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Economic decision analysis model of screening for lung cancer

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Abstract

The objective of this study was to evaluate the potential clinical and economic implications of an annual lung cancer screening programme based on helical computed tomography (CT). A decision analysis model was created using combined data from the Surveillance, Epidemiology and End Results (SEER) registry public-use database and published results from the Early Lung Cancer Action Project (ELCAP). We found that under optimal conditions in a high risk cohort of patients between 60 and 74 years of age, annual lung cancer screening over a period of 5 years appears to be cost effective at approximately $19 000 per life year saved. A sensitivity analysis of the model to account for a 1-year decrease in survival benefit and changes in assumptions for incidence rate and costs generated cost effectiveness estimates ranging from approximately $10 800 to $62 000 per life year saved. Based on the assumptions embedded in this model, annual screening of high risk elderly patients for lung cancer may be cost effective under optimal conditions, but longer term data are needed to confirm if this will be borne out in practice.

Keywords: Lung cancer screening; Cost-effectiveness; Decision analysis; Helical computed tomography

1. Introduction

Lung cancer is one of the most deadly cancers, with an incidence rate almost equal to the mortality rate [1]. Several attributes of lung cancer suggest it may be a good candidate for screening, including its high mortality rate, differential survival by stage of disease, current low rate of early detection (due to lack of symptoms early in disease), availability of effective intervention for very early disease, and high costs associated with treatments for later stages of the disease [2]. At present, screening for early detection of lung cancer is not recommended, in part due to the failure of early clinical studies to demonstrate any reduction in mortality from lung cancer evaluations based on sputum cytology and/or chest X-ray [3]. However, with the introduction of helical computed tomography (CT), a new modality that can detect nodules as small as a few millimetres with better diagnostic accuracy, short scanning times, and low radiation exposure [4,5], the potential benefits of lung cancer screening are being re-examined. Promising results from the Early Lung Cancer Action Project (ELCAP) have led to the speculation that screening for lung cancer using helical CT will not only have a dramatic impact on survival, but also be reasonably cost-effective [5–7].

We previously examined the feasibility of lung cancer screening with helical CT based on a one-time prevalence screen [8]. The goal of the current study was to evaluate the potential clinical and economic implications of an annual lung cancer screening programme using a decision analysis model that combined data from the Surveillance, Epidemiology and End Results (SEER) registry public-use database [9] and published results from the ELCAP [5].

2. Patients and methods

2.1. Decision analysis model

We developed a decision analytic model to compare an annual lung cancer screening strategy to no screening

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in terms of expected outcomes (survival) and costs over a time horizon of 5 years. This analysis was framed based on the assumption that only individuals between the ages of 60 and 74 years of age and at high risk of lung cancer (based on incidence rates) would be screened (Fig. 1). For each year in the analysis, an individual could be diagnosed with lung cancer or not. If no lung cancer diagnosis was made, the individual either lived or died from other causes based on life table estimates for sex and age group. If diagnosed with lung cancer, the individual either lived with lung cancer or died from lung cancer based on survival estimates by sex, age group, stage of disease, and tumour size (Fig. 2). All individuals who were alive at the end of year 1 underwent screening the next year, and the process repeated. The incremental cost-effectiveness ratio (CER) for screening compared with no screening was calculated based on the difference in cumulative survival and costs over a time horizon of 5 years. All analyses of the SEER database were done using SEER Stat 2.0 software, and the decision analysis model was created in an Excel 5.0 spreadsheet. Our model assumes that the capital equipment and resources are already in place to establish a lung cancer screening programme with helical CT, and so represents the 'steady state' when such a programme would be operating.

2.2. Population distribution and lung cancer incidence

Under the scenario of 'no screening', the hypothetical cohort of 100 000 individuals was distributed into categories by sex and 5-year age groupings according to the US population distribution reported by the US Bureau of the Census for 1998. The incidence rate of lung cancer (lung and bronchus) per 100 000 was determined by sex, 5-year age grouping (60–64, 65–69 and 70–74 years), and disease stage (stage I, stage II, stage IIIA, stage IIIB and stage IV) from the SEER registry public-use database using 11 registries for the period 1992–1996. This analysis of the SEER data includes both small cell lung cancer and non-small cell lung cancer because the ELCAP data do not distinguish between cancer types. However, small cell lung cancer is less common than non-small cell lung cancer, which accounts for approximately 85% of incident cases [10]. The 5-year survival rate varies widely depending on disease stage, from approximately 50% for patients diagnosed in stage I non-small cell lung cancer to 2% for those with extensive small cell lung cancer or stages III and IV non-small cell lung cancer [10]. For stage I only, cases were further subdivided according to tumour size ($\leqslant$10 mm, 11–20 mm, 21–45 mm, $>$45 mm), using the extent of disease classification. Actual numbers of cases were calculated from the incidence rates and number of individuals in each sex and age group category, according to the SEER stage distribution. The number of tumours were distributed proportionally by stage, size, age and sex according to the known distribution pattern for tumours with a stage assignment [11] to reflect the total number of tumours, including those classified as unknown and unstaged.

Finally, for the first year of the screening programme, the actual numbers were adjusted using the same pattern of distribution, so that the total proportion of tumours in the screened population, which represents the prevalence of lung cancer (2.7%), was the same as that reported by ELCAP [5], where the cohort had a median age of 67 years and a median number of pack-years of smoking of 45 years. This represents a high-risk

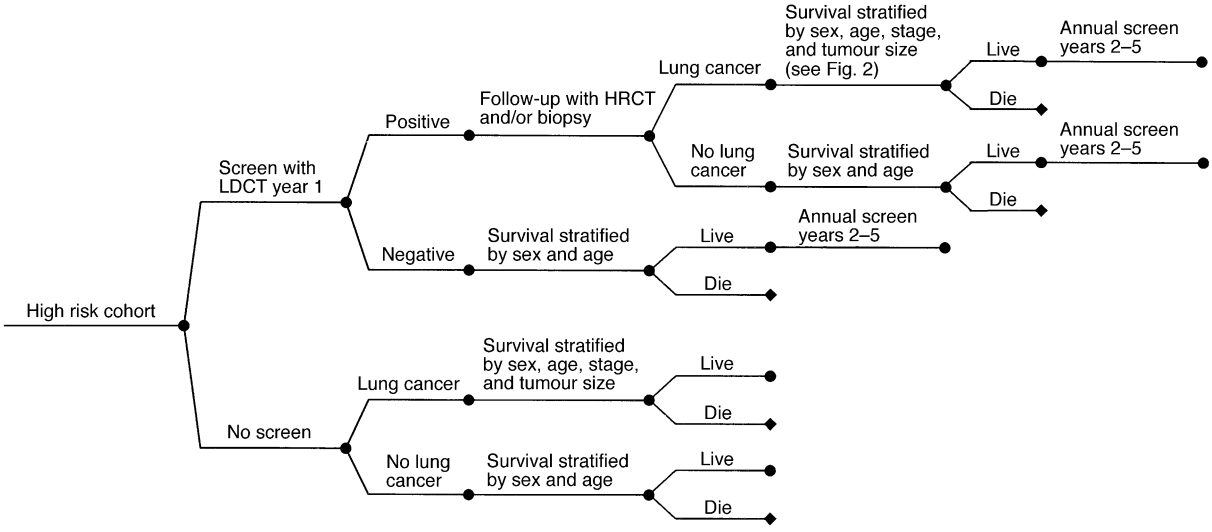

Fig. 1. Decision analysis model of survival with and without annual low dose helical computed tomography (LDCT) screening for lung cancer. Patients with a positive LDCT would receive follow-up tests, including high resolution computed tomography (HRCT) and/or biopsy.

group of the type that would be targeted for lung cancer screening, although the actual prevalence of lung cancer has not been established. Subsequent years reflected the incidence rate found from the SEER database of approximately 0.3% per year.

2.3. Survival

Cumulative estimates of survival for lung cancer cases by year were estimated from the SEER database using nine registries for the period 1973–1996. Only patients

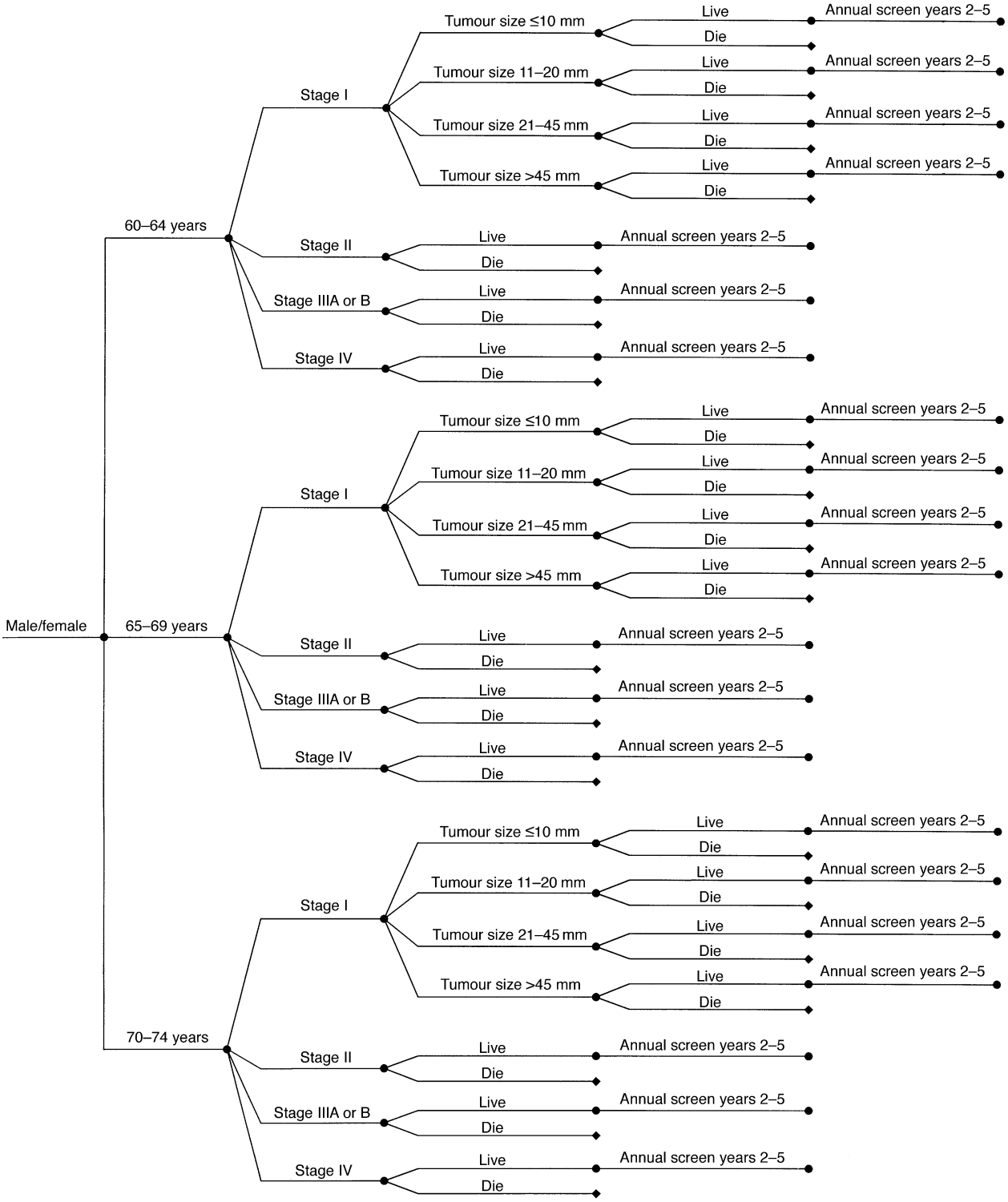

Fig. 2. Stratification scheme for survival of patients diagnosed with lung cancer. In this arm of the model, the survival of patients with lung cancer identified by screening in year 1 (see Fig. 1) is stratified by sex (male, female), age (60–64, 65–69 and 70–74 years), stage (I, II, III, IV) and tumour size ($\leqslant$10, 11–20, 21–45, and $>$45 mm).

with complete demographic information and pathologically confirmed invasive carcinoma were included. Patients were excluded if they had more than one primary cancer, or if the lung cancer was first documented on the death certificate or autopsy report. Expected rates of survival for the general population were those for the 1990 US population standardised by sex, age group and race.

For some analyses, quality adjusted life years (QALY) were calculated. QALYs combine both life expectancy and quality of life into one measure and are calculated by multiplying a utility weight for each health state of interest by the time spent in each health state. For example, if an individual lives 1 year in a state with a utility weight of 0.5, then this is equivalent to 0.5 years in perfect health (utility weight of 1.0). Utility weights were obtained from the literature as reported by Earle and colleagues [12]. They were as follows: Local (utility weight 0.88), Regional (utility weight 0.80), and Distant, Metastatic (utility weight 0.69). In our analysis, we assumed that stage I was represented by Local, stages II and III by Regional, and stage IV by Distant, Metastatic.

2.4. Detection of lung cancer and follow-up investigations in a screening programme

Under the scenario of 'screening with helical CT', an annual screening programme was considered. This program included a baseline scan with low dose helical CT, and follow-up as estimated from the baseline results reported by ELCAP [5]. Patients with non-calcified nodules identified on helical CT were recommended for a baseline high resolution CT and were subsequently either recommended for biopsy or follow-up with high resolution CT at 3, 6 and 12 months. The model assumed the same cancer detection rate of 100% and a false-positive rate of 21%, as in the baseline results of the ELCAP study. The detection of new cancers was assumed to be the same as the SEER incidence rate, which reflects clinically apparent cancers. In the absence of long-term follow-up data, these results were used to approximate the sensitivity and specificity of the screening. The impact of screening was modelled as a stage shift at diagnosis based on the observed distribution reported by ELCAP [5]. The same number of cancers was assumed to be identified in the screening and the non-screening scenarios, but the distribution by stage at time of diagnosis was adjusted. To simulate the impact of screening on stage shifting for diagnosis of lung cancer, the distribution by stage at diagnosis in the ELCAP cohort [5] was applied to the hypothetical high risk cohort. Although the total number of cancers remained the same in both scenarios, 85% were detected in stage I with screening, as compared with approximately 21% detected in stage I in the absence of screening. It was assumed that the age- and sex-adjusted survival experience of individuals diagnosed at early stages of disease through screening would be the same as that for individuals diagnosed at the same stage without screening.

2.5. Costs

All screening programme testing costs were estimated from 1999 Medicare reimbursement rates (national average). Helical CT scanning was assumed to cost $150 per scan based on local institutional estimates. Cost estimates for treatment of lung cancer by stage were obtained from the average annual Medicare payments by stage at diagnosis reported by Riley and colleagues [13], inflated to 1999 dollars using the medical care component of the Consumer's Price Index. Average annual costs of managing non-cancer patients over 65 years were estimated from Taplin and colleagues [14], which used information from the group health cooperative of Puget Sound to estimate costs, including total direct medical costs. Both costs and life years were discounted at 3% per year.

2.6. Model assumptions for costs and probability estimates

The model assumptions for the annual costs of patient management and costs for tests performed during screening and follow-up are shown in Table 1. These data show the annual cost of management for patients with lung cancer exceed that for patients without lung cancer. Moreover, the annual cost of management for patients in late stage disease (stage IV) is considerably higher than that for patients in stages III, II or I.

Estimates for the probabilities of CT scans and biopsies are presented in Table 2. The probability for a low dose helical CT scan is 1.00 since this test would be performed on all individuals that were part of a lung cancer screening programme. Estimates for the probabilities of high resolution CT and biopsy were from the ELCAP study [5] and represent the likelihood that an individual would have these follow-up procedures performed as a result of the initial helical CT scan findings.

2.7. Sensitivity analysis

A sensitivity analysis was performed in order to address some of the most important issues concerning the potential benefit of lung cancer screening, namely lead-time bias and overdiagnosis bias [15]. These issues are difficult to separate, but generally lead-time bias occurs in survival comparisons if screening advances the time of diagnosis without delaying the time of death, whereas overdiagnosis bias occurs if screening detects lesions that are not clinically important and would not impact survival [16–20]. As a proxy to account for these

Table 1
Model assumptions for costs associated with management, detection and follow-up for lung cancer screening

Item	Cost in 1999 US$	Source
Annual cost of management		
Patients with lung cancer		
Stage I	16 242	[13]
Stage II	28 731	[13]
Stage III	28 731	[13]
Stage IV	56 527	[13]
Patients without lung cancer	6146	[14]
Screening and follow-up		
Low dose helical CT scan	150	Local estimate
High resolution CT scan (CPT 71250)	280	1999 Medicare reimbursement rate
Thoracoscopy, with biopsy (CPT 32602)	430	1999 Medicare reimbursement rate
Office visit (CPT 99212)	30	1999 Medicare reimbursement rate

CT, computed tomography; CPT, current procedure terminology.

potential sources of bias, we assessed the cost effectiveness of annual lung cancer screening without and with a 1-year decrease in survival benefit. We did this by subtracting out 1 year of survival for each new case of cancer detected by screening in each of the 5 years. Although not truly an adjustment for bias, this approach allows for assessment of the potential impact of such biases on the cost-effectiveness ratio.

Sensitivity analyses were also performed to evaluate the effects of change in incidence rate, and change in the cost of screening and follow-up tests.

3. Results

3.1. Model-based predictions

The model predictions for life years and costs associated with annual screening for lung cancer versus no screening in a hypothetical cohort of 100 000 individuals over a period of 5 years is shown in Fig. 3. This analysis shows an increase in life years with annual screening for each of the 5 years. In the first year of screening, the total cost of managing the cohort is less than that for the no screen scenario. This is because a higher proportion of individuals with stage IV disease, for whom the cost of care is very high, would be included in the no screen cohort in the first year. Since most individuals with stage IV disease die within 12 months, the cost for the no screen cohort declines in subsequent years. The higher costs associated with annual screening in years 2–5 are due to both the costs associated with the screening programme itself as well as the additional costs incurred for healthcare of those individuals who are diagnosed with lung cancer earlier because of screening, and consequently continue to consume healthcare resources.

Table 2
Estimates for probabilities of CT scans and biopsies

Parameter	Estimate
Probability of low dose helical CT scan	1.00
Probability of follow-up high resolution CT	0.17
Probability of subsequent high resolution CT	0.08
Probability of biopsy	0.03

CT, computed tomography.

3.2. Life year and cost-effectiveness analysis

The effectiveness of annual lung cancer screening in terms of life years and the associated costs estimated by

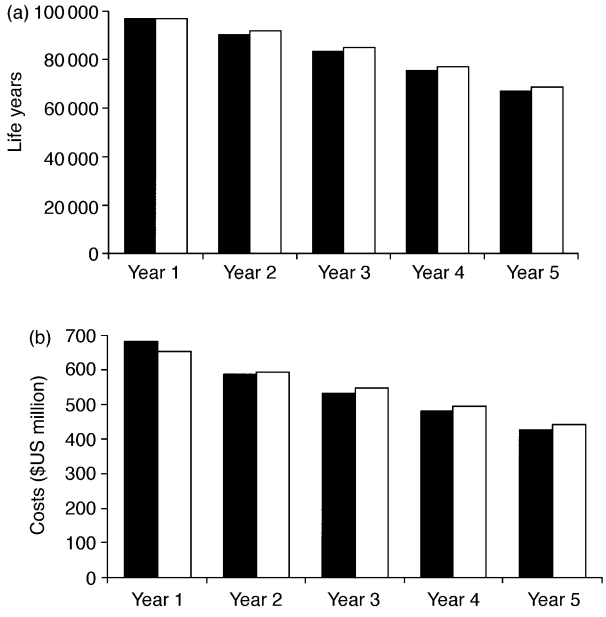

Fig. 3. (a) Summary of life years without (solid bars) and with (open bars) annual lung cancer screening of a high risk cohort of 100 000 people over age 60 years over a 5-year period. Life years were discounted at 3% per year. (b) Summary of costs without (solid bars) and with (open bars) annual lung cancer screening of a high risk cohort of 100 000 people over age 60 years over a 5-year period. Costs were discounted at 3% per year.

Table 3
Model results—cost-effectiveness of lung cancer screening

	No screening	Annual screening	Difference
Base model			
Life years	413 984	419 020	5036
Cost (millions US$)	2718	2814	96
Cost-effectiveness ratio (US$ per life year)			18 968
Cost-utility ratio (US$ per QALY)			19 533
With 1-year decrease in survival benefit			
Life years	413 984	415 532	1548
Cost (millions US$)	2718	2814	96
Cost-effectiveness ratio (US$ per life year)			61 723
Cost-utility ratio (US$ per QALY)			50 473

QALY, quality-adjusted life year.

the model with and without a 1-year decrease in survival benefit (our proxy for a 1-year lead-time bias) is presented in Table 3. Life years were estimated from annual cumulative survival rates for lung cancer cases for each category of sex, age group, stage and tumour size. Life years for non-lung cancer cases were estimated from annual cumulative survival rates for the US population for each category of sex and age group. The base model (discounted at 3%) estimates that a total of approximately 5000 life years would be gained over a 5-year time period for a cohort of 100 000 individuals through annual screening for lung cancer. At a cost of 96 million US dollars, the cost-effectiveness analysis for the base model indicates that annual screening would cost approximately $19 000 per life year saved and the cost utility ratio would be approximately $19 500 per QALY saved. With a one-year decrease in survival benefit, the model estimates that a total of 1548 life years would be generated over a 5-year time period for this cohort. At the same cost of about 96 million US dollars, the cost-effectiveness analysis for the model with a 1-year decrease in survival benefit indicates that annual screening for lung cancer would cost approximately $62 000 per life year saved and $50 000 per QALY saved.

3.3. Sensitivity analysis

Sensitivity analyses were performed to evaluate the effects of a 1-year decrease in survival benefit, change in incidence rate, and change in the cost of screening and follow-up tests (Fig. 4). The incorporation of a 1-year decrease in survival benefit had the greatest effect on the model predictions. However, even with an increase in the cost-effectiveness ratio from the baseline of $18 968–$61 723 per life year saved with a 1-year decrease in survival benefit, the annual screening programme would be considered reasonably cost effective. Lesser effects were observed with changes in the incidence rate. The baseline model assumed an incidence rate of 268 per 100 000 for years 2–5. A 2-fold increase in the incidence rate decreased the cost-effectiveness ratio to $14 449 per life year. Conversely, the cost-effectiveness ratio increased to $21 677 per life year if the incidence rate was reduced by half. Changes in the cost of screening and follow-up tests also influenced the model predictions. As expected, changes in the cost of low dose CT testing, which would be used as the primary screen, had a greater effect on cost-effective ratio than did changes in the cost of follow-up tests which would be performed only on patients identified as positive by screening. Reducing the cost of low dose CT testing from the baseline assumption of $150 to $50 led to a reduction in the cost-effectiveness ratio to $10 809 per life year. Conversely, increasing the cost of low dose CT testing to $300 and $400 increased the cost-effectiveness ratio to $31 205 and $39 364 per life year, respectively. By comparison, increasing the cost of high resolution CT testing from the baseline assumption of $280 to $400 increased the cost-effectiveness ratio to $19 561 per life year. In addition, increasing the cost of biopsy from the baseline assumption of $430 to $800 increased the cost-effectiveness ratio to $21,119 per life year.

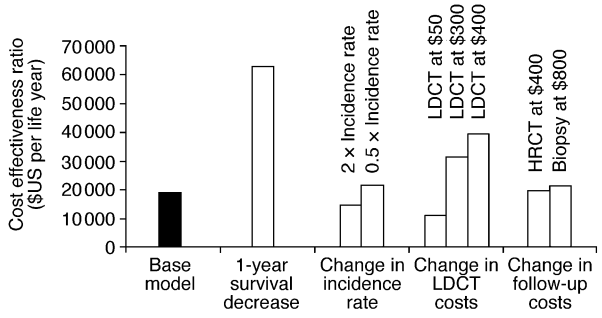

Fig. 4. Sensitivity analysis of the effects of a 1-year decrease in survival benefit, change in incidence rate, and change in the cost of screening and follow-up tests. The base model assumed an incidence rate of 268 per 100 000 and costs for screening and follow-up tests as follows: low dose helical CT (LDCT) = $150, high resolution computed tomography (HRCT) = $280 and biopsy = $430.

4. Discussion

Lung cancer is the leading cause of cancer-related death—lung cancer deaths account for more deaths in men and women than colon, breast, and prostate cancer-related deaths combined [21]. According to estimates from the SEER registry [9], the overall 5-year survival rate for persons diagnosed with lung cancer is approximately 14% in the US. However, the 5-year survival rate varies widely depending on disease stage, from 50% for patients diagnosed with localised disease to 2% for those with distant disease [10]. With surgical intervention, the 5-year survival rate improves to 60–70% for patients with stage I lung cancer, and reaches as high as 70–80% for patients with very early disease (stage 1A or TINO). In addition, patients with smaller tumours have better outcomes than those with larger tumours [2,6,22–25]. These observations suggest that patients in the earlier stages of disease identified through a screening programme would have a very good prognosis.

Low dose helical CT is a promising new technology for early detection of lung cancer . With its better diagnostic accuracy combined with short scanning time and relatively low cost, there has been speculation that helical CT scanning could be an effective and cost-effective approach to lung cancer screening. In earlier work, we developed a feasibility model based on a one-time prevalence screen for lung cancer [8]. We now have extended our initial work in order to understand the implications of establishing an annual lung cancer screening programme with helical CT scanning. Under the assumptions of the base model in this study, we found that in a very high-risk cohort of patients between 60 and 74 years of age, annual screening for lung cancer over a period of 5 years appears to be cost-effective at $18 968 per life year saved. With a 1-year decrease in survival benefit incorporated into the model, annual screening remained reasonably cost effective at $61 723 per life year saved. In addition, sensitivity analyses showed relatively small effects on model predictions with changes in incidence rate and costs for screening and follow-up tests, generating cost-effectiveness ratios ranging from $10 809 to $39 364 per life year saved.

The predictions of our model are consistent with those of another study performed at the H. Lee Moffitt Cancer Center at the University of South Florida [26]. This model was based on estimates that were situation specific to the Moffitt Cancer Center in Florida and included the following assumptions: 5 years of screening, 5 years of follow-up, cancer prevalence rate of 0.7–1.2%, stage I cancers comprised 15% of total lung cancer for non-screened and 60–80% for screened group, low dose helical CT cost of $100–200, high resolution CT cost of $400–500. Consistent with our model predictions, the Moffitt Cancer Center model estimated US $28 000 to $49 000 per life year gained. Compared with the cost-effectiveness of other screening interventions, lung cancer screening seems to be very reasonable (Table 4). Both our model predictions and those of the Moffitt Cancer Center for lung cancer screening are within the range of estimates for colorectal cancer screening, mammography screening (women aged 45–69 years), and hypertension screening, and are well below those for prostate cancer screening and annual mammography for women aged 40–49 years.

It is important to keep in mind that our model was developed from ELCAP data, which were based on an observational cohort and not a randomised controlled trial. As such, it may not be possible to generalise the results, nor is it possible to be certain of the true survival gain. We have used the SEER data as a comparison, but this gives historical estimates of lung cancer survival. The survival estimates for a contemporary equivalent comparison group could be different because the technology for treatment of lung cancer has improved since the SEER data were first collected. Our model also may be improved with additional follow-up data from ELCAP. For the present study, we assumed that resource use intensity for years 2–5 was the same as for year 1. However, it would be important to know the actual resource intensity of a screening programme and associated follow-up after the first year. Helical CT scanning is the current gold standard for detection of lung cancer and, based on the results of the ELCAP study, we assumed that all cases of lung cancer would be detected by helical CT scanning. At the present time, it is not possible to know how many cases of lung cancer may be missed by helical CT scanning because additional follow-up time is needed for these cases to be recognised.

As is the case for all studies of screening, the issue of lead-time bias is a concern for our model. Lead-time bias occurs in survival comparisons if screening advances the time of diagnosis without delaying the time of death [16,17,20]. Our model assessed the cost effectiveness of annual lung cancer screening without and with a 1-year decrease in survival benefit that might occur as a result of lead-time bias. Given the very short survival times for untreated lung cancer patients, a decrease in survival time of 1 year or less seems to be a reasonable assumption. However, valid data on this issue is not available and may be difficult to obtain given the ethical considerations involved in gathering information on the natural history of lung cancer in the early stages. If the mean decrease in survival benefit for stage I cancers detected by screening were found to be greater than 1 year because of leadtime bias, our model predicts there would be no significant improvement in survival. In this case, the impact of early lung cancer detection and treatment on patient's quality of life would take on much greater importance.

Table 4
Comparison of life years and QALYs for other screening interventions

Screening intervention	Cost-effectiveness or cost utility ratio
Mammography screening versus no population-based screening for women aged 45–69 years [12,27]	$18 000 per QALY (1998 US dollars)
Prostate cancer screening versus no screening in 50-year old males [12,28]	Dominated, more costly but not more effective (1998 US dollars)
Annual mammography screening versus current screening practices for women aged 40–49 years [29, 30]	$190 000 per life year (1993 US dollars)
Hypertension screening every 5 years for men aged 55–64 years [29,31]	$31 000 per life year (1993 US dollars)
Colorectal cancer screening every 10 years using sigmoidoscopy followed by colonoscopy if either low-or high-risk polyp diagnosed by sigmoidoscopy in 50-year old males [32]	$16 100 per life year (1998 US dollars)

QALY, quality-adjusted life year.

Another issue of concern is overdiagnosis bias, which occurs if screening detects lesions that are not clinically important and do not impact survival [19]. Although the possibility of overdiagnosis bias was raised in a recent update of the Mayo Lung project [15], this issue is probably less of a concern for lung cancer than for other types of cancer. Randomised controlled trials have failed to show a reduction in mortality as a result of lung cancer screening. However, Strauss and colleagues [18] have argued that data regarding the biology of lung cancer, autopsy evidence and surgical studies are inconsistent with overdiagnosis bias as a possible explanation for this observation. For example, a recent analysis of the SEER data showed that lung cancer was the only cancer of 20 analysed in which the change in incidence and mortality were almost identical [1].

Our model was developed as a speculative efficacy approach to the issue of lung cancer screening. As such, the predictions of the model provide insight into whether a screening programme could be cost-effective in steady state i.e. if the programme was already set up. Our model does not address other very important issues such as the capital costs associated with setting up a screening programme, including equipment, staffing and training. Practical considerations and policy issues raised by the implementation of lung cancer screening such as how individuals at high-risk for lung cancer would be identified are not addressed in this model. Given that the implications of a nationwide screening programme for lung cancer are significant and will depend largely on the capacity of centres to undertake such an effort, these issues warrant a separate analysis.

In summary, promising results from ELCAP have led to speculation that screening for lung cancer using low dose helical CT might have a dramatic impact on the tragic death toll from lung cancer. Although there is, as yet, insufficient evidence to recommend routine population screening for lung cancer, our modelling study suggests that 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.

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