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LUNG CANCER SCREENING BY LOW-DOSE COMPUTERISED TOMOGRAPHY: A COST EFFECTIVENESS ANALYSIS OF ALTERNATIVE PROGRAMMES IN THE UNITED KINGDOM USING A NEWLY DEVELOPED NATURAL HISTORY BASED ECONOMIC MODEL (ENaBL)

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Introduction

- Lung cancer is a continuing major global public health problem, and in the UK it is the leading cause of cancer death (22%).(1) Approximately 46,400 cases of lung cancer were diagnosed in 2014, representing 13% of the total number of cancer cases.(2) The prognosis for long-term survival is poor.
- Although the potential effectiveness of screening with low dose computed tomography (LDCT) has been demonstrated in large clinical trials (E.g. NLST) (3), cost-effectiveness remains uncertain.
- Important factors are: the cost of a LDCT scan; the risk of lung cancer in the screened cohort (pertaining to prevalence but also incidence for studies evaluating more than a single screen); the effectiveness of LDCT screening in broad terms, for example, achieving a stage shift without significant over-diagnosis; extending lung cancer survival beyond lead time; and reducing lung cancer mortality.
- Two UK setting economic concluded that LDCT screening could be cost-effective in the UK (4,5), however these evaluations have not been based on the highest quality evidence, tested multiple screening programmes or populations, or predicted the natural history of lung cancer in the absence of screening.
- This independent economic model is parametrised using high quality evidence (NLST) and adjusts for the positive biases associated with screen detected cases, which may inflate the cost-effectiveness of screening: lead time bias, length bias, and over-diagnosis.

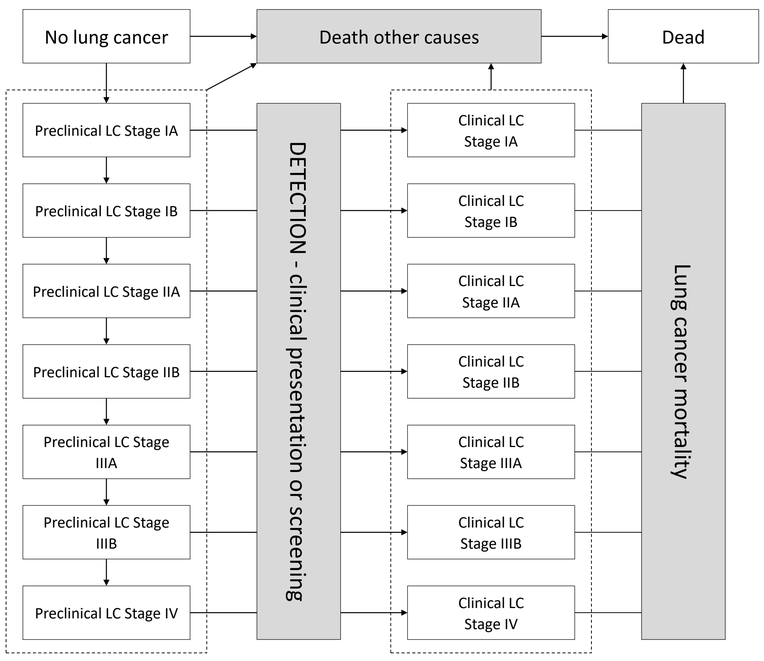
Methods

- ENaBL is an individual patient simulation model developed using a discrete event simulation framework whereby individual patients were sampled according to baseline age, sex, presence of preclinical disease, and predicted minimum risk of disease.
- Individual outcomes were simulated across four alternative screening programmes defined by the number and interval between LDCT screening rounds:
  - (S), Single one-off screen shortly following entry;
  - (T), Triple screen comprising a first screen shortly following entry and subsequent screens at 12 and 24 months;
  - (B), Biennial repeated screening from shortly after entry then 24-monthly from entry date but not beyond 80th birthday;
  - (A), as for (B) but screens are repeated annually.
- The target population was current or former smokers within the aged range 55 and 80 years with a higher risk of lung cancer relative to the general population.
- Twelve population groups were defined by combinations of further age restriction (55-80, 60-80, 55-75, and 60-75 years) and alternative minimum threshold of predicted risk (≥3%, ≥4% and ≥5%) There were 48 intervention strategies.
- A lifetime time horizon was used and future costs and benefits were discounted at 3.5% per year. The setting was the UK NHS, and the cost perspective was the NHS and personal social services.
- The primary outcome was the incremental cost-effectiveness ratios between strategies, expressed in additional cost per QALY gained (£, 2016/2017).
- Costs, QALYs and other outcomes for each strategy were estimated using a decision tree which identified appropriate simulated individuals from the pool and assigned them to either one or more screening interventions or to No screening.
- Individuals began the simulation without clinically diagnosed lung cancer, although they could have preclinical (occult) lung cancer.
- A natural history model was developed to generate disease incidence and progression for individuals in the absence of screen detection.
- A diagram of possible patient flow through the model is depicted in Figure 1. A summary of key input parameters are presented in Table 1, and key assumptions around modelling approach in Table 2.

Table 1. Key input parameters of the model

Description	Base case value
Number of smokers aged 55-80	13,000,000
Probability someone responds to the initial invite and returns the questionnaire	0.307
Probability someone joins screening programme given they are eligible	0.465
Sensitivity of low dose CT test for lung cancer	0.709
Specificity of low dose CT test for lung cancer	0.624
Utility of male smoker in the UK general population/occult lung cancer	0.7816
Utility of female smoker in the UK general population/occult lung cancer	0.7531
Disutility associated with a false positive screen	-0.063
Disutility associated with anxiety of a screening event	-0.010
Duration of disutility from false positive screen (weeks)	3.00
Duration of disutility from screening anxiety (weeks)	2.00
Cost of low dose CT scan	£98.80

Figure 1. Model diagram for simulating individuals



Abbreviations: LC, lung cancer. Key: White boxes represent health states; grey boxes and arrows represent events. An individual begins the simulation without clinically diagnosed lung cancer, because they do not have lung cancer or they have occult lung cancer (health states on the left hand side). He/she is immediately at risk incidental development of lung cancer, preclinical progression of the occult tumour, detection, or death from other causes. It is assumed that death from lung cancer is preceded by a diagnosis. Following detection, the individual is again at risk of progression or death, now from either from lung cancer or other causes.

Results

- Four screening strategies formed a cost-effectiveness frontier (Table 3; Figure 2). None would be considered cost-effective vs no screening at £20,000 per QALY.
- At a threshold of £30,000 per QALY, S-60-75-3% and S-55-75-3% would be cost-effective versus no screening.
- Individuals participating in the S-60-75-3% screening programme were predicted to gain an average 0.054 life years (≈3 weeks) or 0.027 discounted QALYs versus no screening, and mortality from lung cancer was on average delayed 0.16 years (≈8 weeks).
- Screening increased the probability of lung cancer being diagnosed in the early stages (I and II) versus later stages (III and IV): average odds ratios of early diagnosis in programme designs were predicted to be 2.44(S), 3.29(T), 3.83(B) and 5.62(A).
- The forward-shift in diagnosis in the single screen programmes was most significant for stage IA cancers.
- Reduction in risk of lung cancer mortality versus no screening ranged from 2.9% to 8.7% for participants.
- The reduction in lung cancer mortality was 4.2%(S), 4.4%(T), 5.2%(B), and 7.7%(A); and five-year survival was predicted to be 20.3%(S), 26.2%(T), 29.1%(B) and 32.3%(A), compared to 4.7% for no screening.

Table 3. Base case deterministic results of screening strategies forming the cost-effectiveness frontier (per person)

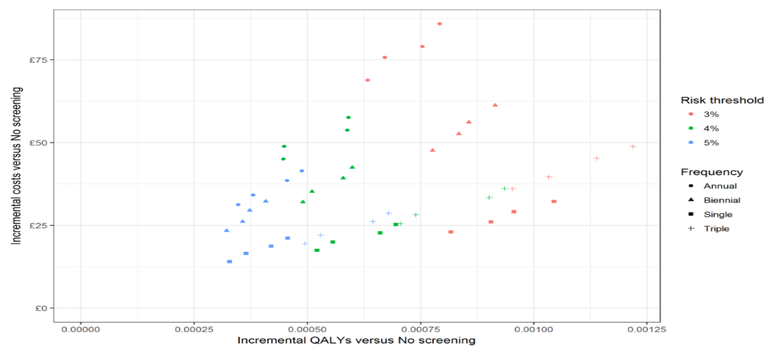
Strategy	Change in 5-year LC survival	Costs	QALYs	ICER (vs current/no screening)	ICER (vs previous)
No screening		£1,103	8.50215		
S-60-75-3%*	+16.1%	£1,126	8.50297	£28,169	£28,169
S-55-75-3%	+16.4%	£1,129	8.50306	£28,784	£35,453
S-55-80-3%	+16.1%	£1,135	8.50319	£30,821	£44,087
T-55-80-3%	+21.0%	£1,151	8.50337	£40,034	£95,292

*In a fully incremental analysis only S-60-75-3% would be cost effective at a threshold of £30,000 per QALY gained. Abbreviations: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; S, Single one-off screen design; T, Triple screen design. Strategy nomenclature: X-XX-XX-X% = Screening programme design type-minimum entry age-maximum entry age-minimum lung cancer risk threshold.

Table 2. Key assumptions of the model

Changes in smoking behaviour are not modelled
Programme uptake will be similar in real life to in the UKLS trial
There is full concordance with screening programme (i.e., no missed appointments)
Health-related quality of life similar for preclinical and diagnosed lung cancer (stratified by stage)
Health-related quality of life similar for clinically presenting and screen-detected lung cancer of the same stage
Health-related quality of life for diagnosed lung cancer is constant until death
Natural history of lung cancers is similar across all included individuals
Lung cancers progress through stages in numerical order without skipping any stages
Sensitivity of LDCT is independent of patient and tumour characteristics
Lung cancer mortality: screening cannot be less effective than no screening
Mortality from preclinical lung cancer assumed to be negligible
Lung cancer incidence in participating population similar to incidence in general smoking (current and former) population
Survival in participating population similar to survival in general population (stratified by stage)
Incidental findings not modelled
True positive results lead to immediate diagnosis and treatment
False positive and indeterminate results are treated equivalently
Non-attendance of screening was not explicitly modelled
Additional cancers caused by radiation exposure not modelled
Risk prediction is dependent only on prevalence of occult lung cancer or short-term incidence (within three years)

Figure 2. Cost-effectiveness plane for base case per person results across all strategies



Abbreviations: QALY, Quality-adjusted life year.

Limitations

- Lung cancer costs have been estimated from a single English teaching hospital so may not be fully generalizable to the whole of the UK.(6)
- It takes the invitation response rate observed in UKLS, but a sample of individuals selected for trial may be biased towards participation.(7)
- The economic evaluation currently assumes that the stage of lung cancer is relevant only to survival, it does not consider the relationship between the stage of lung cancer and the performance of LDCT, relevant because the identification of small nodules in early stage lung cancer may be more challenging.(8)
- The affect of lung cancer type or location on screening performance, costs or survival is not considered.

Conclusions

- LDCT screening for lung cancer may not be cost-effective, depending on the cost-effectiveness threshold. One screening strategy maybe cost-effective £30,000 per QALY.
- Screening may result in a reduction in lung cancer mortality, but also an increase in lung cancer diagnoses, and additional costs.
- Screening strategies with annual or biennial scans are not expected to be cost-effective regardless of the amount one is willing to pay for benefits.
- Early results from the NELSON trial appear to support the positive lung cancer mortality benefits demonstrated by the NLST but may also show our finding to be conservative.(9)

References

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