Adopting Helical CT Screening for Lung Cancer

Potential Health Consequences During a 15-Year Period

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This study used only publicly available, de-identified patient data.

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BACKGROUND. Simulation modeling can synthesize data from single-arm studies of lung cancer screening and tumor registries to investigate computed tomography (CT) screening. This study estimated changes in lung cancer outcomes through 2005, had chest CT screening been introduced in 1990.

METHODS. Hypothetical individuals with smoking histories representative of 6 US cohorts (white males and females aged 50, 60, and 70 years in 1990) were simulated in the Lung Cancer Policy Model, a comprehensive patient-level simulation model of lung cancer development, screening, and treatment. A no screening scenario corresponded to observed outcomes. We simulated 3 screening scenarios in current or former smokers with $\geq$20 pack-years as follows: 1-time screen in 1990; and annual, and twice-annually screenings beginning in 1990 and ending in 2005. Main outcomes were days of life between 1990 and 2005 and life expectancy in 1990 (estimated by simulating life histories past 2005).

RESULTS. All screening scenarios yielded reductions (compared with no screening) in lung cancer-specific mortality by 2005, with larger reductions predicted for more frequent screening. Compared with no screening, annual screening of ever-smokers with at least 20 pack-years of cigarette exposure provided ever-smokers with an additional 11 to 33 days of life by 2005, or an additional 3-10 weeks of (undiscounted) life expectancy. In sensitivity analyses, the largest effects on gains from annual screening were due to reductions in screening adherence and increased smoking cessation.

CONCLUSIONS. The adoption of CT screening, had it been available in 1990, might have resulted in a modest gain in life expectancy. ***Cancer* 2008;113:3440–9.**

KEYWORDS: lung cancer, mass screening, computer simulation, computed tomography.

Interest in lung cancer screening programs has intensified recently, in part on the basis of a single-arm screening study that reported 10-year survival in excess of 80% for patients whose lung cancers were detected by CT screening and then surgically resected.[1] In the absence of screening, only 16% of lung cancer patients survive 5 years,[2] as lung cancers are typically diagnosed by symptoms after distant spread has occurred. Screening is available to participants in studies and those willing to pay out of pocket, yet it is not recommended by major consensus guidelines.[3] Two randomized controlled trials with a combined enrollment of approximately 70,000 will provide information on the effectiveness of lung cancer screening over the next few years.[4,5]

In the interim, simulation modeling may be used to evaluate lung cancer screening programs and inform screening debates. A model integrates available data, including findings from observa-

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tional studies, to predict likely long-term mortality outcomes under various scenarios.[6,7] By varying trial protocols, patient populations, treatments, or adherence rates, models can also be used to interpret and reconcile apparently inconsistent trial results.[8] For example, questions about large, pivotal, hypertension trials remained decades after their completion,[9] whereas modeling performed in the 1970s predicted the subsequent trial results.[10-12]

The objective of this study was to estimate the health consequences the US might have realized by adopting current technology (helical CT) screening for lung cancer during the 15-year period from 1990 through 2005. This analysis, although hypothetical, offers insight into possible effects of screening for lung cancer.

MATERIALS AND METHODS

The Lung Cancer Policy Model

The Lung Cancer Policy Model (LCPM) is a comprehensive, patient-level, microsimulation model of lung cancer development, progression, detection, treatment, and survival. The LCPM's structure, parameters, and assumptions have been previously described.[13,14] The LCPM predicts lung cancer incidence rates and survival curves, stratified by age, sex, cell type, and stage at detection. The LCPM explicitly models survival after diagnosis as a function of treatment and underlying disease characteristics, unlike prior stage-shift models.[15,16] The LCPM, therefore, requires no assumption that patients with screen-detected cancers have identical survival to similarly staged nonscreen-detected cancers.[8,17,18] The LCPM explicitly models benign nodules, which cause high (20.5% to 51%)[19-23] rates of positive-baseline CT-screening exams and can prompt clinical work-ups. The LCPM also accounts for the high competing mortality risks faced by smokers relative to nonsmokers,[24] minimizing the risk of an inflated estimate of the effect of screening on all-cause mortality.

Simulated Cohorts and the No Screening Scenario

This simulation study used only publicly available, de-identified, human subject data.[25-28]

We populated the Lung Cancer Policy Model LCPM with individuals assigned to smoking histories (including nonsmokers) representative of 6 cohorts of US whites (men and women aged 50, 60, and 70 years in 1990).[25,26] In brief, each individual was assigned a smoking status in 1990 (current, former, never); ages at which these individuals started and stopped smoking and cigarettes smoked per day (all drawn from distributions) were also assigned.[14] After 1990, all current smokers face an annual rate of smoking cessation of 3%, based on estimates of 2.5% to 3.2%.[29,30] Cohort ages were consistent with the age ranges of participants in CT-screening trials (minimum ages of 50 to 60 years).[5,19,20]

The LCPM was previously calibrated against age-specific lung cancer incidence rates from tumor-registry data.[14] Nonsmokers were included in the cohorts so that the incidence rates generated by the LCPM in the no screening scenario would correspond to observed rates in the general population. (Lung cancer does develop in nonsmokers,[31,32] and registry data contain no smoking information.) Asymptomatic lung cancers could be detected incidentally by means of thoracic imaging examinations performed for reasons other than screening. Additional calibration targets included characteristics of incident lung cancers (stage and cell-type distributions, sizes) and lung cancer-specific survival curves (stratified by stage at diagnosis, age, and cell type). Details about model fit and validation are available.[14]

Base Case Screening Scenarios

In each of the 6 cohorts, we simulated the introduction in 1990 of 3 alternative screening protocols for current or former smokers with at least 20 pack-years of cigarette exposure as follows: a 1-time helical CT examination in 1990, and annual and twice-annual helical CT screening examinations beginning in 1990 and continuing through 2005. Alternative pack-year requirements were evaluated for a representative cohort (see Sensitivity Analyses).

The base case analysis used our best estimates for all input parameters[14] and assumed perfect adherence with the screening protocol by eligible individuals not already diagnosed with lung cancer. We assumed that participants with screen-detected nodules would undergo a recommended follow-up protocol,[20] which varied by the size of the largest nodule. For the base case, we assumed that helical CT examinations could detect nodules as small as 2 mm, and we derived estimates of test sensitivity by size and location from published results.[20] For the base case, we defined a false-positive imaging examination as one that detected an ultimately benign nodule of any size.

Base Case Outcomes

For each strategy, we calculated annual incidence rates and lung cancer-specific mortality rates from 1990 through 2005. We estimated the average life-years (LY) accrued to each person in the cohort from

1990 to 2005 (maximum of 15 years). Because nonsmokers were included in the cohorts, but not eligible for screening, we also reported the average LY accrued to ever-smokers. We then estimated life expectancy (LE) for each strategy by simulating complete life histories for each individual and assuming that treatment efficacies, competing risks, imaging utilization, and smoking cessation trends remained constant past 2005. Screening was not continued past 2005. LY and LE are undiscounted.

Among individuals who had undergone at least 1 screening examination, we predicted probabilities of having at least 1 false-positive screening result during the 1990-2005 time period. For nonsmall cell lung cancers (NSCLCs) diagnosed in a cohort from 1990 through 2005, we predicted the distribution of stages at diagnosis and a 5-year lung cancer-specific survival rate (all stages combined, with right-censoring at 2005).

Sensitivity Analyses

By using sensitivity analyses, we examined effects on results of alternative programs and uncertainty in estimates. Because none of the sensitivity analyses examined age-specific or sex-specific changes in protocols or behavior, all sensitivity analyses were performed in cohorts of men aged 50 years, and we assumed the introduction of annual screening in 1990. Lung cancer incidence is higher in males, and 50 years is a typical minimum age in past and ongoing CT screening studies. Outcomes from sensitivity analyses are presented as LY gains between 1990 and 2005 and are not influenced by assumptions of secular trends past 2005.

Alternative screening, follow-up, and treatment components

We simulated scenarios with minimal screening eligibilities as in recent or ongoing trials (10 pack-years or 30 pack-years).[19,5] We simulated a scenario with a reduced sensitivity of screening CT for small (<5 mm) nodules, such as could occur with contiguous (vs overlapping) reconstruction of slices or larger slice thicknesses.

To investigate the influence of follow-up and treatment on the effectiveness of screening, we simulated scenarios with 1) reduced operative mortality rates (for lobectomy, mediastinoscopy, and excisional biopsies [video-assisted thoracoscopic surgery, VATS]); 2) a protocol with no follow-up for nodules smaller than 4 mm diameter; 3) a minimum detectable growth of 1 mm diameter (2 mm in base case); and 4) a protocol with more sampling biopsies (fine needle, bronchoscopy, mediastinoscopy) and correspondingly fewer VATS for indeterminate growing nodules (20% vs 50% base case) and large, but stable, nodules (2% vs 11% base case). Details are available online.[14]

Screening adherence and smoking cessation rates

We simulated adherence rates of 70% (informed by US surveys of willingness to undergo lung cancer screening or whole-body CT and a Spanish study),[33,34,35] 80% (observed in a French trial),[23] and 93.5% (used in a published cost-effectiveness analysis and similar to observed rates in US studies).[15,36,37] Additional sensitivity analyses simulated either a 10% or 20% annual smoking cessation rate (constant from 1990) in combination with annual screening.

Statistical Methods

For each age and sex, we simulated a fixed cohort of 500,000 individuals in each base case scenario. We employed parallel random-number streams,[38] so that the same 500,000 individuals in a cohort were simulated in each scenario. Fixed cohorts of 500,000 individuals were large enough to generate precise estimates and stable rank-ordering of strategies (46 minutes on a 2.6 GHz personal computer [PC] with 2 G of random-access memory [RAM]). Specifically, we averaged results across 10 different cohorts of 500,000 men aged 60 years under scenarios of no screening and annual screening. The confidence intervals around mean life-years in the no screening and annual screening scenarios did not overlap. (Standard error of the mean [SE] was <10% of the average change in life-years.) Because the sample size was scalable, *P*-values for comparisons between strategies were not informative and, therefore, are not reported.

RESULTS

Base Case

Lung cancer diagnoses and deaths

Figures 1 and 2 shows annual lung cancer incidence rates for each cohort by screening strategy. Incidence rates in the no screening scenarios (Fig. 1, solid blue) were calibrated against observed incidence rates (shaded regions) derived from tumor registry data.[14,28] One-time screening in 1990 detected asymptomatic (prevalent) cancers in each cohort (Fig. 2), generating a spike in incidence (maroon) followed by an approximately decade-long period of incidence rates lower than the no screening scenario. By contrast, 15 years of annual or semiannual screening yielded incidence rates (green, orange) that remained elevated relative to the no screening scenario.

Figure 3 shows annual lung cancer-specific mortality rates by cohort and by screening strategy. All 3

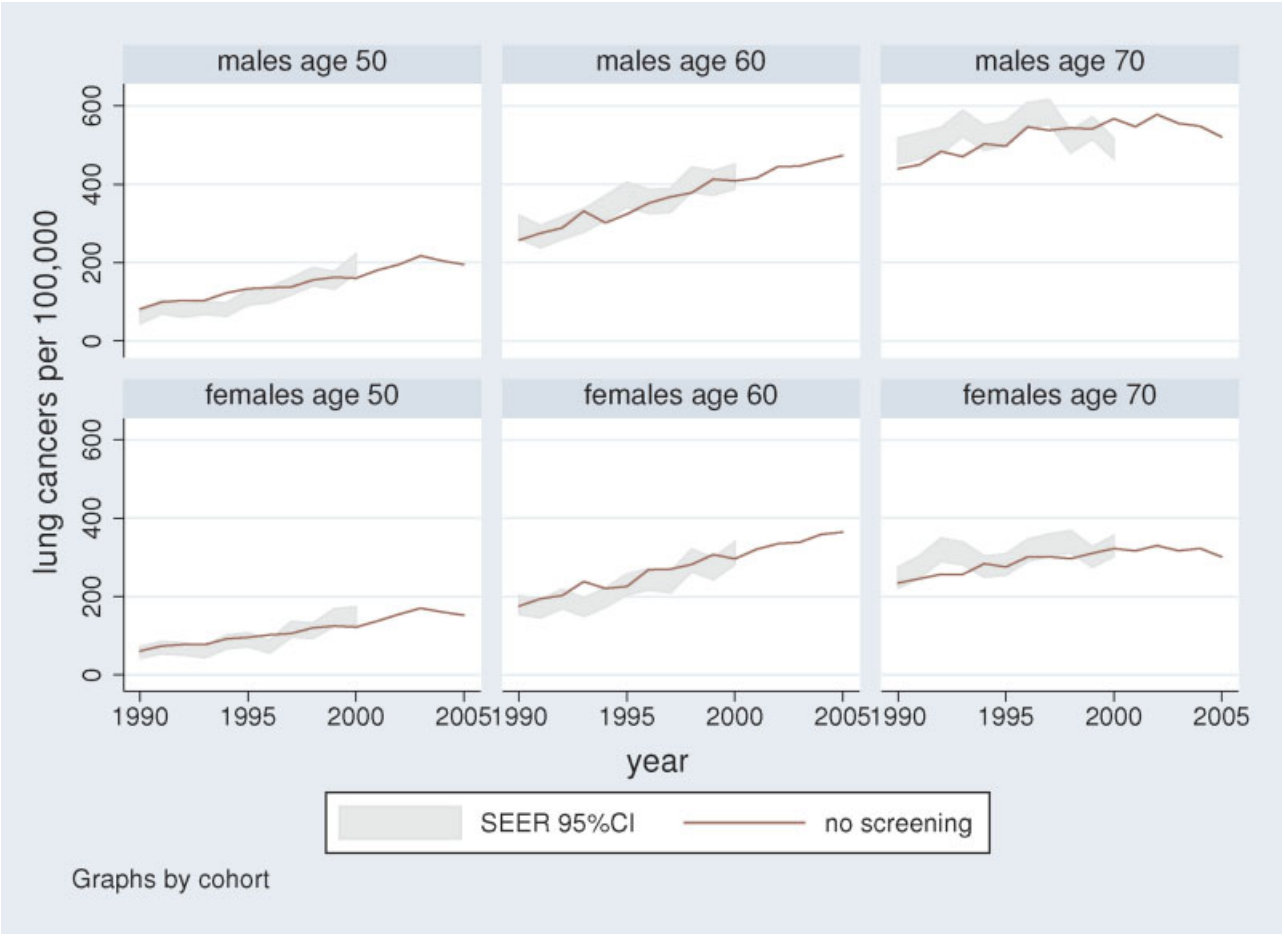

FIGURE 1. Annual lung cancer incidence by cohort, predicted by the LCPM versus observed incidence rates (SEER), includes screen-detected and nonscreen-detected cancers of all cell types.

screening strategies produced decreases in lung cancer-specific mortality, with larger and sustained decreases in the annual screening strategies.

Shift to earlier stage and survival of patients with nonsmall cell lung cancers (NSCLCs)

For NSCLCs diagnosed (by any modality) in the screening strategies, a stage shift was predicted versus the no screening scenario (Table 1). Between 24% and 32% of NSCLCs diagnosed in the no screening scenarios were stage I/II, compared with 69% to 79% in the semiannual screening scenarios. The predicted shift to early stage cancers was consistent with higher predicted 5-year lung cancer-specific survival rates for NSCLCs in the semiannual screening (60% to 69%) versus no screening (21% to 27%) scenarios. For NSCLCs diagnosed in 1990-2005, semiannual screening led to a decrease in the mean age at diagnosis of 0.66 years to 1.21 years, compared with no screening.

Gains in life years (LY) from 1990 to 2005

With no screening, life years (LY) per individual (including nonsmokers) from the year 1990, with right-censoring in the year 2005, ranged from 14.42 years for women aged 50 years to 10.72 years for men aged 70 years (Table 2). One screening examination in 1990 yielded gains of 0.01 LY (approximately 4 days) to 0.03 LY depending on the cohort; annual screening increased gains by an additional 0.01 LY to 0.03 LY. Increasing screening frequency to every 6 months yielded additional gains of 0.01 LY or less.

Excluding nonsmokers from the LY estimates yielded lower average LYs per individual because of competing mortality from smoking (right half of Table 2). In ever-smokers, 1 screen yielded gains of 0.01 LY to 0.04 LY; annual screening increased gains by an additional 0.02 LY to 0.05 LY. Increasing screening frequency to every 6 months yielded additional gains of 0.02 LY or less.

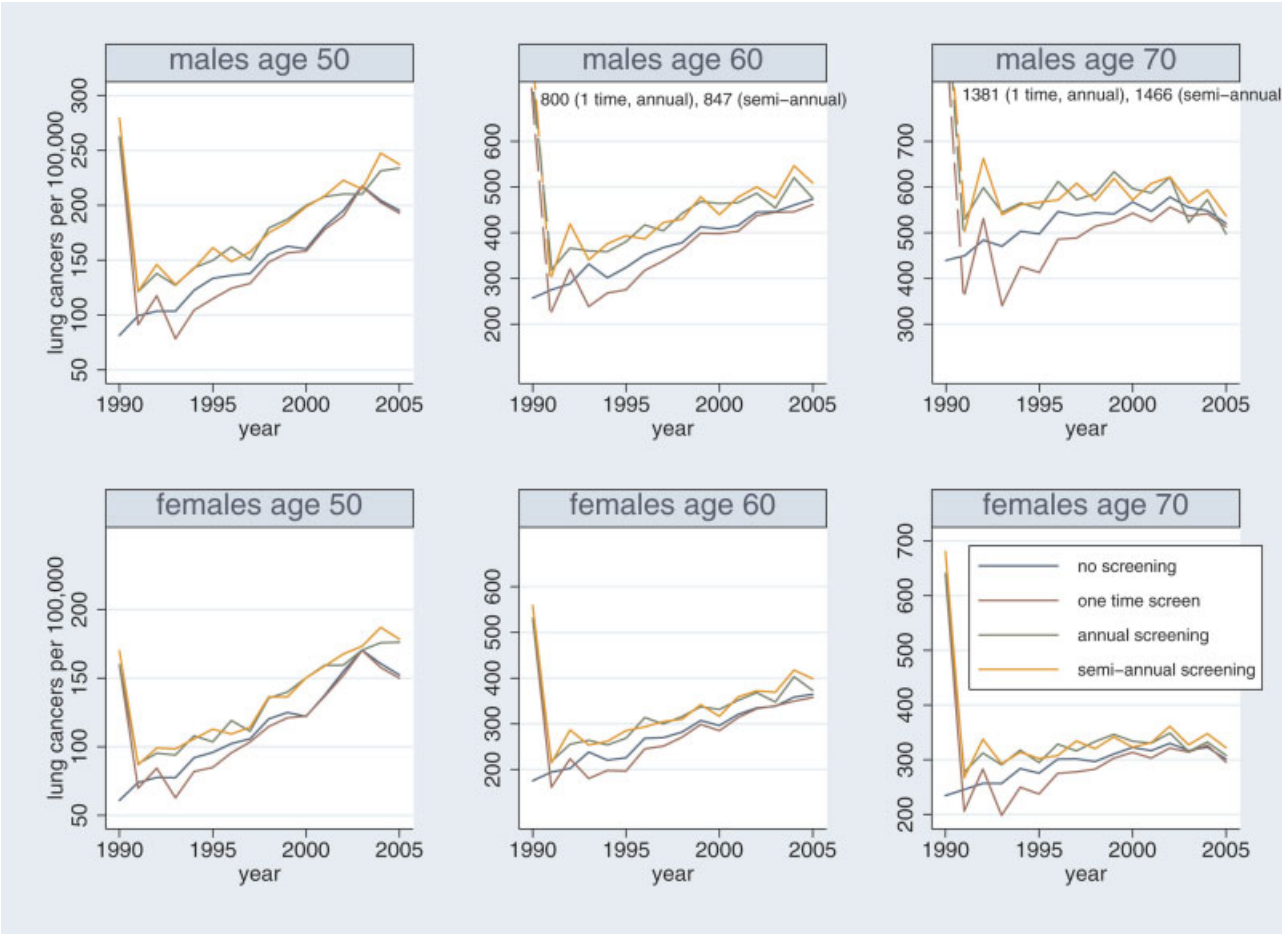

FIGURE 2. Predicted annual lung cancer incidence (ranges not constant) by cohort under scenarios of no screening, 1 screen, and annual or semiannual screening through 2005. Introduction of screening in 1990 (all screening scenarios) detects increased numbers of lung cancers. After the 1-time screen, the incidence rate in the 1-screen scenario drops below that of the no screening scenario. Inset values provide rates outside axis range.

Gains in life expectancy (LE), lifetime time horizon

A 1-time screen yielded gains in LE versus no screening of 0.9 to 2.5 weeks (Table 3). Annual and semiannual screening until 2005 yielded gains of 3.4 to 12.0 weeks.

Sensitivity Analyses

Table 4 shows the incremental change in LY by 2005, converted to days, per 50-year-old human under alternative scenarios, with each scenario compared with the base case no screening scenario estimate of 14.10 LYs (from the first row of Table 2). Base-case estimates of days gained were 5 days (1-time screen) to 12 days (semiannual screening). Relaxing screening eligibility to include lighter smokers (≥10 pack-years) yielded gains in this cohort of 6 to 13 days, whereas stricter eligibility (≥30 pack-years) yielded smaller gains (4 to 9 days). A larger benefit from screening was predicted in the scenario with reduced operative mortality rates from lobectomy, mediastinoscopy, and VATS, which yielded gains of 9 to 17 days. Under scenarios with more accurate, repeated, imaging exams or with no follow-up for lesions smaller than 4 mm diameter, the gains from screening were 5 to 14 days. Under the scenario of fewer excisional biopsies, gains were 6 to 13 days.

Screening strategies in which 10% of continuing smokers quit each year beginning in 1990 yielded gains of 20 to 28 days by the year 2005 compared with no screening. (A 20% cessation rate yielded 32 to 40 days.) Imperfect adherence to screening yielded gains of 4 to 11 days.

Table 5 (first row) provides predicted probabilities that white males aged 50 years would have at least 1 false-positive screening examination. The sub-

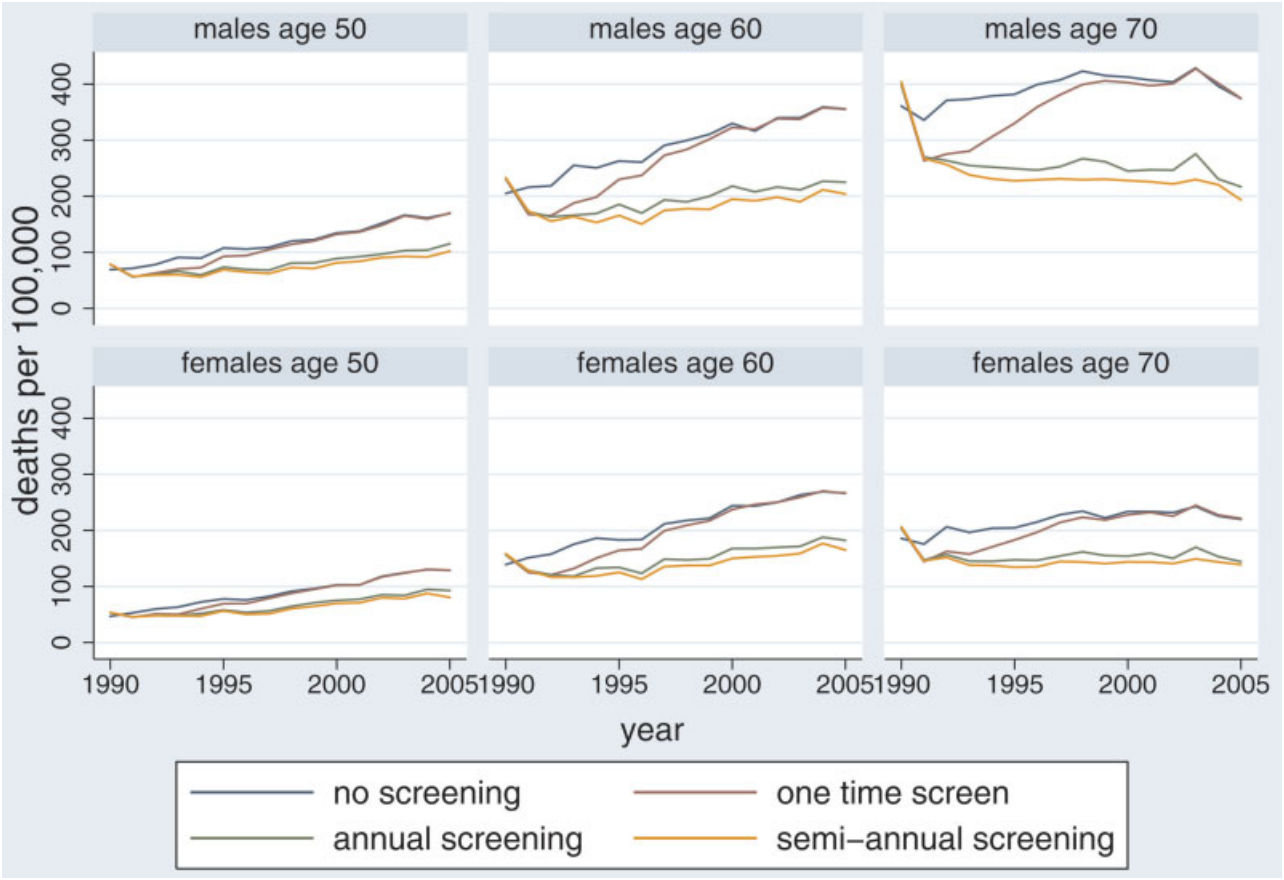

FIGURE 3. Predicted annual lung cancer-specific mortality rates by cohort in 4 screening scenarios.

TABLE 1
Base Case Characteristics of Individuals Diagnosed With Nonsmall Cell Lung Cancer (Any Modality) Between 1990 and 2005

	Mean Age at Diagnosis*				% of Cases Diagnosed in Stages I/II				5-Year Lung Cancer-specific Survival			
Screening Frequency	None	Once	Annually	Twice Annually	None	Once	Annually	Twice Annually	None	Once	Annually	Twice Annually
Men, age, y												
50	58.50	57.75	57.66	57.62	23.88	34.61	71.51	76.82	0.21	0.30	0.63	0.67
60	67.90	67.02	66.98	66.94	27.13	40.12	73.37	77.90	0.23	0.35	0.64	0.68
70	76.88	75.79	75.74	75.67	30.20	46.21	74.55	78.62	0.26	0.41	0.66	0.69
Women, age, y												
50	58.65	58.13	58.03	57.99	24.27	32.05	63.79	68.80	0.21	0.28	0.56	0.60
60	68.18	67.42	67.37	67.32	28.07	39.15	70.66	74.84	0.24	0.34	0.62	0.66
70	77.34	76.56	76.45	76.40	31.59	43.13	69.02	72.85	0.27	0.38	0.60	0.64

*Change in mean age at diagnosis is not an accurate estimate of lead time because of extra incidence in the screened scenarios (see text).

sequent rows in Table 5 reflect the influence of changes in screening program characteristics. Categorizing small (<4 mm diameter) nodules as negative-screen exams reduced the probability of false-positive screen results by >60%, compared with the base-case scenario.

DISCUSSION

We populated the Lung Cancer Policy Model (LCPM) with individuals representative of 6 cohorts of US whites in 1990 and simulated no screening and hypothetical screening scenarios over the time horizon of 1990-2005. Compared with no screening, annual

TABLE 2
Base Case Comparison of Life Years (LYs) Accumulated From 1990 to 2005

	Average LYs per Individual All Smoking Histories				Average LYs per Individual Ever-Smokers Only			
	No Screening	1 Screen	Annual Screens	Twice Annually	No Screening	1 Screen	Annual Screens	Twice Annually
Men, age, y								
50	14.10	14.12	14.13	14.13	13.99	14.01	14.03	14.03
60	12.96	12.99	13.02	13.03	12.74	12.78	12.82	12.83
70	10.72	10.75	10.78	10.79	10.35	10.39	10.44	10.45
Women, age, y								
50	14.42	14.43	14.44	14.44	14.29	14.30	14.32	14.32
60	13.66	13.68	13.70	13.71	13.29	13.33	13.38	13.39
70	12.06	12.07	12.09	12.10	11.31	11.35	11.40	11.42

The maximum number of life years was 15 years from 1990 to 2005. Screening eligibility was defined as at least 20 pack-years of cigarette exposure. Right half of table is limited to individuals who smoked at some point up to and including 2005.

TABLE 3
Base Case Comparison of Life Expectancy (LE) Accumulated From 1990 to Simulated Death (All Smoking Histories)

	Years of Life Expectancy				Weeks of Life Expectancy Gains vs No Screening		
	No Screening	1 Screen	Annual Screens	Twice Annually	1 Screen	Annual Screens	Twice Annually
Men, age, y							
50	28.09	28.11	28.24	28.28	1.4	8.2	10.0
60	19.49	19.53	19.68	19.72	2.5	10.1	12.0
70	12.42	12.46	12.53	12.55	2.1	5.9	6.7
Women, age, y							
50	31.30	31.32	31.42	31.45	0.9	6.0	7.5
60	22.34	22.37	22.50	22.53	1.8	8.2	9.8
70	14.65	14.67	14.71	14.72	1.1	3.4	3.9

Screening eligibility was defined as at least 20 pack-years of cigarette exposure.

screening of ever-smokers with at least 20 pack-years of cigarette exposure would have provided an ever-smoker with an additional 1 to 5 weeks (11 to 33 days) of life by 2005; note that gains in LY from 1990 to 2005 (Tables 2 and 4) leave out days of life that accrue after 2005. Gains in overall life expectancy (LE) (Table 3), in contrast, allow comparison to evaluations of other medical interventions that report LE gains, but our LE estimates are subject to the simplifying assumption of constant secular trends past 2005. Gains of 3 to 10 weeks of LE from annual lung cancer screening of smokers (a secondary prevention) would compare favorably to successful prevention strategies in average-risk populations (eg, breast, cervical, and colorectal cancer screening), for which a gain in LE of 1 month could be considered large.[39,40] Gains of 10 weeks of LE from lung cancer screening would be considered modest, however, compared with prevention strategies in high-risk populations (eg, prophylactic surgery in BRCA1/2 carriers or antihypertensives in patients at high risk of cardiovascular disease), which provide years of LE gain.[39,41,42]

Lung cancer is not the leading cause of death (even in heavy smokers), so relatively large decreases in lung cancer-specific mortality (Fig. 3) may be offset by deaths due to competing causes, limiting the overall gains in LE. Combining smoking cessation with screening, therefore, is potentially attractive and has been investigated in single-arm studies.[43,44] The combination of CT screening and a 10% or 20% annual cessation rate, if achieved, yielded predicted LY gains of more than 20 or 30 days during the time horizon 1990-2005. Whether such combined programs would be a good use of resources relative to stand-alone smoking cessation programs will require cost-effectiveness analyses.

TABLE 4
Sensitivity Analyses of Incremental* Change in Days of Life From 1990 to 2005 in Cohorts of White Males Aged 50 Years in 1990

Scenario	1 Screen	Annual Screening	Twice Annually Screening
Base Case	5	11	12
Screening eligibility			
10 pack-years	6	12	13
30 pack-years	4	8	9
Reduced operative mortality	9	16	17
Ignore <4 mm	6	12	14
Min. detectable growth of 1 mm	5	12	13
Decreased sensitivity of CT†	5	12	12
Change in biopsy types	6	12	13
Adherence to screening			
70%	4	6	6
80%	5	8	8
93.5%	5	11	11
Cessation rate of 10%	20	27	28
Cessation rate of 20%	32	39	40

*Compared with Base Case No Screening scenario (Table 2).
†Base case sensitivity of helical CT for peripheral pulmonary nodules was 0.63 for 1-4 mm nodules, 0.77 for 4-8 mm nodules, and 1.0 for nodules >8 mm. In the decreased sensitivity scenario, sensitivity was 0.44 for 1-4 mm nodules, 0.54 for 4-5 mm nodules, 0.77 for 5-8 mm nodules, and 1.0 for nodules >8 mm. In both scenarios, the sensitivity for a central nodule of the same diameter was reduced by 25%.

TABLE 5
Comparison of False-Positive Screen Results in Representative Cohort of White Males Aged 50 Years in Alternate Scenarios

	Probability of False-Positive Screening Test Anytime Between 1990-2005 Among Persons With ≥1 Screen		
Scenario	1 Screen	Annual Screens	Twice Annually Screens
Base Case	.4979	.7650	.7696
Min. detectable growth of 1 mm	.4978	.7651	.7697
Decreased CT sensitivity	.4071	.7634	.7706
Ignore <4 mm	.1778	.2913	.2903
Change in biopsy types	.4978	.7647	.7693

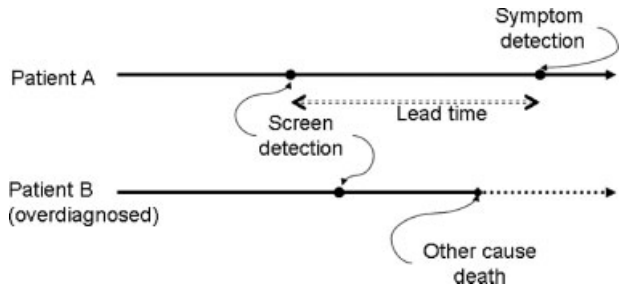

FIGURE 4. Arrows indicate time. The diagram for Patient A demonstrates calculation of lead time (time between screen-detection and symptomatic detection), and the diagram for Patient B demonstrates an overdiagnosed case (screen-detection of a case that would not have presented symptomatically before other-cause death).

Annual and semiannual screening led to increased numbers of lung cancer diagnoses (Fig. 2) compared with the no screening scenario. The magnitude of increased incidence varied across cohorts that differed in smoking history, birth cohort, and sex. Because screening (by design) diagnoses asymptomatic cancers, screening will identify some overdiagnosed cases, such as patients who would have died of other causes before developing symptoms of lung cancer (Fig. 4; Patient B). Overdiagnosis is an inconsistently used term, and there is currently no way to identify which screen-detected lung cancers are overdiagnosed.[45] On a population level, simulation studies can quantify harm from treating overdiagnosed cases and from invasive staging for false-positive screening examinations and then compare these to the benefits possible from screening.

Compared with patients who were diagnosed with nonsmall cell lung cancers in nonscreened scenarios, NSCLC patients in the screened scenarios were diagnosed on average at younger ages and at earlier stages, with concomitant clinically important increases in 5-year lung cancer-specific survival (Table 1). Note that the decrease in age at diagnosis is not equivalent to the lead time, which is defined only in patients diagnosed with lung cancer in both a screening scenario and in a nonscreening scenario (Fig. 4; Patient A). Predicted results from the LCPM correspond to single-arm screening studies and other modeling approaches.[13,14,46] We have previously[13] discussed our findings in relation to 2 high-profile studies that reached different conclusions on the effectiveness of screening.[1,47] Among all NSCLC patients in the annual screening scenario, our predicted proportion stage I/II (64% to 75%) is comparable to the 74% stage I/II observed in 3 screening studies of smokers[47] but lower than that reported by the I-ELCAP study (85%), which also screened never-smokers.[1]

Lung-cancer screening is not currently recommended, so it is unknown how adherence would compare with US rates of adherence to other cancer screening programs, such as cervical (86%), breast (76%), prostate (54%), or colorectal (57%).[48] In our analyses, adherence played an important role in determining the overall gains possible with annual screening. We found that 70% adherence to annual screening provided 55% of the gain from perfect adherence to annual screening (6 days vs 11 days for the base case) in a hypothetical cohort of white men aged 50 years.

False-positive screening results are associated with increased risks of invasive follow-up procedures for benign disease. In the base case, the LCPM simulates all patients as receiving an aggressive diagnostic algorithm consistent with guideline care.[49] More aggressive staging results in higher rates of invasive biopsies and associated mortality than would be observed in usual practice, as demonstrated by the increases in days of life in scenarios with reduced operative mortality, fewer excisional biopsies, and ignoring small nodules. In addition, categorizing small (<4 mm diameter) nodules as negative-screen exams (as per protocol in the NLST) reduced the probability of a false-positive screen result by >60%. We did not assess whether false-positive results would influence subsequent CT screening adherence, because evidence from other screening modalities on the direction of this effect has been mixed, as false-positive exams decreased participation in subsequent chest x-ray screens for lung cancer,[50] but false-positive mammograms may increase subsequent breast-cancer screening participation.[51]

Stricter eligibility for screening (30 pack-years vs 10 or 20 pack-years) had a strong influence on the LY gains from screening. Stricter eligibility in a randomized, controlled trial (RCT) would be expected to increase power to see a statistically significant effect on lung cancer-specific mortality, but results in smokers with many accumulated pack-years may not be generalizable to populations of lighter smokers. Note that the purpose of our study was not to predict results from the NLST. (We did not simulate chest x-ray screening and did not have smoking histories of trial participants.)

This study, like all studies based on modeling largely unobservable disease processes, was subject to limitations[52] and should be viewed as a tool for informing screening debates in the years before publication of long-term trial results.[8] The LCPM is not directly informed by randomized trials of CT screening effectiveness, but was calibrated and validated with observational data.[14] Comparative modeling studies (eg, CISNET) will be helpful to assess the influences of particular natural history assumptions on model predictions compared with the NLST results, once released.

The current LCPM simulates all lung cancer patients to receive guideline care[49] and, therefore, may overestimate benefits from screening. Neither consequences from incidental findings due to screening participation (eg, early diagnosis of other cancers) nor increased lung-cancer risks from CT-radiation exposure was modeled. Sparse data on smoking and lung cancer in minorities (for model inputs and calibration targets) limited this analysis to US whites. We, therefore, did not estimate the possible mortality changes from screening African-American men, who experience the highest lung cancer death rates in the US population. Smoking histories did not incorporate the tendency of beginning smokers to gradually increase the number of cigarettes smoked per day. A closer approximation of such smoking behavior would yield fewer individuals eligible for screening and would reduce the apparent effectiveness of screening.

Our simulations offer insight into the potential effects of screening and suggest that the adoption of screening in 1990 may have offered substantial gains in 5-year survival along with modest gains in life expectancy.

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