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Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort

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Abstract

The development of low-dose helical computed-tomography (CT) scanning to detect nodules as small as a few mm has sparked renewed interest in lung cancer (LC) screening. The objective of this study was to assess the potential health effects and cost-effectiveness of a one-time low-dose helical CT scan to screen for LC. We created a decision analysis model using baseline results from the Early Lung Cancer Action Project (ELCAP); Surveillance, Epidemiology and End Results (SEER) registry public-use database; screening program costs estimated from 1999 Medicare reimbursement rates; and annual costs of managing cancer and non-cancer patients from Riley et al. (1995) [Med Care 1995;33(8):828–841] and Taplin et al. (1995) [J Natl Cancer Inst 1995;87(6):417–26]. The main outcome measures included years of life, cost estimates of baseline diagnostic screening and follow up, and cost-effectiveness of screening. We found that in a very high-risk cohort (LC prevalence of 2.7%) of patients between 60 and 74 years of age, a one-time screen appears to be cost-effective at $5940 per life year saved. In a lower risk general population of smokers (LC prevalence of 0.7%), a one-time screen appears to be cost-effective at $23 100 per life year. Even when a lead-time bias of 1 year is incorporated into the model for a low risk population, the cost-effectiveness is estimated at $58 183 per life year. Based on the assumptions embedded in this model, one-time screening of elderly high-risk patients for LC appears to be cost-effective.

Keywords: Cost-effectiveness analysis; Lung cancer screening; Helical computed-tomography; Early Lung Cancer Action Project

1. Introduction

Lung cancer (LC) is the most common cause of cancer death in both men and women in the US, exceeding the mortality from cancers of the breast, colon, prostate and cervix combined [20]. In theory, LC should be a good candidate for screening because of the high mortality rate, dif-

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ferential survival by stage of disease, the current low rate of early detection because of the lack of symptoms early in disease, the availability of effective intervention for very early disease and the high costs associated with treatments for later stages of the disease [19]. Overall, the 5-year survival rate for all persons diagnosed with LC is about 14% in the US, based on estimates from the Surveillance, Epidemiology and End Results (SEER) registry [21]. However, the 5-year survival rate varies widely, depending on disease stage, from 49% for patients diagnosed with localized disease to 2% for those with distant disease [21]. Studies of surgical treatment in stage I lung cancer indicate improved outcomes in the range of 60–70% in resected patients compared with non-resected patients and most importantly, some have demonstrated 5-year survival rates in the range of 70–80% for patients with very early disease (stage 1A or T1N0) and that patients with smaller tumors do better than those with larger ones [6,9,12,14,17,19]. This suggests that patients with small tumors that can now be detected through a screening program would have a very good prognosis.

The recent introduction of helical computed tomography (CT) scanning has created new opportunities for detecting LC early. In this study, we consider the potential effectiveness and cost-effectiveness of helical CT in a prevalence screen for LC, as a basis for further examination of the potential benefits of LC screening. We used a decision analysis model to examine this question, combining data from the SEER registry public-use database and published baseline results from the Early Lung Cancer Action Project (ELCAP) for evaluation of LC screening by helical CT.

2. Materials and methods

2.1. Decision analysis model

We created a decision analysis model comparing a hypothetical cohort of 100 000 individuals aged 60–74 years, under scenarios of no screening and a baseline screen with helical CT. Survival was estimated over a 5-year time horizon (Fig. 1).

Under the scenario of 'no screening', the hypothetical cohort of 100 000 individuals was distributed into categories by gender 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 LC (lung and bronchus) per 100 000 was determined by gender, 5-year age grouping (60–64, 65–69, and 70–74 years), and disease stage (stage I, II, IIIA, IIIB and IV) from the SEER registry public-use database using 11 registries for the period 1992–1996. For stage I only, cases were further subdivided according to tumor size (≤ 10, 11–20, 21–45, and >45 mm), using the extent of disease classification. Actual numbers of cases were calculated from the incidence rates and number of individuals in each gender and age group category, according to the SEER stage distribution. The number of tumors were inflated proportionally by stage, size, age and gender to reflect the total number of tumors, including those classified as unknown and unstaged as per Gentleman et al. [10]. Finally, the actual numbers were adjusted using the same pattern of distribution, so that the total proportion of tumors in the screened population, which represents the prevalence of LC (2.7%), was the same as that reported by ELCAP [11] for a cohort with a median age of 67 and a median number of pack-years of smoking of 45. This represents a high-risk group of the type that would be targeted for LC screening, although the actual prevalence of lung cancer has not been established.

Cumulative estimates of survival for LC cases by year were estimated from the SEER database using nine registries for the period 1973–1996. The default settings recommended by the National Cancer Institute for survival analysis with SEER Stat 2.0 software were used to select cases for this analysis (i.e. selected only microscopically confirmed, actively followed, malignant behavior and excluded second and later primaries, death certificate and autopsy, unknown races, unknown age, sex neither male or female, invalid age dates). Expected rates of survival for the general population were those for the 1990 US population standardized by gender, age group and race, as provided by the SEER Stat 2.0 analysis package.

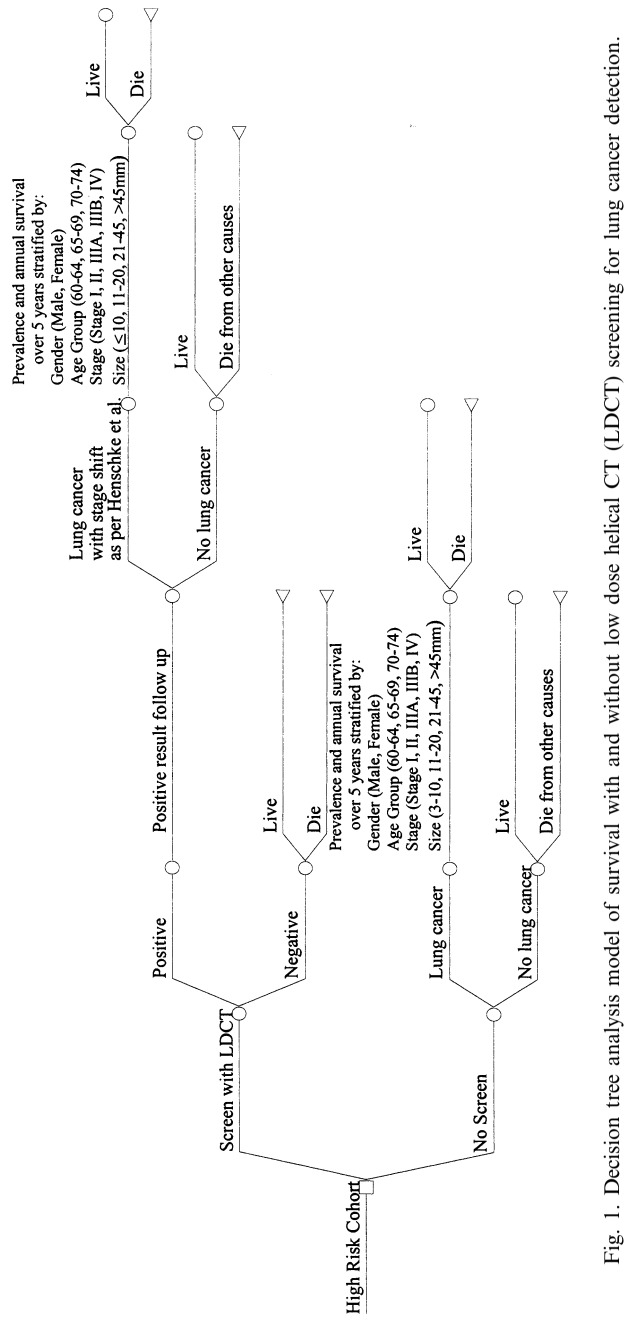

Fig. 1. Decision tree analysis model of survival with and without low dose helical CT (LDCT) screening for lung cancer detection.

Under the scenario of 'screening with helical CT', a one-time screening program was considered. This program included a baseline scan with helical CT and follow-up as estimated from the baseline results reported by ELCAP [11]. 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 base 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. In the absence of long term follow-up data, these results are used to approximate the sensitivity and specificity of the screening. The impact of screening was modeled as a stage shift at diagnosis based on the observed distribution reported by ELCAP [11]. The same number of cancers were assumed to be identified in the screening and the non-screening scenarios, but the distribution by stage at time of diagnosis was adjusted. It was assumed that the age- and gender-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.

2.2. Costs

All screening program-testing costs were estimated from 1999 medicare reimbursement rates. Helical CT scanning was assumed to cost $150 per scan based on local institutional estimates. Cost estimates for treatment of LC by stage were obtained from the average annual Medicare payments by stage at diagnosis reported by Riley et al. [23], 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 et al. [28]. Costs and life years were discounted at 3% per year.

2.3. Analysis

Cost effectiveness ratios (CERs) were calculated based on survival and costs over a time horizon of five years. As defined by Drummond et al. [7], cost effectiveness analysis is a form of full economic evaluation, where both the costs and consequences of health programs or treatments are examined. Commonly, effects are measured as life years and CERs are expressed in terms of cost per life year gained. 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. The effect of varying the baseline cancer risk, lead time bias associated with early detection, the performance characteristics of the screening program, and the costs of screening and diagnosis were assessed with one- and two-way sensitivity analyses.

3. Results

The distribution of individuals in each gender and age group for a hypothetical cohort of 100 000 people aged 60–74 years, based on data from the US Bureau of the Census for 1998, is shown in Table 1. Approximately 45% of the hypothetical cohort were male, and individuals were nearly evenly distributed amongst the age group categories (60–64, 65–69 and 70–74 years).

Table 1
Distribution of hypothetical cohort by gender and age group[a]

Age group (years)	Male number (%)	Female number (%)	Total number (%)
60–64	16 933 (16.9)	18 910 (18.9)	35 843 (35.8)
65–69	15 294 (15.3)	18 145 (18.2)	33 439 (33.5)
70–74	13 436 (13.4)	17 282 (17.3)	30 718 (30.7)
Total: 60–74	45 663 (45.7)	54 337 (54.3)	100 000 (100)

[a] Based on US Bureau of the Census, Current Population Reports, projections for July 1998.

Table 2
Distribution of tumors detected in hypothetical cohort at high risk for LC without screening and with helical CT screening[a]

Disease stage	Without screening[b]			With helical CT screening[c]		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
Stage I	18.7	23.5	20.6	82.4	88.2	85.2
Stage II	4.1	4.1	4.1	4.3	3.0	3.7
Stage IIIA	9.3	9.7	9.4	8.5	6.2	7.4
Stage IIIB	21.7	16.8	19.7	4.8	2.6	3.7
Stage IV	46.2	45.9	46.1	0	0	0

[a] LC, lung cancer; CT, computed tomography.
[b] Based on data from the SEER registry public-use database.
[c] Adjusted for stage redistribution from baseline screening reported by ELCAP [11].

Table 2 shows the distribution of tumors in the hypothetical cohort at high risk for LC without and with helical CT screening. The 'without helical CT screening' distribution is based on incidence rates of LC at diagnosis by stage according to the SEER database. The overall prevalence was 284/100 000 (approximately 0.3%). In order to reflect the prevalence of cancer in a high-risk cohort, the distribution was adjusted so that the total prevalence was approximately 27/1000 (2.7%), as found in the ELCAP cohort [11]. To simulate the impact of screening on stage shifting for diagnosis of LC, the distribution by stage at diagnosis in the ELCAP cohort [11] 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.

The distribution of tumor size was further analyzed for patients in the cohort diagnosed with stage I LC. As shown in Table 3, most unscreened patients diagnosed with stage I LC had tumors 21 mm or above in size. By comparison, with screening over 90% of stage I LC patients had tumors 20 mm or less in size.

The tests and costs estimated for screening a hypothetical cohort of 100 000 individuals at high risk for LC are shown in Table 4. The proportion of helical CT scans, high resolution CT scans, and biopsies performed were estimated from the baseline results reported by ELCAP [11] and the costs of these tests were based on the 1999 Medicare reimbursement rates. Comparison of the estimated costs incurred for the screened versus the reference group indicates that the incremental cost for screening was approximately 25 million US dollars.

The effectiveness of LC screening in terms of life years and the associated costs estimated by the model are shown in Table 5. Life years were estimated from annual cumulative survival rates for LC cases for each category of gender, age group, stage and tumor size. Life years for non-lung cancer cases were estimated from annual cumulative survival rates for the US population for each category of gender and age group. The model results show that a total of approximately 4400 life years would be generated over a 5-year time horizon for this cohort of 100 000 individuals through a prevalence screen. The cost-effectiveness analysis indicates that a one-time screening program in this cohort would cost $6512 per life year saved ($5941 per life year saved with discounting).

Sensitivity analyses were performed to evaluate the effects of a 1-year lead time bias, different levels of risk in the screened population, the cost of screening and the performance characteristics of the baseline helical CT scan. The relationship between the CER and the prevalence of cancers in the population is shown in Fig. 2. These results demonstrate that the higher the prevalence of LC risk in the screened cohort, the more cost-effective the screening intervention. As expected, all prevalence scenarios are more cost-effective with no

lead time bias. Even with a lead time bias of one year, the estimates indicate that the screening program would be considered cost-effective at $15 274 per life year saved for high-prevalence scenarios, and marginally cost effective at $58 183 per life year saved (discounted) for low-prevalence scenarios.

The effect of varying the rate of false positives for the initial low dose helical CT scan in the screening program is shown in Table 6. It should be noted that this analysis assumed that the cancer detection rate was maintained at 100%, but the rate of false positives varied. Although the true sensitivity and specificity is not yet known, these calculations were based on what was found in the baseline experience reported by ELCAP for detecting LC. Incorporating a 1-year lead-time bias, all scenarios generated CERs from $11 500 per life year saved to $20 400 per life year saved (discounted).

With respect to the costing assumptions, if the cost of a helical CT scan was assumed to be $500 (instead of $150) and the cost of a high resolution CT was assumed to be $1000 (instead of $280), the discounted CER would be $17 100 per life year saved. If in addition, a 1-year length-time bias is assumed, the CER rises to $44 000 per life year saved.

4. Discussion

In the 1970s, randomized controlled trials of screening for LC using chest X-ray and sputum cytology failed to demonstrate an impact on mortality [8,27]. Since that time, screening for LC has been discouraged. In fact, LC is the only cancer, for which there is consensus against screening, as recommended by the US Preventative Services Task Force [29], the Canadian Task Force on the Periodic Health Examination [5], the American Cancer Society [1], the American College of Radiology [8], and the National Cancer Institute [25]. Some authors have argued for the results of these trials to be reconsidered based on fatality outcomes (number of LC deaths per number of LC cases) instead of mortality (number of LC deaths per number of patients screened), but this has not changed clinical practice in the US [27]. Furthermore, in Japan, a national mass screening program using chest X-ray was introduced in 1987 for all residents over 40 years of age. Since this program was introduced, the 5-year survival rate has increased to 58%, as compared with 38% in the pre-screening period. The increase in 5-year survival rate was attributed to a 12% increase in the proportion of stage I cancers at diagnosis [15].

Despite the failure of earlier randomized controlled trials to demonstrate an impact on mortality, the recent refinement of computed tomography scanning techniques and developments in the analysis of airway and sputum cell markers have created new opportunities to consider LC screening. For example, the use of helical CT may improve the feasibility of early LC detection, particularly for peripheral lesions, because of its better diagnostic accuracy, short scanning times, and low radiation exposure. In a

Table 3
Distribution of tumor size in hypothetical cohort with stage 1 LC without screening and with helical CT screening[a]

Size of tumors in stage I patients (mm)	Without screening[b]			With helical CT screening[c]		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
≤10	4.8	5.9	5.3	56.1	56.9	56.5
11–20	26.4	33.3	29.5	34.2	35.3	34.8
21–45	48.4	48.0	48.2	9.6	7.8	8.7
≥45	20.4	12.8	17.0	0	0	0

[a] LC, lung cancer; CT, computed tomography.
[b] Based on data from the SEER registry public-use database.
[c] Adjusted for stage redistribution from baseline screening reported by ELCAP [11].

Table 4
Baseline diagnostic testing and follow up for prevalence screen for hypothetical cohort of 100 000 at high risk for LC[a]

Test	Number of tests in screened group (A)	Number of tests in unscreened group (B)[b]	Cost in US $ (C)[c]	Marginal cost for screening in US $ (A − B) C[b]
Low dose helical CT scans	100 000	0	150 + 30	18 000 000
High resolution CT scans baseline	16 500	2702	281 + 30	4 291 200
Follow-up (3, 6, 9, 12 months)	8110	0	281 + 30	2 522 200
Biopsies	3000	2702	430 + 30	137 100
Total marginal cost for screening program ($US)				24 950 500

[a] LC, lung cancer; CT, computed tomography.
[b] This represents the estimated number of CT scans and biopsies that would have been performed in the unscreened group as result of case finding.
[c] Based on 1999 Medicare reimbursement schedule for professional fees, technical fees for tests, and follow-up visit.

Japanese cohort study, the detection rate of helical CT was found to be nearly four times that for chest X-ray (0.48 vs. 0.12%) [13]. More recently, a US-based study of 1000 patients demonstrated that helical CT yielded a higher baseline detection rate for non-calcified nodules and a higher detection rate of malignant disease as compared with chest X-ray (23 vs. 7% and 2.7 vs. 0.7%, respectively) [11]. In addition, this study found that stage I tumors were detected six times more frequently by helical CT as compared with chest X-ray (2.3 vs. 0.4%).

There has been some speculation that helical CT in the context of LC screening may be cost-effective, because of the improved ability to detect early stage cancers combined with the short scanning time and relatively low cost of this technique [18]. This is supported by cost-effectiveness studies of other screening techniques. For example, a decision analysis to investigate the cost-effectiveness of the mass screening program with chest X-ray in Japan estimated that the cost per life year saved was approximately $93 000 for persons over 40 years, and approximately $50 000 for persons over 50 years (with a prevalence of LC of 0.1% for those 50 years, or older) [2]. The authors concluded that the cost-effectiveness of screening was relatively poor, but could be improved by targeting selected populations. In another study, a decision analysis model was used to assess the cost-effectiveness of using sputum cytology as an initial procedure in the diagnosis of LC in patients with suspected, but no prior history of LC [22]. The results suggested that sputum cytology as the first test in suspected LC is likely to be cost saving without adversely affecting patient outcomes. Finally, preliminary results from an economic evaluation of population-based LC screening using a Monte Carlo simulation model developed by Statistics Canada suggest that screening may be effective and cost-effective, if high risk populations are targeted, assuming that screening can achieve a significant shift in stage at diagnosis from advanced disease to earlier disease [3].

Under the model assumptions of the present study, we found that in a very high-risk cohort of patients between 60 and 74 years of age, a one-time screen appears to be cost-effective at $5940 per life year saved. Furthermore, the CER remained below $50 000, even when the prevalence of cancers in the tested population was reduced from 2.7 to 0.7% ($22 629 per life year saved), and a 1-year lead-time bias was incorporated into the model ($58 183 per life year saved). Although these results are optimistic as a consequence of the model being framed as a prevalence screen, they suggest the possibility that screening for LC may be effective and cost-effective with newer technological capabilities. This possibility needs to be explored further.

Table 5
Reference case cost-effectiveness of a one-time prevalence LC screen[a]

	Without screening	With screening	Difference
Not discounted			
Life years	470 284	475 176	4892
Cost (millions US $)	3031	3063	32
Cost-effectiveness ratio (US $ per life year)			6512
Discounted (3%)			
Life years	431 468	435 885	4417
Cost (millions US $)	2785	2812	26
Cost-effectiveness ratio (US $ per life year)			5941

[a] LC, lung cancer.

One of the most problematic assumptions in our model may be related to the issue of lead time bias, which occurs in survival comparisons, if screening advances the time of diagnosis without delaying the time of death [24,26,27]. Our reference case assumed no lead-time bias, and we assessed the effect of a 1-year lead time bias in the sensitivity analysis. A lead-time bias of 1 year or less seems to be a reasonable assumption, given the very short survival times for untreated LC patients. Unfortunately, obtaining valid data on this issue may prove difficult. Gathering information on the natural history of LC in the early stages would require a protocol, in which high-risk patients are screened frequently (e.g. on a quarterly basis), but the results are only read annually so as not to allow screening results to influence treatment decisions. It may, in fact, become impossible to do such a study, if we convince ourselves that screening 'works', even though solid evidence for this type of intervention is lacking. If the mean lead time bias for stage I cancers detected by screening were found to be greater than 1 year, then the impact of early case finding and treatment on patients' quality of life would take on much greater importance, since finding cancers early may not significantly improve survival.

There are issues in addition to lead-time bias that must be taken into consideration before decisions are made to screen for LC on a routine basis. For example, the distribution of the cancers found by a cross-sectional screening effort may be subject to length bias, which occurs when biologically indolent tumors are detected by screening resulting in apparent improvements in survival and fatality in a screened population [24,27]. Although less likely in LC than other malignancies, if there is a significant proportion of stage I patients, who have relatively indolent cancers and who might be over-diagnosed and over-treated due to screening, our model will overestimate the survival gains from screening.

Another issue of concern that arises in all studies of screening is overdiagnosis bias, where screening detects lesions that are not clinically important and would not impact survival [4]. This issue has been highlighted in the updated analysis of the Mayo lung project [16], in which a reduction in mortality as a result of LC screening was

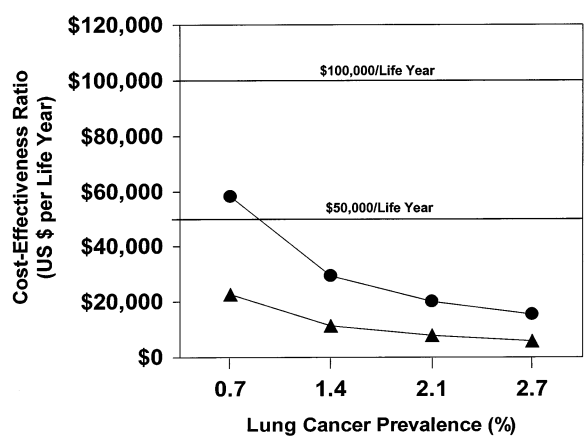

Fig. 2. Sensitivity analysis of lung cancer prevalence. Discounted cost effectiveness ratios were determined with (●) and without (▲) incorporation of 1-year lead-time bias.

Table 6
Sensitivity analysis of helical CT scanning specificity[a]

Specificity (%)	Discounted CER no lead time bias (US $ per life year)	Discounted CER 1-year lead time bias (US $ per life year)
50	7900	20 400
60	7300	18 800
70	6500	16 700
80	5900	15 300
90	5100	13 000
99	4500	11 500

[a] This refers to the specificity calculated based on 1-year follow-up results in an observational study. CT, computed tomography; CER, cost-effectiveness ratio.

not observed even after an extended follow-up period. Although overdiagnosis bias could explain the findings of this and other randomized controlled trials, Strauss et al. [27] have argued that other data regarding the biology of LC, autopsy evidence, and surgical studies are inconsistent with this hypothesis. For example, in a recent analysis of SEER data examining incidence, 5-year survival and mortality, lung cancer was the only cancer of the 20 analyzed, where the change in incidence and mortality were almost identical [30].

It is important to keep in mind that this model considers only a one-time prevalence screen. Data are not yet available for modeling the economic impact of incidence screening. The CER of incidence screening would be higher (i.e. less cost-effective) than our prevalence-based estimate, because the proportion of individuals who develop LC in the population annually would be expected to be a fraction of the population prevalence. The data in Fig. 2 gives an indication of the magnitude of change in the CER to expect from repeat screens based on estimates for the low prevalence group (0.7%). However, the actual CER for repeat screens would differ because the prevalence of patients with advanced stage cancer in a serially screened population would be very low, and this would change the cost structure for the population.

There is as yet insufficient evidence to recommend routine population screening for LC with helical CT. In light of current technology and available data, the results from this modeling study indicate that we should reconsider the possibility that LC screening could be an effective and cost effective approach to cancer control in high-risk populations.

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