certain that the NHS can afford as much as that.

CT studies planned or in progress

Table 18 briefly outlines the CT screening studies for lung cancer that were identified with the search strategy as being underway at present. Some of these studies will eventually provide information relating to the effect of screening on mortality. Others may add to our understanding of the natural history of NCNs detected by screening, about the protocols used for screening and about which populations will benefit most from screening. Only the LUCAS trial is anticipated to occur in the UK, but it currently remains unfunded. Although the US trial[117] has progressed through the pilot stage, it will not provide answers

TABLE 18 Studies of CT screening planned or in progress

Trial	Country	Methods	Timing and current status
DEPISCAN[118]	France	RCT of CT vs CXR. Pilot of 1000 smokers. Full trial 20,000. Outcomes include economics and QoL	Unclear: protocol published in 2002
LUCAS[119]	UK	Pilot 2000 smokers. Full trial 40,000–60,000 smokers RCT of CT vs usual care. Outcomes include QoL and economics	Currently unfunded
ACRIN and NCI Lung Screening Trial[117]	USA	RCT of CT vs CXR. 50,000 smokers. Pilot study known as LSS[27]	Recruiting in 2003 with anticipated end in 2009
Paci[120]	Italy	RCT of CT vs usual care. 1500 smokers. Using ELCAP protocol for collaboration. ?10,000 participants in full trial	Apparently 2002–2007, but financial support was still being confirmed
Denmark[120]	Denmark	RCT of CT vs usual care. Full trial of 10,000 current smokers. Outcomes include QoL and economics	Unknown
Holland[120]	Holland	RCT of CT vs usual care. Full trial of 24,000 smokers. Outcomes include QoL and economics	Unknown
Norway[120]	Norway	RCT of CT vs usual care. Full trial of 24,000 smokers	Unknown

ACRIN, American College of Radiology Network; NCI, National Cancer Institute.

about the effect of screening on lung cancer mortality for approximately 10 years. In the meantime, addressing the other research needs above would facilitate a rapid response to studies if they did demonstrate effectiveness of screening.

Research needs

In terms of what information is needed to make such a decision, the following research needs were identified.

- RCT evidence is needed that CT screening reduces mortality, either with whole-population screening or for particular subgroups.
- UK data about the rate of positive screening CT and detected lung cancers could be obtained from an RCT or a cohort study. Even relatively small-scale studies would provide valuable information when trying to assess the generalisability of RCT data currently being conducted elsewhere.
- There is a need to understand better the natural history and epidemiology of screening-detected lung cancers, particularly small, well-

differentiated adenocarcinomas. This could be met, in part, by lung cancer screening RCT or cohort studies, but a review of existing published epidemiological and pathological data along with primary analysis of UK lung cancer epidemiology would valuably inform current understanding.
- Information about the quality of life impact of CT screening, acceptability of screening, and uptake and retention rates in the UK would be valuable in any future assessment of the cost-effectiveness of screening in the UK.
- Increased routine collection is needed of UK health service data regarding resource availability, utilisation and safety data for lung cancer management and services.
- Research is needed into the feasibility and methods of tracking those who were previously occupationally exposed to lung carcinogens.

The authors believe that screening for lung cancer using CT cannot be recommended based on current evidence and, while more definitive evidence of effectiveness is being sought, priority should be given to reducing exposure to risk factors for lung cancer, in particular smoking.

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Contribution of authors

Dr Corri Black (Clinical Lecturer in Public Health), as lead author, drafted the protocol, conducted the review of effectiveness, undertook data extraction and prepared the manuscript for publication. Professor Adrian Bagust (Professor of Health Economics) conducted the economic appraisal and contributed to the economic literature review. Ms Angela Boland (research assistant) conducted the economic literature review and prepared the results for publication, assisted by Ms C McLeod (research assistant). Dr Shonagh Walker (Specialist Registrar in Radiology), Ms Robyn De Verteuil (research fellow) and Ms Sian Thomas (systematic reviewer) undertook the data extraction. Professor Jon Ayres (Professor of Occupational, Environmental and Respiratory Medicine) reviewed the epidemiology of lung cancer in high-risk occupational groups and provided methodological and expert advice throughout, reading and commenting on drafts. Professors Norman Waugh (Chair of Public Health) and David Godden (Director of the Centre for Rural Health, Consultant in Respiratory Medicine) provided expert input throughout the project, advising on methodology, providing expert input, and reading and commenting on drafts. All authors assisted in preparing the manuscript, reading and commenting on drafts, and reading the final draft.

Publication information

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The HTA Group carries out independent health technology assessments (TARs) for the UK HTA Programme, which commissions TARs for NICE and other bodies, such as the National Screening Committee. In addition, a joint venture between the Health Services Research Unit at Aberdeen and the Medical Care Research Unit at Sheffield University forms the Review Body for Interventional Procedures Programme within NICE (ReBIP). ReBIP undertakes systematic reviews and establishes UK registries, where appropriate, to collect and analyse data on the efficacy and safety of selected procedures, and to produce an evaluation report.

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Appendix 1
Summary of occupational associated risk
of lung cancer

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Study	Exposure	Workforce	Effect size (estimated RR)	Comments
Medline Tweedale, 2004[121]	ETS	–	–	Meta-analysis suggests no dose–response effect
Baan, 2004[122]	Vitreous fibres	Wide range	None	Report of IARC review group. Concluded that there was inadequate evidence to assess carcinogenicity
Armstrong, 2004[123]	PAHs	Full range	1.2 (1.19–1.29) at 100 μg m^{-3}·years	Meta-analysis
		Coke oven, gas workers and aluminium workers	1.15–1.17	
		Asphalt workers	17.5 (4.21–72.28)	
		Chimney sweeps	16.2 (1.64–160.7)	
Kurihara, 2004[124]	Silica	Many	Silica 1.32 (1.23–1.41) Silicosis 2.37 (1.98–2.84)	Meta-analysis. Excluded papers that did not account for asbestos or radioactive co-exposures. Silica without silicosis probably does not cause lung cancer. Some argument among experts about this
Neuberger, 2003[125]	All occupational exposures	Review of the literature (non-systematic)	–	An IARC critical review asking for more research into occupational lung cancer in women and in non-smokers. Believes there is evidence for lung cancer in non-smokers for asbestos, ETS, radon products and, possibly, arsenic
Gordon, 2003[126]	Beryllium	Machining of beryllium, ceramics or alloys	1.22 and 1.26	Non-systematic review. Lung cancer seen more in those with acute berylliosis and where higher exposures experienced, i.e. before 1950
Mastrangelo, 2002[127]	Textile fibres	Cotton workers	1936: 0.4 1990s: 0.7	Although RR lower than 1, RRs increasing over time. High risk for nasal cancer (4.14)
Verougstraete, 2002[128]	Cadmium	Many	Meta-SMR 120 (103–139)	Cadmium effect more marked with co-exposure to arsenic, chromium or nickel. Important point
Berrigan, 2002[129]	MMVFs	Glass wool Glass filament Rock wool	1.23 (1.10–1.38) 1.08 (0.93–1.26) 1.32 (1.15–1.52)	Superseded by Baan and Grosse for the present purposes.
Greenberg, 2001[130]	Chemicals	Chemical industry workers	1.12 (1.05–1.19)	SMRs for chromium and other chemical exposures range from 2 to 8. For one study on bischloromethyl ether (ion-exchange resin), SMR-9.26

| Study	Exposure	Workforce	Effect Size (estimated RR)	Comments
Morgenstern, 2001[131]	Chemicals and low level-ionising radiation	Employees at Rocketdyne/Atomics International	Dose cf 200 mSv leads to increased risk of lung cancer but falls with increasing lags SMR for leukaemia 1.6 (0.95–2.42)	Small numbers of cases; probable healthy worker effect
Hodgson, 2000[132]	Asbestos	Chrysotile workers Crocodilite and amosite	0.1–0.5% 5% excess lung cancers for f.mill.years	Risk for lung cancer lies between linear and square relationship
Zhou, 2000[133]	ETS	Women (non-smokers)	1.2 (1.12–1.29)	Case–control studies 1.9. Cohort studies 1.29
Lipsett, 1999[134]	Exposure to diesel exhaust	A range	1.47 (1.29–1.67)	Meta-analysis of 30 studies. Considerable heterogeneity
Collins, 1997[135]	Exposure to acrylonitrile	–	0.9 (0.9–1.1)	Publication bias. No effect on lung cancer. Effect on bladder cancer, but probably due to co-exposure
Tolbert, 1997[136]	Mineral oil	Metal machine workers, print press operaters, cotton and jute spinners	RRs range from 0.6 to 2.8 with one real oddity at 19.3 (women only employed in grinding ever). Pressmen more likely to have a positive effect than metalworkers	Wide ranging review: 21 papers addressing lung cancer and mineral oil exposure
Paddle, 1997[137]	Chromium	–	–	Highlights difficulty with differential exposures; so did not estimate an effect size, yet recommended continued surveillance of this workforce
Steenland, 1996[138]	–	–	Arsenic 3.69, nickel 1.56, chromium 2.78, diesel 1.31; cadmium 1.49, asbestos 2.00, asbestotics 5.91	Important point about past high exposures and falling exposures over time
Sullivan, 1995[139]	Various	Construction industry	Broad statements around 'increased risk' but few specific data given and then very selective	Increased rates apply to asbestos and silica exposure
Fu, 1995[140]	Inorganic lead	–	1.29 (1.1–1.5), for heavily exposed 1.42	In many studies smoking not adequately accounted for and probably also co-exposures to cadmium

Study	Exposure	Workforce	Effect Size (estimated RR)	Comments
Sjogren 1994,[141]	Stainless steel welding fume	Stainless steel welders	1.94 (1.28–2.93)	Meta-analysis of 5 studies accounting for smoking and asbestos. Does not apply to mild steel welding
EMBASE				
Finkelstein, 2004[142]	Asbestos and welding fume	Plumbers	1.27 (1.13–1.42)	
Goodman, 2004[143]	Asbestos, possibly diesel fume	Motor vehicle mechanics	1.09 (0.92–1.28)	This estimate was limited to those studies that used adequate control for smoking
Wong, 2000[144]	Petroleum	Petroleum workers	No increase in any cases	Large meta-analysis. Only possible positive was a trend towards an increase in prostate cancer
Bhatia, 1998[145]	Diesel exhaust	–	Pooled RR 1.33 (1.24–1.44)	Cohort studies with internal comparisons are 1.43 (1.29–1.50)
Steenland, 1997[146]	Silica	Foundry workers, pottery workers, brick workers, miners	Silicosis 2.3 (2.2–2.4)	Meta-analysis of 19 studies
Moulin, 1998[147]	Welding fumes	Welders	1.38 (1.29–1.48)	Broadly the same whether they are working in shipyards or not. Authors conclude a 30–40% increase in the relative risk of lung cancer probably due to hexavalent chromium and nickel. Asbestos may play a part
Merler, 1997[148]	Asbestos	–	–	This is specifically a surveillance paper. States that there is no evidence that screening for lung cancer using CXR reduces mortality

Search strategy used on MEDLINE and EMBASE; with the key terms 'respiratory tract neoplasm' and 'occupational disease', 'occupational', 'environmental exposure' or 'workplace' and limiting to English-language reviews since 1994, identified 28 useful reviews of the risk of lung cancer associated with specific workplace exposures.

ETS, environmental tobacco smoke; MMVF, man-made vitreous fibre; SMR, standardised mortality ratio.

Appendix 2

Literature search results
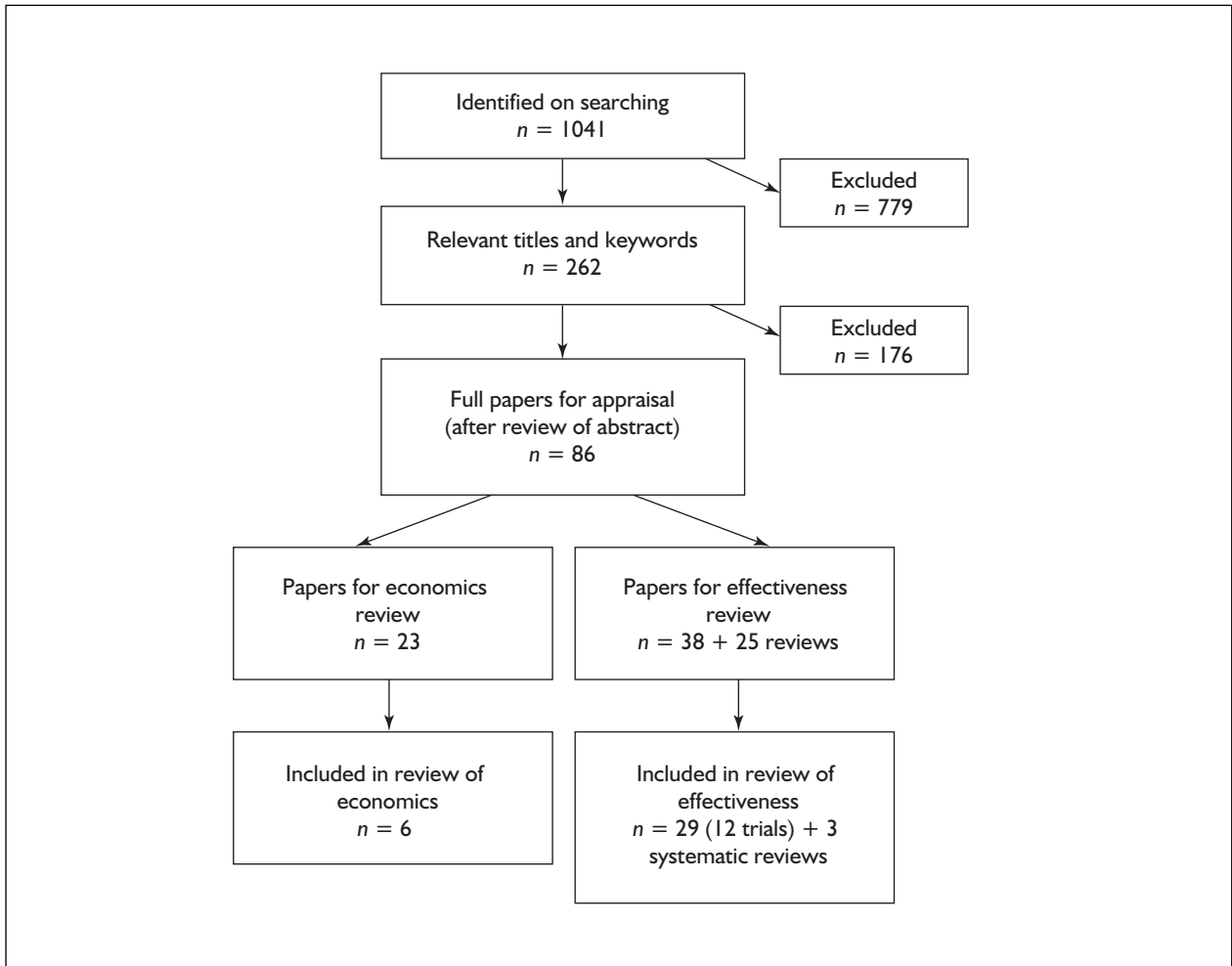
Flowchart of identification and inclusion of studies: systematic reviews, RCTs and other trials. Reviews were included if English language only.

Appendix 3

Search strategy

The following search terms were used to identify relevant articles:

MEDLINE

1994–2005
 1. exp Lung Neoplasms/all subheadings
 2. exp Carcinoma, Non-Small-Cell Lung/
 3. exp Carcinoma, Small Cell/
 4. lung cancer$
 5. lung neoplasm$
 6. small cell carcinoma
 7. lung adj1 carcinoma
 8. 1 or 2 or 3 or 4 or 5 or 6 or 7
 9. exp Mass Screening/all subheadings
10. screen$
11. exp Tomography, X-Ray Computed/all subheadings
12. CT screening OR CT scan$
13. 9 or 10 or 11 or 12
14. 8 and 13

Last searched 1 February 2005

Embase

1994–2005
 1. exp Computer Assisted Tomography/ or exp Spiral Computer Assisted Tomography/all subheadings
 2. exp MASS SCREENING/ or exp SCREENING/
 3. CT scanning
 4. CT screening
 5. computer assisted tomography
 6. 1 or 2 or 3 or 4 or 5
 7. exp cancer screening/
 8. exp Lung Cancer/all subheadings
 9. exp Lung Tumor/all subheadings
10. exp Lung Nodule/all subheadings
11. exp lung carcinoma/ or exp lung sarcoma/
12. lung cancer
13. lung neoplasm$
14. lung tumour$
15. lung tumor$
16. lung carcinoma$
17. lung nodule$
18. lung sarcoma$

19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 6 and 19
21. lung$
22. 7 and 21
23. 20 or 22

Last searched 1 February 2005

The Cochrane Library

Issue 3 2004 (including CRD databases DARE, NHS EED and HTA)
Searched on lung neoplasms (MESH exp all trees) or lung cancer or lung neoplasm* AND Tomography, X-ray computed (MESH exp all trees) or CT screening or CT scanning.

Bandolier

Searched on lung cancer, CT screening, cancer.

American Society of Clinical Oncology (ASCO) meeting abstracts

Searched on lung cancer screening, CT screening and lung, computed tomography and screening, CT scanning, whole body, full body.

Science Citation Index and Social Science Citation Index

1994–2004

ISI Proceedings
Searched lung cancer OR lung neoplasm* AND CT Scan* OR CT Screen* OR computer assisted tomography

HMIC

Searched exp lung cancer AND screening OR exp mass screening OR screening policy OR screening

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services. Also searched cancer screening OR screening programmes.

ReFeR (Research Register)

Searched lung cancer, lung AND screening, cancer AND screening, computed tomography, CT scanning, CT screening.

National Research Register

Searched exp lung neoplasms (MESH) AND mass screening (MESH), lung cancer AND mass screening, cancer AND CT screen*.

Appendix 4
Data extraction summaries

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Gohagan, 2004, USA[28] Design: RCT vs CXR Funding: NCI (not commercial)	Selection: population Age: 55–74 y Smoking: 30 pack-year (quit <10 y) High risk: yes	Definition: NCN Size: > 3 mm (any for spiculated NCN) No. of NCN: 1–6	HRCT: not specified Follow-up: CT controls (not specified) Biopsy: indicated where necessary	**Screened:** CT: 1586 CXR: 1550 **Positive scan:** CT: 20.5% CXR: 9.8% **Lung cancer:** CT: 30 (1.9%) CXR: 7 (0.5% **Resected:** No data **Diagnosis AEs:** CT: 6 CXR: 6 **5-y survival:** no data **QoL:** no data

Quality
Randomisation? Adequate
Allocation concealment? Not adequately described
Similar at baseline? Adequate
Eligibility criteria specified? Adequate
Withdrawals described? Only baseline screen reported
Outcome valid? Adequate
Follow-up adequate? Pilot study

Comments
NNS to detect 1 lung cancer = 53
NNS to detect 1 resectable lung cancer = 99
1.5% of screening CT examinations led to biopsy for benign disease

AE, adverse event.

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Garg, 2002, USA[27] Design: RCT vs no screening Funding: independent	Selection: population (Veterans Affairs medical centres) Age: 50–80 y Smoking: 30 pack-years High risk: yes; atypical sputum cytology+ COPD (*n* = 55)	Definition: NCN Size: any No. of NCN: 1–6	Follow-up: nodules ≤ 5 mm repeat HRCT at 3, 6, 12, 24 months 6–10 mm individual assessment >10 mm: enhanced CT then biopsy	**Screened:** CT: 92 No screen: 98 **Positive scan:** 33% **Lung cancer:** CT: 3 (3.2%) **No screen:** NR not reported **Resected:** NR **AEs:** no data **5-yr survival:** no data **QoL:** no data

Quality
Number of cancers in the text does not match table data (table data used)
Randomisation? Not adequately described
Allocation concealment? Not adequately described
Similar at baseline? Adequate
Eligibility criteria specified? Adequate
Withdrawals described? Only baseline screen reported
Outcome valid? Adequate
Follow-up adequate? No; not for mortality

Comments
NNS to detect 1 lung cancer = 31
NNS to detect 1 resectable lung cancer = NR

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
ELCAP, 2001, USA[30] Design: no comparator group Funding: NIH + Eastman – Kodak Corporation + General Electric Corporation	Selection: population Age: median 60+ y Smoking: 10 pack-years High risk: asbestos exposure in 14%	Definition: NCN or ground glass Size: any No. of NCN: 1–6	All: HRCT immediately, antibiotics then HRCT at 1 month Follow-up: ≤ 5 mm HRCT at 3, 6, 12, 24 months Biopsy: >5mm	**Screened:** Baseline: 1000 Incidence: 1184 **Positive scan:** Baseline: 23.3% Incidence: 3.4% **Lung cancer:** Baseline: 27 (2.7%) Incidence: 7 (0.6%) **AEs:** no complications from biopsy **5-y survival:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Interim report
Withdrawals described? Adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
Also identified 4 mediastinal/central tumours; not included in total by trialists
NNS to detect 1 lung cancer = 37 (baseline); 169 (incidence)
NNS to detect 1 resectable lung cancer = 37 (baseline); 197 (incidence)
0.2% of screenees offered biopsy for what was eventually confirmed as benign disease from baseline round

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Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Kaneko, 2002, Japan[37] Design: no comparator group Funding: non-commercial	Selection: population Age: 40+ y Smoking: 20 pack-years	Definition: (a) inadequate image (b) normal (c) scar lesion caused by previous inflammatory episode (d) benign tumour or an active inflammatory disease (e) suspected lung cancer Size: any No. of NCN: 1 or more	Follow-up: if graded (d) or (e) followed up with HRCT If still considered possibly malignant then biopsied	**Screened:** Baseline: 1611 Incidence: 7891 **Positive scan:** Baseline: 11.5% Incidence: 9.1% **Lung cancer:** Baseline: 13 (0.8%) Incidence: 19 (0.2%) **Resected:** Baseline: 12 Incidence: 17 **5-y survival:** 71%, with overall higher survival rate for those detected at baseline screening (76.2% vs 64.9%) **Lung cancer mortality:** no data **Surgical AEs:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Not adequate
Comparator group? None
Eligibility criteria described? adequate
Follow-up adequate? 5-year follow-up for some participants
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
Also found 3 cancers from sputum cytology alone (CT negative)
NNS to detect 1 lung cancer =115 (baseline); 420 (incidence)
NNS to detect 1 resectable lung cancer =134 (baseline); 464 (incidence)
0.25% of screening CT examinations led to biopsy for benign disease

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Diederich, 2004, Germany[40] Design: no comparator group Funding: non-commercial	Selection: population Age: 40+ y Smoking: 20 pack-years	Definition: NCN Size: any No. of NCN: 1 or more	Follow-up: All: immediate thin-section LDCT <10 mm: follow-up with HRCT at 3, 6, 12, 24 months >10 mm: biopsy immediately if suspected malignant (otherwise follow-up as above) If growth then contrast-enhanced CT and/or PET used	**Screened:** Baseline: 817 Incidence: 1735 **Positive scan:** Baseline: 43% Incidence: 5.1% **Lung cancer:** Baseline: 17 (2.1%) Incidence: 3 (0.2%) **Resected:** Baseline: 16 (100%) Incidence: 3 (100%) **5-y survival:** no data **AEs:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Interim report
Withdrawals described? Adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
Funding limitations resulted in changes to follow-up procedures during trial. Reported as number of lesions rather than people, therefore data extraction complicated. Large numbers of patients lost to follow-up

NNS to detect 1 lung cancer = 48 (baseline); 578 (incidence)
NNS to detect 1 resectable lung cancer = 51 (baseline); 578 (incidence)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Sone, 2001, Japan[29] Design: no comparator group Funding: non-commercial	Selection: population Age: 40+ y Smoking: smokers and non-smokers High risk: dependent on smoking status	Definition: (A) examination unsatisfactory; (B) normal; (C) lung abnormality of little clinical importance; (D) non-cancerous lung lesion; (Ed) non-cancerous but suspicious lung lesion; (E) suspicion of lung cancer; (F) small lung nodule (<3 mm in diameter) Ed, E or F seem to be considered suspicious Size: any No. of NCN: any	Follow-up: HRCT for Ed, E and F. If nodules indeterminate then follow-up CT at 3, 6, 12, 18, 30 months Biopsy: indicated 'where necessary'	**Screened:** Baseline: 5483 Incidence: 8303 **Positive scan:** Baseline: 5.1% Incidence: 3.7% **Lung cancer:** Baseline: 22 (0.4%) Incidence: 34 (0.4%) **Resected:** Baseline: 22 Incidence: 34 **AEs:** no data **5-yr survival:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Not adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Not adequate: 5-year survival only for people with tumours detected at baseline
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 249 (baseline); 755 (incidence)
NNS to detect 1 resectable lung cancer = 249 (baseline); 755 (incidence)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Swenson, 2003, USA[46] Design: no comparator group Funding: non-commercial	Selection: population Age: 50–85 y Smoking: 20 pack-years (quit <10 y)	Definition: NCN Size: any No. of NCN: 1 or more	Follow-up: <4 mm: HRCT within 6 months 4–8 mm: HRCT within 3 months 8–20 mm: HRCT ASAP Immediate biopsy for nodules >20 mm Repeat scans for 2 y to assess for growth (frequency not specified) Biopsy: if >20 mm or is indicated from HRCT scan or if growth	**Screened:** Baseline: 1520 Incidence: 2916 **Positive scan:** Baseline: 51% Incidence: 11.5% **Lung cancer:** Baseline: 26 (1.7%) Incidence: 9 (0.3%) **AEs:** 7 benign lesions biopsied **5-y survival:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? 2 year follow-up; not adequate for survival
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 58 (baseline); 324 (incidence)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Pastorino, 2003, Italy[50] Design: no comparator group Funding: non-commercial	Selection: population Age: 50–84 y Smoking: 20 pack-years High risk: yes	Definition: NCN Size: >5 mm No. of NCN: 1 or more	Follow-up: >5 mm follow-up with HRCT within 1 month. If >5 mm and density >0 Hounsfield units on HRCT then assessment of contrast enhancement. Nodules ≥ 7 mm on HRCT followed by PET Biopsy: nodules biopsied if positive enhancement (>30 Hounsfield units) or positive PET scan or NCN ≥ 20 mm unless unequivocally benign at HRCT. Also biopsied if >7 mm in contrast enhancement on CT but negative PET or >7 mm with no enhancement but positive PET	**Screened:** Baseline: 1035 Incidence: 996 **Positive scan:** Baseline (5.9%) Incidence (3.4%) **Lung cancer:** Baseline: 11 (1.1%) Incidence: 11 (1.1%) **Resected:** Baseline: 10 Incidence: 11 **5-y survival:** no data **AEs:** 6 resections for benign disease **QoL:** no data

Quality
Sample representative? Not described
Groups described? Adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? 2-year report of 5-year project
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 94 (baseline); 91 (incidence)
NNS to detect 1 resectable lung cancer = 104 (baseline); 91 (incidence)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Nawa, 2002, Japan[51] Design: no comparator group Funding: not stated	Selection: employee health insurance group Age: 50+ y Smoking: some current and past smokers High risk: some (current and past smokers)	Definition: NCN Size: >7 mm No. of NCN: 1–6	Follow-up: NCNs >7 mm: detailed CT at 1 month. NCNs 8–10 mm: examined with detailed CT scans at 3, 6 months Biopsy: growth or NCNs ≥ 11 mm	**Screened:** Baseline: 7956 Incidence: 5568 **Positive scan:** Baseline: (6.8%) Incidence: (2.7%) **Lung cancer:** Baseline: 36 (0.45%) Incidence: 4 (0.07%) **Resected:** no data **AEs:** 18 underwent biopsy for benign disease **5-y survival:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Not adequate
Comparator group? None
Eligibility criteria described? Not adequate
Follow-up adequate? Interim report
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 221 (baseline); 1392 (incidence)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
MacRedmond, 2004, Ireland[52] Design: no comparator group Funding: non-commercial	Selection: population Age: 50+ y Smoking: 10 pack-years, still smoking at 45 y High risk: yes	Definition: NCN Size: any No. of NCN: 1–6	Follow-up: positive screen follow-up with HRCT for nodules ≤ 5 mm at 6, 12, 24 months. 6–10 mm: individual assessment indicating further follow-up (as for ≤ 5 mm) or biopsy Biopsy: >10 mm	**Screened:** Baseline: 449 **Positive scan:** Baseline: 24% **Lung cancer:** Baseline: 2 (0.4%) **Resected:** Baseline: 1 (100%) **AEs:** benign hamartoma removed **5-y survival:** no data **QoL:** no data

Quality
Sample representative? Not described
Groups described? Adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Not for 5-year survival
Withdrawals described? Only baseline screen reported
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 225 (baseline)
NNS to detect 1 resectable lung cancer = 449 (baseline)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Huuskonen, 2002, Finland[53] Design: no comparator group Funding: non-commercial	Selection: population Age: mean age 63 (38–81) y Smoking: average 24 pack-years High risk: yes; all with occupational exposure to asbestos	Definition: NCN Size: > 5mm No. of NCN: 1 or more	Follow-up: poorly reported. Biopsy: 'when malignancy could not be ruled out'; otherwise follow with CT	**Screened:** 602 **Positive scan:** 18.4% **Lung cancer:** 5 (0.8%) **Resected:** 1 **5-y survival:** all died within 21 months of prognosis **AEs:** no complications from biopsy **QoL:** no data

Quality
Sample representative? Not described
Groups described? Adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Adequate (lung cancer patients all died, screen negatives followed for 3 years using cancer registry; no additional lung cancers reported)
Withdrawals described? Only baseline screen reported
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 120 (baseline)
NNS to detect 1 resectable lung cancer = 602 (baseline)

Reference and design	Study population and selection	Screening criteria	Diagnostic criteria	Outcome
Miller, 2004, USA[55] Design: cohort Funding: not reported	Selection: nuclear fuel workers Age: ≥ 45 y Smoking: 34% non-smokers; 15% current smokers; 51% ex-smokers (71% of whom quit ≥ 15 y earlier) High risk: yes; occupational exposure	Definition: not specified. Indeterminate or suspicious scans deemed positive Size: not specified No. of NCN: not specified	Follow-up: positive scan rescanned with HRCT. If scan remained indeterminate then rescans performed at 3-, 6-, 12-, 18-month intervals Biopsy: not specified	**Screened:** 3598 **Positive scan:** 32% **Lung cancer:** Baseline: 22 (0.64%) Incidence: 1 (%?) No other details of incidence screening reported **AEs:** no complications from biopsy **5-y survival:** no data **QoL:** no data

Quality
Reported as a brief letter with very little detail
Sample representative? Not described
Groups described? Not adequate
Comparator group? None
Eligibility criteria described? Adequate
Follow-up adequate? Not for 5-year survival
Withdrawals described? Not adequate
Outcome valid? Assessment of lung cancer valid. Not designed to assess mortality

Comments
NNS to detect 1 lung cancer = 163 (baseline)

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We look forward to hearing from you.