Cost-Effectiveness of Computed Tomography Screening for Lung Cancer in the United States

Pamela M. McMahon, PhD,† Chung Yin Kong, PhD,*† Colleen Bouzan, MS,* Milton C. Weinstein, PhD,‡§ Lauren E. Cipriano, BSc, BA,*‖ Angela C. Tramontano, MPH,* Bruce E. Johnson, MD,‡¶ Jane C. Weeks, MD, MS,‡# G. Scott Gazelle, MD, MPH, PhD*†§*

Introduction: A randomized trial has demonstrated that lung cancer screening reduces mortality. Identifying participant and program characteristics that influence the cost-effectiveness of screening will help translate trial results into benefits at the population level.

Methods: Six U.S. cohorts (men and women aged 50, 60, or 70 years) were simulated in an existing patient-level lung cancer model. Smoking histories reflected observed U.S. patterns. We simulated lifetime histories of 500,000 identical individuals per cohort in each scenario. Costs per quality-adjusted life-year gained ($/QALY) were estimated for each program: computed tomography screening; stand-alone smoking cessation therapies (4–30% 1-year abstinence); and combined programs.

Results: Annual screening of current and former smokers aged 50 to 74 years costs between $126,000 and $169,000/QALY (minimum 20 pack-years of smoking) or $110,000 and $166,000/QALY (40 pack-year minimum), when compared with no screening and assuming background quit rates. Screening was beneficial but had a higher cost per QALY when the model included radiation-induced lung cancers. If screen participation doubled background quit rates, the cost of annual screening (at age 50 years, 20 pack-year minimum) was below $75,000/QALY. If screen participation halved background quit rates, benefits from screening were nearly erased. If screening had no effect on quit rates, annual screening costs more but provided fewer QALYs than annual cessation therapies. Annual combined screening/cessation therapy programs at age 50 years costs $130,500 to $159,700/QALY, when compared with annual stand-alone cessation.

Conclusions: The cost-effectiveness of computed tomography screening will likely be strongly linked to achievable smoking cessation rates. Trials and further modeling should explore the consequences of relationships between smoking behaviors and screen participation.

Key Words: Lung cancer, Screening, Cost-utility analysis, Microsimulation model.

(*J Thorac Oncol.* 2011;6: 1841–1848)

The National Lung Screening Trial (NLST) released results earlier than planned on demonstrating that screening with computed tomography (CT) (when compared with screening with chest x-ray) reduced lung cancer mortality by 20%.[1,2] As noted by NLST investigators,[1] the mortality reduction observed in the self-selected, volunteer population (n = 53,456) under controlled trial settings will not eliminate all uncertainties surrounding the effectiveness or value of screening in the general population.[3] Modeling can complement randomized trials by simulating screening in populations with characteristics different than trial participants under different scenarios and comparing screening with other lung cancer control interventions.

Because of the strong causal link between smoking and lung cancer, mortality reductions possible with screening will depend in part on whether screen participation alters a smoker's likelihood of quitting. CT screening has been described as a potential "teachable moment" for motivating continuing smokers to quit.[4–7] Alternatively, if no lung cancer is detected, smokers could believe that they will not develop cancer and have been given license to continue to smoke. Which of these effects, if either, will be observed in the NLST is not yet clear. European studies have reported that trial participants have higher quit rates than the general population but small or no differences in quit or relapse rates between participants in the control and screened arms.[8,9]

For this analysis, we used an existing microsimulation model that previously predicted mortality reductions between 15% (15 years of follow-up) and 28% (6 years of follow-up) for five annual screens in smokers with 20 pack-years of exposure,[10] compared with 20% reduction (6 years of follow-up) for three annual screens in smokers with 30 pack-years of exposure as reported by the NLST.[1] Our model simulated

*Institute for Technology Assessment, Massachusetts General Hospital; †Department of Radiology; ‡Department of Medicine, Harvard Medical School; §Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts; ‖Department of Management Science and Engineering, Stanford University, Stanford, California; ¶Lowe Center for Thoracic Oncology; and #Center for Outcomes and Policy Research and Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts.

Disclosure: The National Electrical Manufacturers Association funded Tramontano and Gazelle for an unrelated project. Gazelle is a consultant to GE Healthcare. All other authors declare no conflicts of interest.

Address for correspondence: Pamela M. McMahon, PhD, Institute for Technology Assessment, 101 Merrimac Street 10th floor, Boston 02114, MA. E-mail: pamela@mgh-ita.org

ISSN: 1556-0864/11/0611-1841

cohorts of individuals representative of the U.S. population and not specifically the NLST cohort. Treatment costs and measures of health-related quality of life (QOL), as well as risks of secondary lung cancers due to radiation exposure from CT examinations, were incorporated. The mortality reduction reported from the NLST was not used as an input or calibration endpoint for this analysis.

The purpose of our study was to estimate the cost-effectiveness of CT screening for lung cancer in the U.S. population and to identify characteristics of lung cancer screening programs (i.e., screen frequency and adherence, eligibility, follow-up program, effects on cessation, and costs) with the largest influences on the cost-effectiveness of screening. We compared smoking cessation therapies with screening and with programs that combined smoking cessation and screening.

MATERIALS AND METHODS

This study used publicly available deidentified human subject data and the single cohort Lung Cancer Policy Model (LCPM), previously used to predict the long-term effectiveness of screening[10,11] (see Supplemental Digital Content 1, http://links.lww.com/JTO/A134, which provides additional methods and model details, Supplemental Digital Content 2, http://links.lww.com/JTO/A135, which provides a schematic of the model, Supplemental Digital Content 3, http://links.lww.com/JTO/A136, which provides model inputs specific to this analysis, Supplemental Digital Content 4, http://links.lww.com/JTO/A137, which provides costs used for this analysis, and www.cisnet.cancer.gov/profiles for details on the LCPM, including references for model inputs, calibration and validation, and prior applications).

The LCPM is a patient-level microsimulation model of lung cancer development, progression, detection, treatment, and survival. Lung cancer natural history parameters were previously estimated by calibration against tumor registry data on age-specific lung cancer incidence rates, distributions of size, stage and cell types of incident lung cancers, and lung cancer-specific survival. Lung cancers have varied progression rates and can be five major histologies. Model validation included reproducing endpoints from two screening studies (rates of positive screens, stage, and cell type distributions) and two cohort studies (mortality).

The model simulates symptomatic, incidental, and (for screening scenarios) screen detection of benign and malignant pulmonary nodules. Sensitivity of screening CT examinations is a function of the diameter and location (central versus peripheral) of a pulmonary nodule. CT has a sensitivity of 0.63 for peripheral nodules of 1 mm in diameter, 0.77 for peripheral nodules of 4 mm in diameter, and 1.0 for peripheral nodules of 8 mm in diameter or larger. CT was assumed to have lower sensitivity for central nodules (75% of that for peripheral nodules of the same size) to account for obstruction by the aorta, etc. Pulmonary nodules (benign and malignant) detected on imaging examinations are triaged by size. In the base case, nodules less than 4 mm are not followed, nodules 4 to 8 mm are followed by serial high-resolution CT (at months 1, 3, 6, 9, 12, and 24), and nodules $\geq$8 mm are biopsied with bronchoscopy, fine-needle biopsy, or video-assisted thoracoscopy. In sensitivity analyses, we simulated fewer high-resolution CT examinations (4–6 mm nodules were followed at months 9 and 24 and 6 to 8 mm at months 6, 12, and 24).

Survival after diagnosis is modeled explicitly as a function of treatment and underlying disease characteristics (not using a stage shift as in previous studies[12]). Staging and treatment of non-small cell lung cancer and small cell lung cancer followed National Comprehensive Cancer Network consensus guidelines in place in 2000. Invasive examinations and surgical resection are associated with operative mortality in the model.

Smoking histories (ages of starting and stopping smoking and an average dose) representative of six cohorts of U.S. white males and females aged 50, 60, and 70 years in 1990 were derived from survey data and used to generate six fixed cohorts of 500,000 individuals.[11,13] Competing mortality risks were stratified by smoking status, age, and sex. No lung cancer screening was recommended during the 1990s; thus, the no-intervention scenario corresponds to observed incidence.

Smoking Cessation

Current smokers faced an annual background rate of smoking cessation of 3%,[14] uncorrelated with pack-years. Except where noted, screen participation was uncorrelated with the probability of cessation.

We investigated the effects of a smoking cessation therapy consisting of bupropion and nicotine replacement therapy prescribed to current smokers. Omitting the distinction between therapy uptake and efficacy, 1-year abstinence rates evaluated were 4%, 8%, 16%, or 30% (versus 3% background), reflecting estimates that vary widely depending on the population and intervention.[15–19] Unless offered cessation therapy at the next program visit, individuals with elevated cessation rates were assumed to revert to the background 3% after 1 year.

Benefits and Harms of Screening

In the model, features of the screening program (CT sensitivity, frequency of screening examinations, and eligibility for screening) are translated into estimates of the effectiveness of screening. In other words, the effectiveness of screening (i.e., the relative reduction in mortality) is a model output, generated as a nonlinear function of the benefits and harms of screening. Screening effectiveness cannot be directly varied to identify thresholds for screening to be cost-effective.

Screening leads to detection of asymptomatic, prevalent lung cancers, and benign pulmonary nodules. The proportion of screening examinations with positive results (both false positive [benign] and true positive [cancer]) varies with the age of the cohort, the number of screens, and the definition of a positive test. On a baseline (prevalent) screen with small ($<$4 mm) nodules categorized as "not suspicious for lung cancer," the positivity rate is approximately 20%.[13] The model predicts that screening leads to an excess of lung cancer cases; the magnitude of the excess varies with numbers of screens and length of follow-up.[10,11] Harms from

screening include operative mortality, costs of follow-up examinations (for both cancer and ultimately benign nodules), and an increased risk of subsequent lung cancers (with all attendant costs and outcomes) arising from radiation exposure from screening and follow-up CT examinations (see Supplemental Digital Content 1, which provides details of radiation risk component). No disutilities from screening-related anxiety were considered.

Except where noted, all eligible individuals were assumed to participate in screening. In a sensitivity analysis, 70% of eligible individuals adhered to their screening schedule.

Except where noted, screening had no effect on the probability of smoking cessation.[8] The direction and magnitude of any independent effect of screening on smoking cessation are unknown, so we postulated a wide range of pessimistic to optimistic scenarios in sensitivity analyses: each instance of screening participation could reduce (to 1.5%; pessimistic scenario) or increase (to 4% or 6%; optimistic scenarios) an individual's probability of quitting smoking over the subsequent year.

Costs and QOL

Diagnosis, staging, and treatment costs were derived from Medicare reimbursements. Costs of diagnostic tests (including screening CTs) were estimated by 2006 Medicare payments (per CPT code in the Physician Fee Schedule). Details of treatment costs by phase of care are available elsewhere.[20] Surveillance, Epidemiology and End Results-Medicare linked data were used to create patient-level monthly costs, grouped into baseline (prediagnosis), initial (30 days to 7 months after diagnosis), continuing, and terminal (final month of life) phases of care and stratified by stage, histology (non-small cell lung cancer versus small cell lung cancer), and treatment (surgery, radiation, and chemotherapy). The initial phase excluded the first 30 days postdiagnosis, which encompassed costs of dissimilar staging algorithms. Baseline (nonlung cancer) medical costs were estimated as costs accrued in a 12-month period before presentation with lung cancer (excluding 3 months immediately preceding diagnosis to subtract costs of treating undiagnosed lung cancer). This analysis used constant costs (averaged during 1992–2003, in constant 2006$). We replaced continuing-phase treatment costs with baseline costs for long-term (>3 or 5 years) survivors in a sensitivity analysis.

Patient-time costs for diagnostic tests and treatments were estimated using age-specific wages of an average worker in 2006 (U.S. Bureau of Labor Statistics). Caregiver time (e.g., accompanying patient to chemotherapy) was assumed equal to patient time for diagnostics, surveillance, and initial phases of care and represented by the cost of hospice care for the terminal phase. Costs of pharmaceuticals (e.g., antiemetics and smoking cessation therapies) were estimated by average wholesale prices (Red Book, Thompson Reuters).

The cost of a smoking cessation intervention (see later) was estimated at $300, based on a combination of 1 month of 24-hour nicotine transdermal patches (Watson labs, 7 or 14 mg; $188) plus 30 days of 300 mg bupropion HCl (Watson labs, 150 mg tablets; $116). Separately, the cost of cessation was increased sixfold to represent a longer treatment duration and/or additional costs required to achieve the same cessation rates.

Baseline QOL weights for nonlung cancer states, stratified by age and gender, were U.S.-specific standardized values derived from survey participants' self-reported health as measured by the EQ-5D.[21] To avoid a possible increase in health-related QOL from treatment for lung cancer, we multiplied the baseline weights by weights for lung cancer states. Studies of QOL in patients with lung cancer provide cell type, stage, and treatment-specific QOL scores derived from patients using a variety of assessment instruments[22–24] and transformed into utilities.[22] In the base case, patients undergoing resection (lobectomy) experienced a 3-month disutility and then a return to baseline.[25]

Analyses

Costs and quality-adjusted life-years (QALYs) were discounted at 3% annually.[26] Incremental cost-effectiveness ratios were calculated for nondominated strategies in 2006 U.S. $/QALY.[26] A strategy was dominated if it costs more but provided fewer benefits than a comparator or if it had a higher incremental cost-effectiveness ratio than a more effective strategy (weakly dominated).

Ratios were first calculated for CT screening versus no intervention. For the base case and the scenarios that incorporated risks of radiation-induced lung cancer, individuals with ≥20 pack-years were eligible. Scenarios with more restrictive eligibility or independent effects of screen participation on cessation but no radiation risks were also evaluated.

Alternative program characteristics (CT sensitivity, screening adherence, diagnostic test costs, operative mortality, and follow-up of nodules <4 mm) and assumptions regarding QOL (a return to baseline QOL at 1, 6, 12, or 24 months after lobectomy or never[27]) were simulated in 50-year-old men.

Cessation alone and a combined cessation/screening were simulated in 50-year olds. The combined program consisted of screening CT for current and former smokers, plus bupropion and nicotine replacement therapy prescribed to current smokers at the screening examination.

Statistical Methods

We simulated lifetime histories of the six fixed cohorts of 500,000 individuals described earlier in each scenario. The number of first-order trials is scalable, and second-order uncertainty is not considered in these analyses. Thus, p values for comparisons between strategies are uninformative and not reported.

RESULTS

Per person screened (≥20 pack-years), the incremental lifetime healthcare costs for a single screen (versus no screen) varied from $1778 to $3637 and provided between 0.009 and 0.022 additional QALYs ($144,000–$207,000/QALY). Corresponding gains in undiscounted life-years ranged from 0.018 to 0.045 (7–16 days). One-time screening provided reductions in lung cancer-specific mortality of between 5.02 and 7.52% compared with no screening.

In all cohorts, single screening was excluded by weak dominance. Compared with no screening, annual screening of persons with at least 20 pack-years of smoking history reduced lung cancer-specific mortality by 17.98 to 25.16% at 10 years at a cost of $126,000 to $169,000/QALY (Table 1).

TABLE 1. Annual CT Screening (≥20 Pack-Year Smoking History) vs. No Intervention

Cohort Sex	Cohort Age (Yr)	Screen Frequency/ Age Range (Yr)	% of Cohort Screened	Risk of Radiation-Induced Lung Cancer	Fewer Follow-Up CT Examinations	Incremental Cost-Effectiveness Ratio ($/QALY)	Mortality Reduction (%) Versus No Intervention, (10-Yr Follow-Up)	Mortality Reduction (%) Versus No Intervention, (15-Yr Follow-Up)
Males	50	Annual/50–70	69	−	−	149,000	25.16	28.69
				+	−	158,000	25.06	28.08
				−	+	147,000	23.15	24.80
				+	+	150,000	23.14	24.69
	60	Annual/60–74	72	−	−	135,000	25.06	27.66
				+	−	139,000	24.96	27.18
				−	+	129,000	23.01	23.80
				+	+	130,000	22.99	23.71
	70	Annual/70–74	70	−	−	169,000	20.94	16.21
				+	−	172,000	20.85	15.92
				−	+	160,000	19.45	14.81
				+	+	160,000	19.43	14.77
Females	50	Annual/50–70	40	−	−	137,000	19.48	22.37
				+	−	203,000	19.18	19.63
				−	+	135,000	18.09	19.44
				+	+	152,000	18.03	19.00
	60	Annual/60–74	47	−	−	126,000	23.07	25.21
				+	−	151,000	22.80	22.87
				−	+	121,000	21.15	21.60
				+	+	127,000	21.08	21.16
	70	Annual/70–74	39	−	−	159,000	17.98	13.26
				+	−	172,000	17.76	12.00
				−	+	153,000	16.10	11.61
				+	+	156,000	16.11	11.35

Scenarios that included (+) risks of radiation-induced lung cancer assumed 3.8–3.9 mGy (screening CT) and 58 mGy (follow-up CT) organ doses and a 10-yr lag between exposure and incidence. See text for details of scenarios that modeled (+) less-intensive follow-up. Costs and QALYs discounted at 3% annually.

CT, computed tomography; QALY, quality-adjusted life-year.

Including risks of radiation-induced lung cancer yielded smaller mortality reductions and higher costs ($139,000–$203,000/QALY, Table 1, follow-up CT dose of 58 mGy). Alternate estimates for organ doses for follow-up CTs (both 10 mGy and 90 mGy were used) yielded a range of $133,000 to $247,000/QALY (not shown). Follow-up algorithms with fewer CT examinations yielded ranges of $121,000 to $160,000/QALY without radiation risks and $127,000 to $160,000/QALY with radiation risks (Table 1).

Restricting screening to individuals with ≥40 pack-years, current smokers, or current smokers and recent quitters yielded ratios from $110,000 to $166,000/QALY (Table 2). Single screens were weakly dominated.

In cohorts of 50-year olds, if screen participation itself was associated with a doubling (to 6%) of the background cessation rate, annual screening (perfect adherence) was associated with a cost (versus no screening) of $73,000/QALY (men) and $40,000/QALY (women), whereas a 33% increase (to 4%) of background cessation resulted in cost-effectiveness ratios of $105,000/QALY (men) and $97,000/QALY (women). In the pessimistic scenario in which screen participation was associated with a 50% reduction (to 1.5%) in cessation, the cost-effectiveness ratios were $880,000/QALY (men) and more than $1 million/QALY (women; Table 3).

Treatment costs that return to baseline at 36 or 60 months after resection (versus base case 100 months) yielded ratios of $134,000/QALY or $135,000/QALY (women) and $145,000/QALY or $146,000/QALY (men; Table 3).

In a cohort of 50-year-old men, imperfect (70%) adherence to annual screening was associated with a cost (versus no screening) of $180,000/QALY (Table 4). Perfect sensitivity of CT for peripheral pulmonary nodules yielded a ratio of $141,000/QALY (Table 4), comparable with the base case: most of the additional nodules detected were less than 4 mm and therefore not followed. Neither following nodules less than 4 mm nor a reduction in the cost of screening CT was associated with a ratio of less than $100,000/QALY. Reductions in operative mortality for lobectomy and invasive staging examinations reduced the ratio to $141,000/QALY. Prolonged delays before a return to baseline health after resection yielded greater costs per QALY.

One-time smoking cessation therapy costing $300 costs between $11,400/QALY (30% cessation, men) and $69,300/QALY (4% cessation, women), compared with no intervention (Table 5). Annual smoking cessation therapy programs offered additional benefits at costs from $12,500 to $69,400/QALY. An annual combination strategy yielded more benefits than annual cessation therapy alone but at an incremental

TABLE 2. Annual CT Screening with Varying Eligibility vs. No Intervention

Eligibility	Cohort Sex	Cohort Age (Yr)	% of Cohort Screened	$/QALY Compared with No Intervention
Current and former heavy smokers (minimum PY = 40)	Male	50	29	$126,000
		60	60	$132,000
		70	58	$166,000
	Female	50	<1	n/r
		60	15	$110,000
		70	14	$142,000
Current and former smokers who quit ≤10 yr ago (minimum PY = 20)	Male	50	31	$126,000
		60	25	$122,000
		70	16	$147,000
	Female	50	27	$127,000
		60	22	$112,000
		70	14	$142,000
Current heavy smokers (minimum PY = 40)	Male	50	29	$130,000
		60	23	$123,000
		70	16	$149,000
	Female	50	<1	n/r
		60	15	$112,000
		70	13	$145,000

PY, pack-years; n/r, not reported because <1% of simulated women aged 50 years had accumulated >40 PY; CT, computed tomography; QALY, quality-adjusted life-year.

TABLE 3. Annual CT Screening vs. No Intervention: Sensitivity Analyses in Cohorts of Men and Women Aged 50 Yr

Scenario	$/QALY Compared with No Intervention, Men Age 50 Yr	$/QALY Compared with No Intervention, Women Age 50 Yr
Base case[a]	$149,000	$137,000
Screen participation increases cessation rate to 6%	$73,000	$40,000
Screen participation increases cessation rate to 4%	$105,000	$97,000
Screen participation cuts cessation rate in half to 1.5%	$880,000	$1,034,000
Duration of increased treatment costs after resection		
3 yr	$145,000	$134,000
5 yr	$146,000	$135,000

[a] Base case assumed 3% annual background cessation rate, perfect adherence, and 8-yr continuing treatment costs after resection.

CT, computed tomography; QALY, quality-adjusted life-year.

TABLE 4. Annual CT Screening vs. No Intervention: Sensitivity Analyses in Cohorts of Men Aged 50 Yr

Scenario	$/QALY Compared with No Intervention
Base case[a]	$149,000
70% adherence to screening	$180,000
CT sensitivity = 100%	$141,000
Less-costly helical CT ($188, HOPPS)	$120,000
Follow-up nodules <4 mm	$148,000
Lower operative mortality (3%, lobectomy; 0.1% mediastinoscopy; 0.2% VATS)	$141,000
Delay before return to baseline health after resection	
1 mo	$147,000
6 mo	$150,000
12 mo	$154,000
24 mo	$161,000
No recovery	$209,000

[a] Base case values: perfect adherence; CT sensitivity based on diameter; screening CT cost of $283 based on Physician Fee Schedule; no follow-up of nodules <4 mm; operative mortality 4% (lobectomy), 0.3% (mediastinoscopy), and 0.5% (VATS); and 3 mo recovery after resection.

HOPPS, Hospital Outpatient Prospective Payment System; VATS, video-assisted thoracoscopy; CT, computed tomography; QALY, quality-adjusted life-year.

cost from $130,500 to $159,700/QALY (see Supplemental Digital Content 5, http://links.lww.com/JTO/A138, which is a figure legend for Supplemental Digital Content 6, http://links.lww.com/JTO/A139, which is a plot of costs versus effects).

Cessation therapy costing $1800 and yielding 4% abstinence was weakly dominated by annual screening in 50-year olds. Results for abstinence rates of 8% or higher followed a pattern similar to the $300 cessation therapy: ratios less than $60,400/QALY for annual cessation therapy and more than $100,000/QALY for annual combination programs (not shown).

DISCUSSION

The NLST recently provided evidence that individuals randomized to three annual CT screens had 20% lower lung cancer-specific mortality than individuals randomized to

TABLE 5. Screening or Cessation Alone vs. Combination (Cessation Therapy Offered at Screening of Both Current and Former Smokers ≥20 Pack-Years), in Cohorts of 50-Yr Olds

	Men: 1-Yr Abstinence with Cessation Therapy				Women: 1-Yr Abstinence with Cessation Therapy			
Strategies	**4%**	**8%**	**16%[a]**	**30%**	**4%**	**8%**	**16%**	**30%**
Cessation alone, single	$49,100	$17,700	$12,900	$11,400	$69,300	$20,800	$14,400	$12,400
Cessation alone, annual	$57,600	$20,800	$14,900	$12,500	$69,400	$23,900	$16,600	$13,700
Combination, annual	$144,500	$153,900	$158,800	$159,700	$130,500	$139,300	$145,800	$146,800

[a] Shown in Figure 1 (Supplemental Digital Content 6, http://links.lww.com/JTO/A139). Table based on $300 cessation therapy and 3% baseline annual cessation in no-intervention and screening-alone scenarios (screening alone was dominated).

three annual chest x-ray screens.[1] The NELSON trial (n = 15,822) is powered to show a mortality reduction of 25% from CT screening, compared with usual care.[28] It was not possible to simulate these trials or to calibrate to the NLST results, because we did not have individual level demographics and smoking histories (pack-years decomposed into dose and duration over time) necessary to predict lung cancer risks. We, therefore, simulated cohorts of individuals representative of the U.S. population. Further, we did not include a module for chest x-ray screening and could not simulate the NLSTs follow-up patterns for individuals with millimeter-sized nodules (the study design did not specify a protocol). Our analysis, completed before release of the NLST results, predicted a range of 17.76 to 25.16% reduction in lung cancer-specific mortality at 10 years, depending on the number of screens (4–10), the cohort, and whether radiation risks are included (Table 1), compared with no intervention. Other modeling studies of the effectiveness of CT screening completed before the NLST predicted benefits ranging from no benefit[29] to reductions in lung cancer-specific mortality of 8.0 to 45.6%, depending on model assumptions and screening program characteristics (e.g., eligibility criteria, screening modality and frequency, patient management, and length of follow-up).[10,12,30–34]

We found that unless screen participation increases smoking cessation, lung cancer screening was considerably more expensive than other U.S. screening programs. Colorectal cancer screening—widely viewed to be cost-effective—has cost-effectiveness ratios (versus no screening) in the range of $13,000 to $32,000/LY (2006$).[35] Breast cancer screening of women aged 40 years or older with mammography has a cost-effectiveness ratio compared with no screening of $47,700/QALY (2006$).[36]

We predicted low costs per QALY for cessation therapy, consistent with estimates that range from cost saving to $17,000/QALY (2006$).[37–39] Much of the gain in life expectancy after cessation is due to decreases in deaths from causes other than lung cancer.[40]

Our base case estimates of $126,000 to $169,000/QALY for annual screening of 50–70-year-old ever smokers is comparable with a prior estimate of $143,000/QALY (2006$) for annual CT screening of current smokers.[12] Our microsimulation approach includes a natural history model calibrated to tumor registry data rather than a stage shift as the mechanism for screening effectiveness, so did not require estimates of screening biases as inputs. Our approach simulates symptom-related and incidental detection of lung cancers in addition to screen detection and permitted evaluation of strategies using cessation therapy and programs that used different follow-up algorithms and eligibility. We showed that the influences of eligibility, screening frequency, adherence, frequency of follow-up CT examinations, and accumulated radiation risks on cost-effectiveness were smaller in magnitude than influences of cessation. Our model suggests that results from screening trials should be interpreted with consideration given to the specifics of any cessation component.

Our "no-intervention" scenarios were fit to observed incidence rates and used contemporaneous inputs but are historical and omit advances in staging and targeted therapies. Our assumption that patients undergo guideline care was common to all scenarios but overestimates the percentage of patients who undergo lobectomy. Our results may thus overestimate the gain in QALYs attributable to screening. We allow for nonoperative candidates (7.7%), but an additional 16 to 20% (depending on age) of early-stage patients in Surveillance, Epidemiology and End Results do not undergo surgery for unspecified reasons. Our analysis was limited to whites due to insufficient individual level data in other populations on smoking histories and cancer outcomes necessary for model development.

We assumed a societal perspective, which dictated inclusion of all costs without regard to who pays them. We used Medicare fee schedules, which were in part designed to approximate the resource use costs of all medical interventions, including the initial screening examination, which is not typically reimbursed.[26] Use of health-related QOL indexes other than the EQ-5D for the general population would have yielded different QALY totals, but because trends by age are similar across standard indexes,[41] the incremental change in QALYs and therefore costs per QALY between scenarios would be similar to those we estimated.

Imperfect uptake of cessation therapies would likely translate to abstinence rates closer to the lower end (4%) of the range we evaluated than the maximum (30%). We did not vary screening's effect on cessation according to the test result and did not consider perceptions of lung cancer risk, which may influence participation and cessation.[7,42] Our predicted mortality reduction from annual screening in the absence of radiation-induced lung cancers (>16% in all cohorts) exceeded a threshold (1–4%) postulated to outweigh risks of radiation-induced lung cancers (50–52-year-old male current smokers).[43] When risks of radiation-induced lung

cancers were included in the model, estimated mortality reductions at 15 years were within 1% (on an absolute scale) of the base case estimates in male cohorts and within 3% in female cohorts. Reducing the frequency of follow-up CT examinations reduced the magnitude of the effect of radiation risk on 15-year mortality reductions (within 1% in all cohorts) from screening but did not alter the conclusions: the risk of radiation-induced lung cancers was outweighed by the reduction in deaths from lung cancer attributed to screening. Fewer follow-up CT examinations not only reduced radiation risks but also delayed detection of some small, growing cancers: mortality reductions were lower compared with the base case, and the cost for all six cohorts remained more than $120,000/QALY.

Changes to several model inputs could result in higher costs per QALY than estimated in this study: an increased cost of the screening CT examination or other treatments (for instance, to reflect retail prices rather than opportunity costs and the societal perspective we adopted); addition of positron emission tomography-CT in the staging algorithm (although costs of positron emission tomography-CT would be offset by some reductions in excisional biopsies); and addition of targeted therapies for lung cancer such as erlotinib (although the cost per QALY would offset by increased survival for patients with sensitizing mutations).

In conclusion, results from a microsimulation model suggest that the cost-effectiveness of CT screening programs will be strongly influenced by smoking cessation rates among screen participants. The specific eligibility criteria will be more influential on the cost-effectiveness of screening than other program characteristics such as the screening test cost or radiation risks. Unless screen participation increases the probability of cessation, screening with helical CT may cost more than $100,000/QALY compared with no intervention and be more expensive and provide fewer QALYs than an annual cessation intervention. A combined screening/cessation program would offer benefits to both current and former smokers but would cost more than $100,000/QALY. Understanding behaviors surrounding smoking and screen participation[6,7] will be critical for translating trial results into population benefits.

ACKNOWLEDGMENTS

Supported by American Cancer Society (RSG 2008A060554) and National Cancer Institute (R01CA97337 [to G.S.G.] and R00CA126147 [to P.M.M.]).

Rob Boer, PhD, David Levy, PhD, Karen M. Kuntz, ScD, David C. Christiani, MD, MPH, CISNET Lung investigators, Michael Gilmore, MBA.

REFERENCES

1. National Lung Screening Trial Results, 2010. Available at http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease. Accessed November 4, 2010.
2. National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243–253.
3. Dominioni L, Rotolo N, Poli A, et al. Self-selection effects in smokers attending lung cancer screening: a 9.5-year population-based cohort study in Varese, Italy. *J Thorac Oncol* 2010;5:428–435.
4. Cox LS, Clark MM, Jett JR, et al. Change in smoking status after spiral chest computed tomography scan screening. *Cancer* 2003;98:2495–2501.
5. Townsend CO, Clark MM, Jett JR, et al. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. *Cancer* 2005;103:2154–2162.
6. Taylor KL, Cox LS, Zincke N, et al. Lung cancer screening as a teachable moment for smoking cessation. *Lung Cancer* 2007;56:125–134.
7. Park E, Ostroff J, Gareen I, et al. Risk perceptions among national lung screening trial participants. *Ann Behav Med* 2009;37:268–279.
8. Ashraf H, Tonnesen P, Pedersen JH, et al. Smoking habits were unaffected by CT screening at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). *Thorax* 2008;64:388–392.
9. van der Aalst CM, van den Bergh KA, Willemsen MC, et al. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. *Thorax* 2010;65:600–605.
10. McMahon PM, Kong CY, Johnson BE, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT screening study. *Radiology* 2008;248:278–287.
11. McMahon PM, Kong CY, Weinstein MC, et al. Adopting helical CT screening for lung cancer: potential health consequences during a 15-year period. *Cancer* 2008;113:3440–3449.
12. Mahadevia P, Fleisher L, Frick K, et al. Lung cancer screening with helical computed tomography in older adult smokers. *JAMA* 2003;289:313–322.
13. Model profiler of the MGH-ITA Lung Cancer Policy Model. CISNET. Available at: http://cisnet.cancer.gov/profiles/. Accessed May 6, 2010.
14. The Commit Research Group. Community Intervention Trial for Smoking Cessation (COMMIT): II. Changes in adult cigarette smoking prevalence. *Am J Public Health* 1995;85:193–200.
15. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685–691.
16. Prevention and Cessation of Cigarette Smoking: Control of Tobacco Use (PDQ(R)), Health Professional Version. U.S. National Institutes of Health, 2008. Available at: www.cancer.gov/cancertopics/pdq/prevention/control-of-tobacco-use/HealthProfessional. Accessed February 5, 2009.
17. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007:CD000031. Review.
18. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008:CD000146.
19. Paluck EC, McCormack JP, Ensom MH, et al. Outcomes of bupropion therapy for smoking cessation during routine clinical use. *Ann Pharmacother* 2006;40:185–190.
20. Cipriano LE, Romanus D, Earle CC, et al. Lung cancer treatment costs, including patient responsibility, by stage of disease and treatment modality, 1992–2003. *Value Health* 2010;14:41–52.
21. Hanmer J, Lawrence W, Anderson J, et al. Report of nationally representative values for the non-institutionalized US adult population for seven health related quality of life scores. *Med Decis Making* 2006;26:391–400.
22. Earle C, Chapman R, Baker C, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncolgy* 2000;18:3302–3317.
23. Handy JR Jr, Asaph JW, Skokan L, et al. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. *Chest* 2002;122:21–30.
24. van den Hout WB, Kramer GW, Noordijk EM, et al. Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. *J Natl Cancer Inst* 2006;98:1786–1794.
25. Balduyck B, Hendriks J, Lauwers P, et al. Quality of life evolution after lung cancer surgery: a prospective study in 100 patients. *Lung Cancer* 2007;56:423–431.
26. Gold MR, Siegel JE, Russell LB, et al. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
27. Cannon J, Win T. Long-term quality of life after lung resection. *Thorac Surg Clin* 2008;18:81–91.
28. Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer* 2006;54:177–184.

29. Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. *JAMA* 2007;297:953–961.
30. Chien CR, Chen TH. Mean sojourn time and effectiveness of mortality reduction for lung cancer screening with computed tomography. *Int J Cancer* 2008;122:2594–2599.
31. Manser R, Dalton A, Carter R, et al. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer* 2005;48:171–185.
32. Plevritis S, Sigal B. Estimating the stage shift and mortality reduction from CT lung cancer screening. Chicago, IL: Radiological Society of North America, 2003.
33. Gorlova OY, Amos C, Henschke C, et al. Genetic susceptibility for lung cancer: interactions with gender and smoking history and impact on early detection policies. *Hum Hered* 2003;56:139–145.
34. Foy M, Yip R, Chen X, et al. Modeling the mortality reduction due to computed tomography screening for lung cancer. *Cancer* 2011;117:2703–2708.
35. Pignone M, Saha S, Hoerger T, et al. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;137:96–104.
36. Stout NK, Rosenberg MA, Trentham-Dietz A, et al. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst* 2006;98:774–782.
37. Hall S, Lightwood J, Humfleet G, et al. Cost-effectiveness of bupropion, nortriptyline, and psychological intervention in smoking cessation. *J Behav Health Serv Res* 2005;32:381–392.
38. Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counseling. *JAMA* 1996;275:1247–1251.
39. Krumholz HM, Weintraub WS, Bradford WD, et al. Task force #2—the cost of prevention: can we afford it? Can we afford not to do it? 33rd Bethesda Conference. *J Am Coll Cardiol* 2002;40:603–615.
40. Kenfield SA, Wei EK, Rosner BA, et al. Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. *Tobacco control* 2010;19:248–254.
41. Fryback DG, Palta M, Cherepanov D, et al. Comparison of 5 health-related quality-of-life indexes using item response theory analysis. *Med Decis Making* 2010;30:5–15.
42. van den Bergh KA, Essink-Bot ML, van Klaveren RJ, et al. Informed participation in a randomised controlled trial on CT screening for lung cancer. *Eur Respir J* [published online ahead of print March 12, 2009] doi: 10.1183/09031936.00098908.
43. Berrington de Gonzalez A, Kim KP, Berg CD. Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. *J Med Screen* 2008;15:153–158.