Annals of Internal Medicine | ORIGINAL RESEARCH

Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

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Background: The optimum screening policy for lung cancer is unknown.

Objective: To identify efficient computed tomography (CT) screening scenarios in which relatively more lung cancer deaths are averted for fewer CT screening examinations.

Design: Comparative modeling study using 5 independent models.

Data Sources: The National Lung Screening Trial; the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial; the Surveillance, Epidemiology, and End Results program; and the U.S. Smoking History Generator.

Target Population: U.S. cohort born in 1950.

Time Horizon: Cohort followed from ages 45 to 90 years.

Perspective: Societal.

Intervention: 576 scenarios with varying eligibility criteria (age, pack-years of smoking, years since quitting) and screening intervals.

Outcome Measures: Benefits included lung cancer deaths averted or life-years gained. Harms included CT examinations, false-positive results (including those obtained from biopsy/surgery), overdiagnosed cases, and radiation-related deaths.

Results of Best-Case Scenario: The most advantageous strategy was annual screening from ages 55 through 80 years for ever-smokers with a smoking history of at least 30 pack-years and ex-smokers with less than 15 years since quitting. It would lead to 50% (model ranges, 45% to 54%) of cases of cancer being detected at an early stage (stage I/II), 575 screening examinations per lung cancer death averted, a 14% (range, 8.2% to 23.5%) reduction in lung cancer mortality, 497 lung cancer deaths averted, and 5250 life-years gained per the 100 000-member cohort. Harms would include 67 550 false-positive test results, 910 biopsies or surgeries for benign lesions, and 190 overdiagnosed cases of cancer (3.7% of all cases of lung cancer [model ranges, 1.4% to 8.3%]).

Results of Sensitivity Analysis: The number of cancer deaths averted for the scenario varied across models between 177 and 862; the number of overdiagnosed cases of cancer varied between 72 and 426.

Limitations: Scenarios assumed 100% screening adherence. Data derived from trials with short duration were extrapolated to lifetime follow-up.

Conclusion: Annual CT screening for lung cancer has a favorable benefit–harm ratio for individuals aged 55 through 80 years with 30 or more pack-years' exposure to smoking.

Primary Funding Source: National Cancer Institute.

Ann Intern Med. 2014;160:311-320. www.annals.org

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This article was published online first at www.annals.org on 31 December 2013.

The burden of lung cancer in the world remains extremely high: The International Agency for Research on Cancer estimated 1.6 million new diagnoses in 2008 (12.7% of total cases of cancer) and 1.4 million deaths (18.2% of total cancer mortality) (1). In the United States and Canada, incidence (per 100 000) is 48.5 for men and 35.8 for women; mortality (per 100 000) is 37.9 and 24.2, respectively; and cumulative risk (to age 74 years) of dying of lung cancer is 3% in women and 4.6% in men. In the United States, 228 000 new cases of lung cancer and about 160 000 deaths are estimated for 2013 (2). Despite substantial reductions in smoking prevalence in the United States, which translated into an approximately 32% reduction in lung cancer mortality between 1975 and 2000 at the population level (3), lung cancer remains the leading cause of cancer death.

Recently, the National Lung Screening Trial (NLST) demonstrated that in a volunteer population of current and former smokers who were aged 55 to 74 years at entry, had at least 30 pack-years of cigarette smoking history, and had quit no more than 15 years previously (for former smokers), 3 annual computed tomography (CT) screening examinations reduced lung cancer–specific mortality by 20% relative to 3 annual chest radiography screening examinations at a median follow-up of 6.5 years (4). This trial did not directly address the effects of additional rounds of screening, long-term benefits or harms, or multiple alternative screening policies with different screening intervals and different eligibility criteria. Moreover, long-term outcomes must be quantified to understand the tradeoffs be-

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tween benefits and potential harms involved with alternative screening strategies (5). In this study, we estimate future harms and benefits of lung cancer screening and identify a set of possible efficient lung cancer screening policies by using 5 separately developed microsimulation models calibrated to the 2 largest randomized, controlled trials on lung cancer screening. This work was initiated by the U.S. Preventive Services Task Force (USPSTF) to inform its recommendations on lung cancer screening.

METHODS

Calibration of 5 Models to Deidentified Lung Cancer Screening Data From the NLST and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

We used 5 models calibrated to individual-level, deidentified data from the NLST (6) and the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening) trial (7). The NLST enrolled 53 452 persons at high risk for lung cancer at 33 U.S. centers from August 2002 through April 2004. Participants were randomly assigned to undergo 3 annual screening examinations with low-dose CT (26 722 participants) or single-view posterior–anterior chest radiography (26 730 participants). The PLCO trial randomly assigned 154 901 participants aged 55 through 74 years at entry, 77 445 of whom were assigned to annual chest radiography and 77 456 to usual care between November 1993 and July 2001. There was no eligibility requirement concerning smoking. Although the PLCO trial compared chest radiography with no screening, it provided information on the natural history of lung cancer.

Groups of investigators at the following 5 institutions independently developed the models: Erasmus Medical Center in Rotterdam, the Netherlands (model E); Fred Hutchinson Cancer Research Center in Seattle, Washington (model F); the Massachusetts General Hospital in Boston, Massachusetts (model M); Stanford University in Stanford, California (model S); and the University of Michigan in Ann Arbor, Michigan (model U). Each model estimates screening effectiveness on the basis of a different set of assumptions that are key in predicting the effects of earlier treatment, and each model uses different mathematical formalisms and model structures. In essence, all the models account for the individual's age-specific smoking-related risk for lung cancer, date and stage of lung cancer diagnosis, the corresponding lung cancer mortality, and the individual's life expectancy in the presence and absence of screening (**Appendix Figure 1**, available at www.annals.org).

For correct extrapolation of different possible screening scenarios, one must obtain the best estimates on several key parameters, including the duration of the screening-detectable preclinical period (by test, age, histologic characteristics, and sex), sensitivity (by test, age, and sex), and improvement in prognosis by earlier detection and treatment. All models were first set to mimic the design of both trials (for example, setting the numbers of screening examinations and screening method, ages at screening, smoking history and sex of enrollees, and screening intervals). The models are validly calibrated when the key parameters—which may differ by model—can be estimated or adjusted to replicate the trial data closely. After calibration, the models reproduce the observed cumulative incidence of lung cancer (by stage, histologic characteristics, sex, age, type of detection, and round of screening) and lung cancer mortality in both groups of the trials. Close calibration to the 19% (95% CI, 7% to 25%) lung cancer mortality difference between groups of the NLST at 6 years of follow-up was prioritized (see **Appendix Figure 2** and **Appendix Table**, available at www.annals.org, for key similarities and differences among the 5 models in calibration targets.)

Choosing Screening Programs and Expressing Harms and Benefits

The modeling groups standardized input data on smoking histories and non–lung cancer mortality to simulate life histories of the U.S. cohort born in 1950 by using an updated version of the National Cancer Institute's Smoking History Generator (8–11). All models included other-cause mortality to differ by sex, age, smoking status, and smoking intensity. A set of 576 programs that varied frequency of CT screening for lung cancer (1-, 2-, or 3-year intervals), ages of starting (45, 50, 55, or 60 years) and stopping (75, 80, or 85 years) screening (assuming that a last screening examination is included at this age), and eligibility based on smoking history (10, 20, 30, or 40 pack-years; having quit smoking 10, 15, 20, or 25 years previously) was examined, with analyses run separately for men and women.

In all scenarios, perfect screening adherence was assumed. Once a person's characteristics did not satisfy the eligibility criteria (such as passing the limit of years since smoking cessation), he or she would not be invited for future screenings. Potential benefits are expressed as lung cancer deaths averted and life-years gained. Potential harms are expressed as the number of screening examinations plus follow-up imaging examinations, number of false-positive results (including findings on surgery and biopsy), number of overdiagnosed lung cancer cases, and number of radiation-related lung cancer deaths. Follow-up procedures were assumed to be consistent with the observed rate of examinations per positive screening examination in the NLST; 2 models used explicit follow-up algorithms based on nodule size thresholds. False-positive results were estimated as a direct proportion to the number of CT screening examinations, as based on the average in 3 rounds of the NLST; we assumed that a false-positive result in a

given round did not influence the probability of a false-positive result in subsequent rounds.

Overdiagnosed cases are the additional number of lung cancer cases detected in the screening scenarios compared with the estimated number of cases diagnosed in the absence of screening (12). All models simulate the underlying natural history of lung cancer (separately by histologic type) in individuals and include dose–response modules that relate a detailed cigarette smoking history over time to lung cancer risk. Each comparison is based on an identical underlying simulated cohort of individuals with the same smoking histories, sex composition, and potential times of other-cause death. Another scenario that reflects overdiagnosis is a person who has lung cancer that is expected to be clinically detected after death from other causes but whose cancer in the screening scenario is detected before death from other causes.

For all measures of benefits and harms, expressed per 100 000 persons, a cohort of persons born in 1950 was followed from ages 45 to 90 years. We identified "efficient" scenarios as those that prevented the most lung cancer deaths for the same number of CT screening examinations (not including follow-up scans). Model results were compared by using the data envelopment analysis method (13), which is an engineering-based approach for selecting efficient scenarios from among a collection of alternatives. In simple terms, it finds programs that are near the efficient frontier, with consideration given to whether one is prioritizing maximizing benefits (that is, deaths averted [*y*-axis]) or minimizing harms (that is, CT screening examinations [*x*-axis]). For each model's results, we generated a rank score (decile of distance from the model's frontier) for each scenario not on the frontier. We identified scenarios on (score 0) or closest to (first 3 deciles) the frontier of at least 3 models. Two models (F and M) were used to estimate radiation-related lung cancer cases (see the **Appendix**, available at www.annals.org). All results were averaged across all 5 models. Finally, an advantageous scenario was selected that was efficient and led to a substantial reduction in lung cancer mortality and life-years gained at reasonable harms. The number of screening examinations needed was similar to (a continuous) NLST scenario and to breast and colorectal cancer screening guidelines, given manpower and resources.

Role of the Funding Source

The National Cancer Institute supported the infrastructure for the Cancer Intervention and Surveillance Modeling Network models. The Agency for Healthcare Research and Quality funded this work and provided review. The authors worked with USPSTF members to specify the overall questions. These data did not include personally identifying information and were therefore exempt from institutional review board review.

RESULTS

Benefits and Harms of Efficient Scenarios

Of the 576 possible programs, 120 were on or close to the efficient frontier, where no alternative that provides more lung cancer deaths averted for fewer CT screening examinations exists. **Table 1** shows the benefits of 26 top-ranked triennial, biennial, and annual scenarios, as well as benefits of a 27th program that was most similar to the NLST strategy but was not among the consensus efficient programs. None of the top-ranked scenarios had a starting age of 45 years. For the top-ranked triennial and biennial efficient programs, the starting age was 60 years and the minimum number of pack-years was 40 (with 1 exception). Triennial screening programs led to limited reductions in lung cancer mortality: from 4.6% to 6% in this cohort (range, 1.7% to 9.5% across models). Biennial programs led to 6.5% to 9.6% reductions in lung cancer mortality (range, 2.3% to 14.8% across models). When we compared the least intensive program (60-80-40-10, with values arranged per the following order: start age–stop age–minimum pack-years–maximum years since quitting smoking) of triennial to biennial screening, the additional percentage of lung cancer deaths averted was about 40%, at the expense of about 50% additional screening examinations (see **Appendix Figure 3**, available at www.annals.org). Annual screening scenarios provided substantially more benefit, leading to 11% to 21.2% reductions in lung cancer mortality (range, 4.3% to 39.1% across models). In these scenarios, 48.1% to 56.9% of lung cancer cases were detected at stage I/II, compared with 37.4% without screening. The scenario most similar to the NLST criteria (A [annual]-55-75-30-15) led to fewer lung cancer deaths averted but more screenings compared with the next-most-intensive program (A-60-80-30-25).

Table 2 summarizes the most important harms associated with the scenarios. The number of follow-up imaging procedures and false-positive results increased proportionally to the number of CT screening examinations needed in each scenario, leading to 1.0 to 4.9 false-positive results per person screened. Decreasing the minimum pack-years eligibility criteria from 30 to 20 pack-years and to 10 pack-years in annual scenarios provided a relatively small increase in lung cancer deaths averted versus the large number of additional CT scans. Although these are still efficient scenarios, they require substantially more CT screening examinations (both overall and per person) and follow-up procedures, and false-positive results increase proportionally. Overdiagnosis ranged from 1.5% to 6.6% of all lung cancer cases, or 8.7% to 13.5% of screening-detected lung cancer cases.

Lung Cancer Deaths Averted and Life-Years Gained

Clinical concerns about the potential for increased operative mortality in older individuals with a history of heavy smoking, as well as increased comorbidity and reduced eligibility for surgery with curative intent at higher

Table 1. **Benefits of 26 Selected Efficient Screening Programs and a Screening Program Most Similar to Eligibility Criteria for the National Lung Screening Trial***

Frequency–Start Age (*y*)–Stop Age (*y*)–Pack-Years–Years Since Quitting	Cohort Eligible, %	CT Screening Examinations, *n*	Screening-Detected Cases, *n*	Total Cases Detected at an Early Stage, %†	Reduction in Lung Cancer Mortality, %	Lung Cancer Deaths Averted, *n*‡	Life-Years Gained	Life-Years Gained per Lung Cancer Death Averted	Screening Examinations per Life-Year Gained, *n*	Screening Examinations per Lung Cancer Death Averted, *n*
T-60-80-40-10	11.2	45 685	787	42.0	4.6	172	1823	10.6	25	265
T-60-85-40-10	11.3	48 317	943	42.6	5.1	190	1894	10.0	26	254
T-60-85-40-15	12.0	55 316	1043	43.3	5.4	201	2000	10.0	28	275
T-60-85-40-25	13.0	66 333	1139	44.1	6.0	225	2252	10.0	29	294
B-60-80-40-10	11.2	67 167	1072	44.0	6.5	241	2526	10.5	27	278
B-60-85-40-10	11.3	69 662	1181	44.3	6.9	256	2665	10.4	26	272
B-60-85-40-15	12.0	79 757	1279	45.3	7.4	275	2882	10.5	28	290
B-60-80-40-25	13.0	90 337	1279	45.5	7.7	286	3017	10.6	30	315
B-60-85-40-25	13.0	95 914	1536	46.3	8.4	312	3045	9.8	32	307
B-60-85-30-20	17.9	127 046	1744	47.5	9.6	358	3451	9.6	37	354
A-60-80-40-25§	13.0	171 924	1664	48.1	11.0	410	4211	10.3	41	419
A-60-85-40-25	13.0	185 451	1911	49.4	12.1	449	4203	9.4	44	413
A-55-85-40-20	14.0	220 505	1967	50.0	13.0	485	4811	9.9	46	454
A-55-80-40-25§	13.9	221 606	1782	49.2	12.3	458	4777	10.4	46	483
A-60-80-30-25§	18.8	253 095	1983	50.4	13.3	495	4940	10.0	51	511
A-55-75-30-15‖	19.2	265 049	1646	48.4	12.3	459	5375	11.7	49	577
A-60-85-30-25	18.8	271 152	2263	52.1	14.7	547	5322	9.7	51	495
A-50-85-40-25	14.6	281 218	2159	51.4	14.6	542	5908	10.9	48	518
A-55-80-30-15§	19.3	286 813	1971	50.5	14.0	521	5517	10.6	52	550
A-60-80-20-25§	24.8	327 024	2419	51.9	15.4	573	5707	10.0	57	570
A-55-80-30-25§	20.4	342 880	2288	52.1	15.8	588	6321	10.8	54	583
A-60-85-20-25	24.8	348 894	2779	53.7	16.8	624	5934	9.5	59	559
A-55-80-20-25§	27.4	455 381	2543	53.9	17.9	664	7092	10.7	64	685
A-55-85-20-25	27.4	477 334	2955	55.6	19.1	712	7490	10.5	64	670
A-55-80-10-25§	36.0	561 744	2803	55.2	19.4	721	7693	10.7	73	777
A-50-80-20-25	29.0	588 516	2732	55.2	20.0	743	8530	11.5	69	792
A-50-85-20-25	29.0	610 443	3153	56.9	21.2	787	8948	11.4	68	775

A = annual; B = biennial; CT = computed tomography; T = triennial.

* Numbers are per a 100 000-person cohort followed from ages 45 to 90 years and are based on averaged estimates across the 5 models. The screening programs are labeled as follows: Frequency–age start–age stop–minimum pack-years–maximum years since quitting. Note that these mortality reductions are different from the observed point estimate in the National Lung Screening Trial because in our cohort analysis only eligible persons are screened (dilution) and it is a lifetime reduction compared with 6-years' follow-up in the trial.

† Average percentage of cases detected at an early (I/II) stage in the no-screening scenario was 37.4%. Incident number of cases in the no-screening scenario was 5119 per 100 000 persons.

‡ Average number of lung cancer deaths in the no-screening scenario was 3719 (per 100 000-person cohort).

§ Seven programs are the consensus-efficient, annual programs (minimum start age 55) with a stop age of 80 years and screening counts between 200 000 and 600 000, plus an eighth program (A60-80-40-25) with just under 200 000 screening examinations included as a reference program. Note that in this table the columns that include lung cancer deaths averted do not include radiation-related lung cancer deaths (these are presented in **Table 2**).

‖ Denotes eligibility most similar to that in the National Lung Screening Trial.

age limits, led us to focus on scenarios with stopping ages of 80 years or younger. **Figure 1** shows the effect of expanding the smoking eligibility in the age range of 55 through 80 years, beyond the criteria similar to those used in NLST: for example, to 25 years since quitting (A-55-80-30-25) or 20 or fewer pack-years (A-55-80-20-25 or A-55-80-10-25). More lung cancer deaths may be averted with more CT screening examinations, but there are diminishing returns (although not at a single distinct point). The A-60-80-20-25 scenario, which extends eligibility to individuals with fewer pack-years but starting at a later age, was still efficient with respect to number of screening examinations and lung cancer deaths averted, but it provided relatively fewer life-years gained than did A-55-80-30-15. For the 3 consecutive scenarios of A-55-80-30-15, A-60-80-20-25, and A-55-80-30-25, the number of screening examinations per lung cancer death averted increased progressively (550, 570, and 583 examinations), whereas the number of screening examinations per life-year gained was the highest (that is, the worst) for A-60-80-20-25 (52, 57, and 54 examinations). The A-60-80-20-25 scenario also resulted in the highest number and percentage of overdiagnosed cases.

Advantageous Scenario

Of the efficient scenarios, annual screening in the age range of 55 through 80 years had substantial benefits while maintaining a moderate level of harms. We judged a strategy that was similar to the NLST criteria—starting screening at age 55 years, but ending through age 80 years for ever-smokers with a smoking history of at least 30 pack-years, and no more than 15 years since quitting for former smokers (A-55-80-30-15)—as the advantageous scenario with the optimum balance of benefits and harms.

Table 3 summarizes the modeled data (14–19) about harms and benefits associated with that scenario expressed per 100 000 45-year-old persons born in 1950 and followed through age 90 years. The upper- and lower-bound estimates presented in the table are ranges found across the 5 different models and not CIs. The table illustrates that 19 300 of 100 000 individuals would be eligible for screening at some point in their lifetime. Without screening, lung cancer will be diagnosed in 5119 and 3719 will die of the disease. Assuming 100% adherence to screening, 50.5% of cases of lung cancer will be detected at an early (I/II) stage. There will be 497 fewer lung cancer deaths, and these persons will on average gain 10.6 life-years per death averted. They will also be prevented from experiencing advanced disease and its treatment. On the negative side, 67 550 false-positive results would be expected (19 300 individuals × 3.5 average false-positive results per individual), leading to 910 surgeries or biopsies for benign disease. There would be 1970 persons with a diagnosis of lung cancer made earlier than would have occurred if they had not been screened, and about 10% of these cancer cases would otherwise never have been diagnosed during their lifetime (190 cases).

Increasing the number of pack-years to 40 but extending the years since having quit smoking from 15 to 25 in the age range of 55 to 80 years decreased the percentage eligible from 19.3% to 13.9%; however, these individuals would have an average of 1 more screening examination during their lifetime, thereby increasing harms (**Table 2**). The same scenario for persons with 20 pack-years (instead of 30) or more increased the number of lung cancer deaths averted by 12.9%, but this means 33% more CT screening examinations in the population, with a proportional increase in false-positive test results (**Tables 1** and **2**). Extending eligibility to 10 pack-years or more resulted in 8.6% more deaths averted for 23% more CT scans.

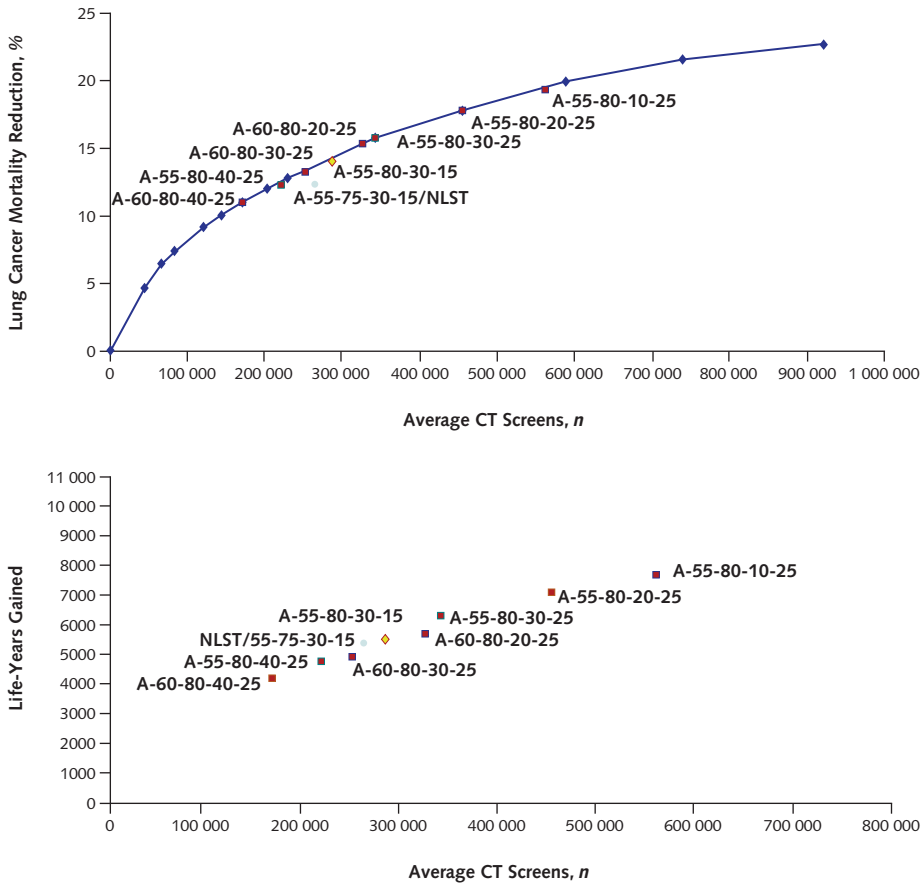
Figure 2 (top) shows the reductions in lung cancer mortality for the 8 (labeled) scenarios for each model

Table 2. **Harms of 26 Selected Efficient Screening Programs and a Screening Program Most Similar to Eligibility Criteria for the National Lung Screening Trial***

Frequency–Start Age (*y*)–Stop Age (*y*)–Pack-Years–Years Since Quitting	CT Screening Examinations, *n*	Total CT Examinations, Including Screening, *n*	Average Screening Examinations per Person Screened, *n*	Average False-Positive Results per Person Screened, *n*	Overdiagnosed Cases, *n*	Overdiagnosis, *% of all cases*†	Overdiagnosis, *% of screening-detected cases*	Radiation-Related Lung Cancer Deaths, *n*‡
T-60-80-40-10	45 685	55 696	4.1	1.0	79	1.5	10.1	9
T-60-85-40-10	48 317	58 677	4.3	1.0	98	1.9	10.5	10
T-60-85-40-15	55 316	66 677	4.6	1.1	119	2.3	11.6	10
T-60-85-40-25	66 333	79 267	5.1	1.2	147	2.8	13.1	11
B-60-80-40-10	67 167	80 068	6.0	1.4	116	2.2	10.9	11
B-60-85-40-10	69 662	82 874	6.2	1.4	129	2.5	11.0	11
B-60-85-40-15	79 757	94 383	6.7	1.6	156	3.0	12.4	12
B-60-80-40-25	90 337	106 512	7.0	1.6	151	2.9	12.0	13
B-60-85-40-25	95 914	112 810	7.4	1.7	184	3.5	12.2	13
B-60-85-30-20	127 046	148 518	7.1	1.7	197	3.8	11.5	16
A-60-80-40-25§	171 924	199 035	13.3	3.1	183	3.5	11.2	17
A-60-85-40-25	185 451	214 351	14.3	3.3	241	4.6	12.9	17
A-55-85-40-20	220 505	254 083	15.8	3.7	224	4.3	11.6	19
A-55-80-40-25§	221 606	255 398	15.9	3.7	194	3.7	11.1	20
A-60-80-30-25§	253 095	291 667	13.5	3.1	231	4.4	11.9	21
A-55-75-30-15‖	265 049	305 181	13.8	3.2	141	2.7	8.7	24
A-60-85-30-25	271 152	312 130	14.4	3.4	296	5.6	13.5	20
A-50-85-40-25	281 218	323 024	19.3	4.5	243	4.6	11.5	22
A-55-80-30-15§	286 813	329 809	14.9	3.5	190	3.7	9.9	24
A-60-80-20-25§	327 024	376 098	13.2	3.1	232	4.4	9.8	25
A-55-80-30-25§	342 880	393 611	16.9	3.9	224	4.3	10.0	25
A-60-85-20-25	348 894	400 898	14.1	3.3	328	6.2	12.2	23
A-55-80-20-25§	455 381	521 943	16.6	3.9	258	4.9	10.4	31
A-55-85-20-25	477 334	546 838	17.4	4.1	348	6.6	12.2	30
A-55-80-10-25§	561 744	643 001	15.6	3.6	259	4.9	9.5	35
A-50-80-20-25	588 516	673 103	20.3	4.7	256	4.9	9.6	38
A-50-85-20-25	610 443	697 962	21.1	4.9	344	6.5	11.3	37

CT = computed tomography.
* Numbers are per a 100 000-person cohort followed from ages 45 to 90 years and are based on averaged estimates across the 5 models. The screening programs are labeled as follows: frequency (A = annual, B = biennial, and T = triennial)–age start–age stop–minimum pack-years–maximum years since quitting. Overdiagnosed cases are slightly overestimated because all counts are up to age 90 years (some cases detected early will appear clinically after age 90 years).
† Incident number of cases in the no-screening scenario was 5119 per 100 000 persons; the number of lung cancer deaths was 3719 per 100 000 persons.
‡ Average of 2 models.
§ Seven programs are the consensus-efficient, annual programs (minimum start age 55) with a stop age of 80 years and screening counts between 200 000 and 600 000, plus an eighth program (A60-80-40-25) with just under 200 000 screening examinations included as a reference program.
‖ Denotes eligibility most similar to that of the National Lung Screening Trial.

Figure 1. **Estimated lung cancer mortality reduction (as percentage of total lung cancer mortality in cohort) and life-years gained (averages of 5 models) from annual CT screening, for programs with minimum eligibility age of 55 years and maximum of 80 years at different smoking eligibility cutoffs and NLST scenario (A-55-75-30-15).**



The average number of CT screening examinations (5 models) is shown on *x*-axis. The graph plots the average number of CT screening examinations against the percentage reduction of lung cancer mortality (*top*) or life-years gained (*bottom*) for each screening scenario (versus no screening) that was estimated for 100 000 individuals of the 1950 cohort followed from ages 45 to 90 years. Programs are labeled as follows: frequency–start age–stop age–minimum pack-years–maximum years since quitting smoking. The reductions in lung cancer mortality differ from the point estimate of the reduction reported at the 6.5-year follow-up in the NLST because only eligible persons are screened in this cohort analysis (dilution) and lifetime reduction in lung cancer mortality is modeled. The top panel shows the efficiency frontier for all models combined. When the slope in the efficiency frontier plot levels off, the additional reductions in mortality per unit increase in use of CT screening examinations are small relative to the previous strategies. A = annual; CT = computed tomography; NLST = National Lung Screening Trial.

group and the average of the 5 models. The reference scenario (A-60-80-40-25) led to a 6.5% to 17.0% decrease in lung cancer mortality, and the A-55-80-30-15 scenario resulted in an 8.6% to 23.5% reduction. The most intensive scenario (A-55-80-10-25) led to an estimated 12% to 34% decrease in lung cancer mortality. The percentage of overdiagnosed screening-detected cases varied between 5% and 17% almost uniformly across inclusion criteria.

DISCUSSION

Our models show that annual lung cancer screening of individuals aged 55 to 80 years with a smoking history of at least 30 pack-years offers substantial benefits. There would be a 14% overall lung cancer mortality reduction and a 25% reduction in those eligible for screening, with relatively limited harms. Extending eligibility to individuals with fewer pack-years, although still efficient, leads to additional benefits along with relatively more harms. The models provide valuable tools to project trial results to different screening scenarios over the course of a lifetime and show the strategies that provide the greatest benefits for a specified level of resources.

The advantageous scenario for lung cancer screening compares favorably with the USPSTF guidelines for breast and colorectal cancer screening. Applying current USPSTF breast cancer screening recommendations to a similar 1950 U.S. cohort translates to about 1.1 million screening examinations (per 100 000 women) and 700 breast cancer

deaths averted through use of the Erasmus model (20). Applying current colorectal screening guidelines translates to about 227 000 screening colonoscopies and 1910 colorectal cancer deaths averted through use of the Erasmus model (21). If we examine eligibility of the advantageous scenario by age in 2013 for the 1950 birth cohort, 17% of the 55- to 64-year-old age group, 12.5% of the 65- to 74-year-old age group, and 7% of the 75- to 80-year-old age group would be eligible for lung cancer screening. Applying these percentages to the current U.S. population means that about 10.5 million persons in the United States would be eligible for screening and that more than 18 000 lung cancer deaths per year might be avoided. That estimate is more optimistic than the recently reported estimates under the NLST criteria of about 8.6 million persons eligible for screening and about 12 000 averted lung cancer deaths (22). Simulating 3 screening examinations as was done in NLST would, in our cohort-based approach, have led to a lifetime 3.7% reduction in lung cancer mortality (not shown). This is notably different from the observed mortality reduction point estimate reported at 6 years' follow-up in the NLST because only eligible persons are screened in our cohort analysis (dilution) and we modeled a lifetime reduction rather than short-term follow-up.

Overdiagnosis is a general concern with screening. There are few estimates of the magnitude of overdiagnosis with CT lung cancer screening (23). We estimated overdiagnosis with CT screening to be less than 17% of screening-detected cases (upper range in **Figure 2**). Although most published reports describing overdiagnosis in breast cancer screening apply to populations (that is, multiple cohorts), our average of 10% of overdiagnosed screening-detected lung cancer cases in the advantageous scenario is equal to that for breast cancer screening every 2 years in women aged 50 to 74 years in relatively low-referral programs (24) and far less than that for breast cancer screening in high-referral countries, such as the United States (25). Two groups explicitly modeled radiation risk and found the number of radiation-related lung cancer deaths to be very small, in line with earlier reports (26).

Several limitations that affect generalizability and certainty of findings are worth noting. First, models assumed 100% adherence to screening. Second, models extrapolated benefits and harms derived from trials with short-term duration to lifetime follow-up in the U.S. population. Although the models were calibrated and are consistent with the NLST and PLCO trial, extrapolations beyond those trials' time horizons, screening intervals, and eligibility criteria introduce uncertainty. Third, 5 models, with different structures and assumptions, showed some variability in their absolute predictions of benefits and harms (**Table 3**), although the ranking of strategies was consistent across models (**Appendix Figure 4**, available at www.annals.org). Moreover, there is variance in the absolute

Table 3. **Number of Individuals Having Benefits and Harms of Annual CT Screening From Ages 55 Through 80 Years***

Benefits/Harms	Average of 5 Models	Lower-Bound Estimate	Upper-Bound Estimate
Benefits			
Persons no longer dying of lung cancer†	497	177	862
Life-years gained	5250	2020	10 153
Persons no longer needing treatment for advanced lung cancer	550	200	950
Life-years with advanced disease prevented‡	550	200	950
Not estimated here			
Persons receiving less intensive or mutilating primary treatment			
Possible additional effect of quitting smoking when offered together			
Harms			
Times persons undergo CT screening examination, *n*	287 000	272 000	301 000
False-positive test results experienced, *n*	67 550	61 250	70 700
Times persons undergo CT follow-up (regular dose), *n*	43 000	23 175	50 100
Persons receiving the diagnosis of lung cancer earlier, *n*	1970	1370	2845
Persons undergoing surgery/biopsy for lesions that ultimately seem benign, *n*	910	825	955
Persons diagnosed with lung cancer who would otherwise never have had the diagnosis (overdiagnosed cases), *n*	190	72	426
Not estimated here			
Persons possibly falsely reassured by a negative test result (postponing future visits when noticing symptoms or signs)			
Persons possibly increasing smoking after a negative test result			

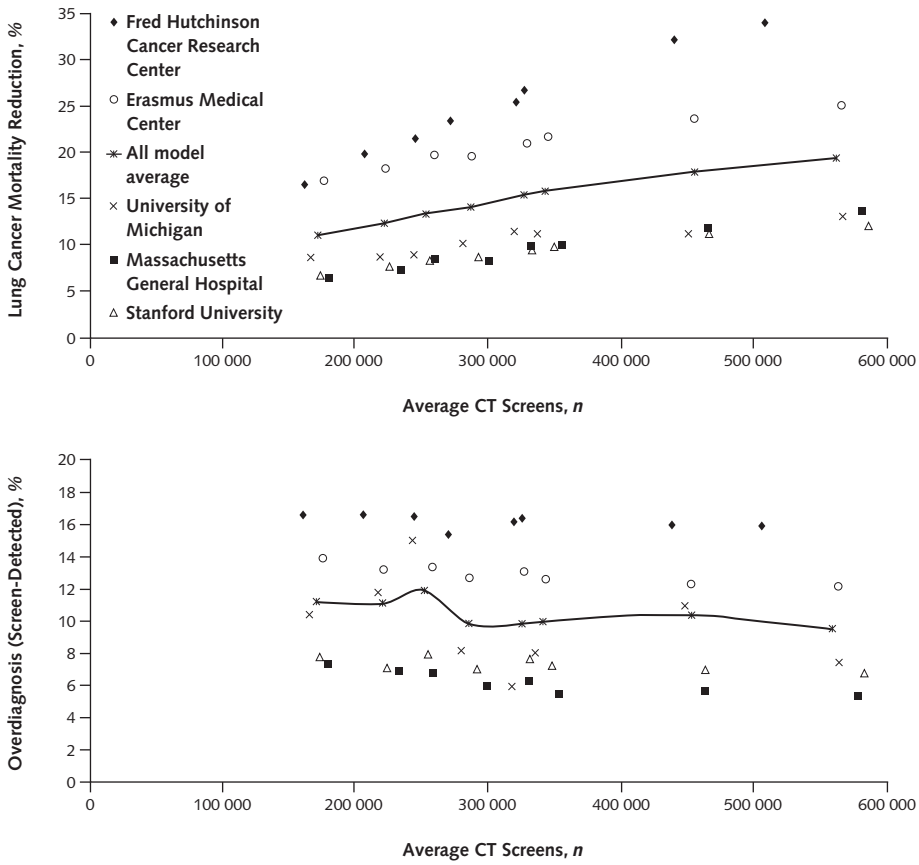
CT = computed tomography.

* Current and former smokers have a minimum smoking history of 30 pack-years, and former smokers quit in the past 15 years. Numbers for 100 000 individuals from the 1950 U.S. cohort followed from ages 45 to 90 years; 19 300 persons eligible, assuming 100% compliance. A total of 5119 lung cancer cases was diagnosed without screening, and 5307 were diagnosed with screening; 37% were screening-detected (average of 5 models). A total of 3719 lung cancer deaths occurred without screening.

† Incorporates 24 radiation-related deaths.

‡ The number of life-years with advanced disease prevented was derived from reference 14. The number of biopsies performed for ultimately benign lesions was based on the National Lung Screening Trial: There were 164 surgeries and 66 needle biopsies for benign nodules out of 17 053 false-positive test results or 75 126 CT screening examinations, making up 1.3% of false-positive test results. Differences in the range of results reflect differences in modeling approaches but should not be seen as formal 95% CIs. We did not consider that the earlier knowledge of the diagnosis of cancer has been shown to negatively affect quality of life (15), including adverse effects of treatment, anxiety regarding assessment, and longer hospitalizations; the possible risks of false reassurance (a false-negative screening test may lead to postponing access to care) (16); or the possibility of a behavioral change (that is, relapsing to smoking) after the screening examination (17–19).

Figure 2. **Estimated percentage of reduction in lung cancer mortality and overdiagnosed cases (of screening-detected cases) for the highlighted scenarios in Tables 1 and 2 (average number of CT screening examinations is shown on the *x*-axis) for all individual models and the average of the 5 models.**



Presentation of a 100 000-person 1950 cohort followed from ages 45 to 90 years. CT = computed tomography.

level of lung cancer deaths averted between the models, ranging from 177 to 862, and variance in the overdiagnosis estimates, ranging from 72 to 426, for the A-55-80-30-15 scenario. Fourth, although extrapolations to the age span of 75 to 80 years seem reasonable (for example, the oldest participants in the NLST were screened until age 78 years), there are still limited observational data on screening in older individuals. We did note, however, that sicker individuals who were deemed less favorable candidates for possible surgical cure did not affect ranking of the strategies (data not shown).

Benefits were extrapolated from 1 large-scale trial in the United States with positive results, whereas 2 small fair-quality (27) European trials have published negative interim results (28, 29). However, these are not large enough to have statistical power to show a clinically plausible effect, in contrast to the NELSON (Nederlands-Leuven Screening Onderzoek) trial, which enrolled 15 822 individuals aged 50 to 75 years and compared CT screening with no screening (30). Preliminary analyses showed that the percentage of lung cancer detected early is more favorable than in the NLST (31–33). Mortality results are still pending. The NELSON trial has primarily used volume-doubling times and volume measurements of lung nodules to define its referral strategy, thereby substantially reducing the number of positive and false-positive results: About 60% of referrals were for false-positive results, and the percentage of referrals was about 2% (32). It may therefore be feasible to reduce one of the important harms of lung cancer screening via changes in follow-up guidelines.

The criteria we simulated in our scenarios may not be ideal in clinical practice. Number of pack-years is a known moderate surrogate measure of risk (34); its use for inviting persons to participate in a program may lead to "screening desirable" answers. Use of a risk prediction model in the PLCO trial, as compared with the NLST criteria, would have led to 41% fewer lung cancer cases being missed (35). In the coming years, it may be possible to improve eligibility criteria for screening and adapt our models to incorporate broader eligibility criteria based on more complex measures of risk (36). It will also be important to investi-

gate possible important differences between men and women. In general, studies demonstrate that women receive diagnoses at an earlier age and at a more favorable cancer stage and more frequently are identified as having adenocarcinomas compared with men (14, 37–41). Recently, subgroup analyses of NLST showed statistically significant reductions in lung cancer mortality in persons diagnosed with adenocarcinoma (relative risk, 0.75 [95% CI, 0.60 to 0.94]) and not for other histologic types. These results also showed borderline-significant interaction with sex (relative risk, 0.73 for women vs. 0.92 for men; $P = 0.08$) (42).

Inviting asymptomatic individuals for screening and implementing a large-scale screening program should be considered only when the benefits clearly outweigh the harms. Our analysis provides a detailed account of the balance between harms and benefits of annual lung cancer screening to inform individuals, clinicians, and policymakers. However, our predictions have some uncertainty and are contingent on high-quality screening, 100% adherence to screening, and closely coordinated follow-up and treatment protocols. Future providers and possible recipients of lung cancer screening should be fully aware of this and opt for screening only after having been informed about these harms and benefits.

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Disclaimer: The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the Agency for Healthcare Research and Quality.

Acknowledgment: The authors thank Melecia Miller, MPH (formerly of Massachusetts General Hospital); Suresh Moolgavkar (Fred Hutchinson Cancer Research Center); and Arry de Bruijn (Erasmus Medical Center).

Grant Support: This report is based on research conducted by the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network through support from an interagency agreement with the Agency for Healthcare Research and Quality, Rockville, Maryland (administrative supplement to U01 CA152956).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-2316.

Reproducible Research Statement: *Study protocol:* Available from Dr. Meza (e-mail, rmeza@umich.edu). *Statistical code:* Please go to http://cisnet.cancer.gov/lung/profiles.html. *Data set:* Please go to https://biometry.nci.nih.gov/cdas.

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Administrative, technical, or logistic support: S.K. Plevritis.
Collection and assembly of data: S.K. Plevritis.

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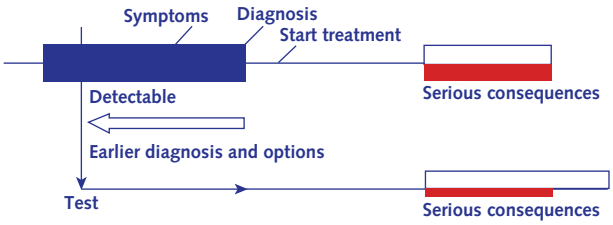
Appendix: Estimating Radiation-Related Lung Cancer Cases

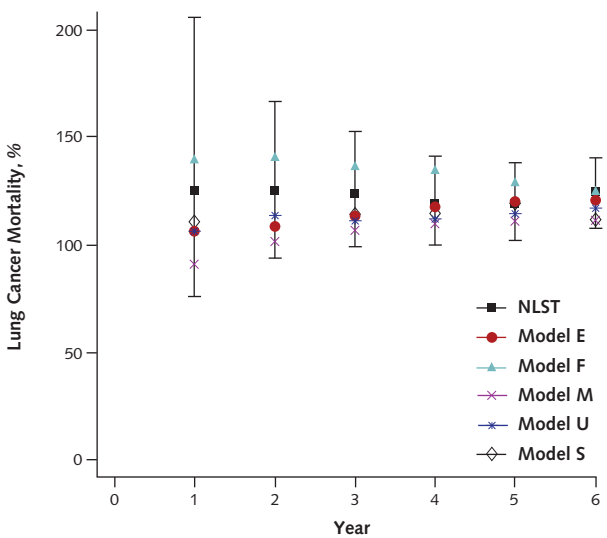
The Fred Hutchinson Cancer Research Center group included a radiation dose–response component in its lung cancer model to estimate lung cancer risk associated with each simulated individual's history of CT screening and CT follow-up examinations. Each scheduled CT screening examination was modeled as contributing a radiation exposure of 1 mSv, and each was assumed to have a 25% chance of leading to a follow-up CT examination that included a 4-mSv exposure. The biological effects of these radiation exposures were modeled as occurring within a 1-year window through an increase in the premalignant clonal expansion rate and the malignant transformation rate. The nonlinear dose–response relationship and parameters affecting premalignant clonal expansion and malignant transformation were based on an earlier calibration to radiation risk for lung cancer incidence using the 2-stage clonal expansion model. Data for the calibration included 191 042 individuals with complete records in the Canadian National Dose Registry cohort for low-dose exposure to x-ray, gamma, and other types of ionizing radiation exposure between 1951 and 1988, with follow-up for lung cancer between 1969 and 1988 (43). This 2-stage clonal expansion model of radiation-related lung cancer risk was also used to estimate risk among Japanese atomic bomb survivors in the Life Span Study cohort, finding good agreement with observed lung cancer cases (43), and was found to have reasonable estimates of lung cancer risk compared with other studies (44). Radiation risk has generally been extrapolated from individuals with atomic bomb exposure in Japan. Although there is no evidence that a single large exposure to radiation equates proportionally to multiple miniscule radiation exposures as in CT lung cancer screening, this method has been adopted because it seems to be the safest assumption to make. Massachusetts General Hospital used a radiation risk model with the parameters from the Biological Effects of Ionizing Radiation (BEIR) VII report and the absorbed doses to the lung to estimate the number of excess lung cancer cases and deaths. Estimated from the historical data, organ-absorbed (lung) doses for screening CT examinations were 3.8 mGy (men) and 3.9 mGy (women) (26). For follow-up CT examinations, the doses are 15.4 mGy (men) and 15.0 mGy (women). The BEIR VII report recommended combining excess additive risk and excess relative risk estimates, but the former were not available by histologic cell type or by smoking status.

Appendix Figure 1. **Diagram of how earlier detection (followed by treatment) may have an effect on reducing serious consequences of the disease and/or increasing life expectancy.**



All models account for the individual's age-specific smoking-related risk for lung cancer, the date and stage of lung cancer diagnosis, the corresponding lung cancer mortality, and the individual's life expectancy in the presence and absence of screening. By replicating trial detection, models estimate key parameters of the screening-detectable period and/or sensitivity and can subsequently estimate cancer detected in the screening scenarios. In essence, when a model incorporates the exact demographic characteristics of participants and the design of a trial, it should be able to reproduce cumulative incidence of lung cancer (by stage, histologic features, sex, age, type of detection, and round) and lung cancer mortality in both groups as closely as possible. The best fit is often defined as the lowest deviance between observed and model-expected numbers.

Appendix Figure 2. **Percentage and 95% CI of lung cancer mortality in chest radiography group compared with computed tomography group in the NLST, by follow-up duration and comparison with 5 model group results.**



As stated in the Methods section, close calibration to difference in lung cancer mortality between groups of the NLST at 6 years' follow-up was prioritized, but not the slope before year 6. This was done on purpose because mortality differences in the first years of trials are subject to chance and small numbers. E = Erasmus Medical Center; F = Fred Hutchinson Cancer Research Center; M = Massachusetts General Hospital; NLST = National Lung Screening Trial; S = Stanford University; U = University of Michigan.

Appendix Table. **Key Similarities and Differences Between the Models in Estimating Effects on Life Expectancy With an Effective Lung Cancer Screening Test***

Variable	Erasmus Model	FHCRC Model	MGH Model	Stanford Model	University of Michigan Model
Simulation runs	10 million per scenario	100 000 per scenario (likelihood-based approach)	500 000	100 000	2 million per scenario
Risk mechanism	2-stage clonal expansion model	Longitudinal multistage observation model	Probabilistic	2-stage clonal expansion model	Multistage clonal expansion
Incidence per 100 000 (no screening), *n*†	4683	5275	4152	5857	5628
Mean age at diagnosis (no screening), *y*	74.01	76.32	69.28	71.90	71.14
Early (I/II) clinical stage (no screening), %	28	37	47	36	40
Adenocarcinoma (no screening), %	45.57	50.12	54.43	48.41	48.29
Clinical survival	SEER 2004–2008	NLST/PLCO	SEER 2004–2008	SEER 1988–2003	SEER 2004–2008
5-y survival rate (no screening), %	19	20	30	22	24
Lung cancer deaths in no-screening scenario, *n*†	3513	3773	2449	4531	4331
Sensitivity/screening detectability	By stage/histologic features/sex	By number of cells/histologic features/sex	By size and location in lung (correlates with histologic features)	By size/histologic features	By number of cells/histologic features/sex
Follow-up procedures	Based on NLST (1.5 examinations per positive screening result)	Based on NLST	Algorithms based on size thresholds and risk factors, adjusted to NLST rates	Algorithms based on size thresholds, calibrated to NLST rates for annual screening	Based on NLST
Stages	Ia, Ib, II, IIIa, IIIb, IV	Ia1, Ia2, Ib, II, IIIa, IIIb, IV	Ia1, Ia2, Ib, II, IIIa, IIIb, IV	Early (I–II), late (III–IV)	Ia1, Ia2, Ib, II, IIIa, IIIb, IV
Early stage (in A-55-80-30-15‡ screening scenario), %	48	45	54	53	53
General mechanism of effect	Cure model	Cure and stage shift	Not stage-shift model	Cure model	Stage shift
Effect of earlier detection	Screening-detected cases (which are treated earlier) are associated with a reduced risk for dying of lung cancer compared with stage-specific survival had the same tumor been clinically diagnosed later. The improved prognosis is represented as a cure fraction specific to stage at detection, but if curative treatment fails, patient survival will equal the survival in the case that the tumor had been clinically diagnosed.	Estimates cure rates, which depend on sex and tumor stage, size, and histologic features	Assumes that most patients with early-stage non–small-cell lung cancer would undergo resection; therefore (for patients without undetected distant metastases or additional primary lung cancers in another lobe), this resection is curative	Estimates the probability of fatal metastases as a function of tumor size, histologic features, and sex. Patients with advanced-stage lung cancer are, by definition, identified after the onset of fatal metastases, but some early-stage patients are identified before this occurs. With screening, patients are more likely to be identified at an early stage and cured of their disease following standard of care.	Time to death from lung cancer is based on survival models that define cure by histologic features, stage, sex, and age at diagnosis. Mortality reduction due to screening is due to the earlier stage and younger age at detection.
Estimated relative risk for death from lung cancer 6 y after randomization (observed, 0.81; updated results, 0.84 [95% CI, 0.75–0.95])§	0.83	0.81	0.89	0.90	0.85
Life-years gained per lung cancer death averted (A-55-80-30-15)‡	10.6	11.8	11.4	8.7	10.4

FHCRC = Fred Hutchinson Cancer Research Center; MGH = Massachusetts General Hospital; NLST = National Lung Screening Trial; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SEER = Surveillance, Epidemiology, and End Results.

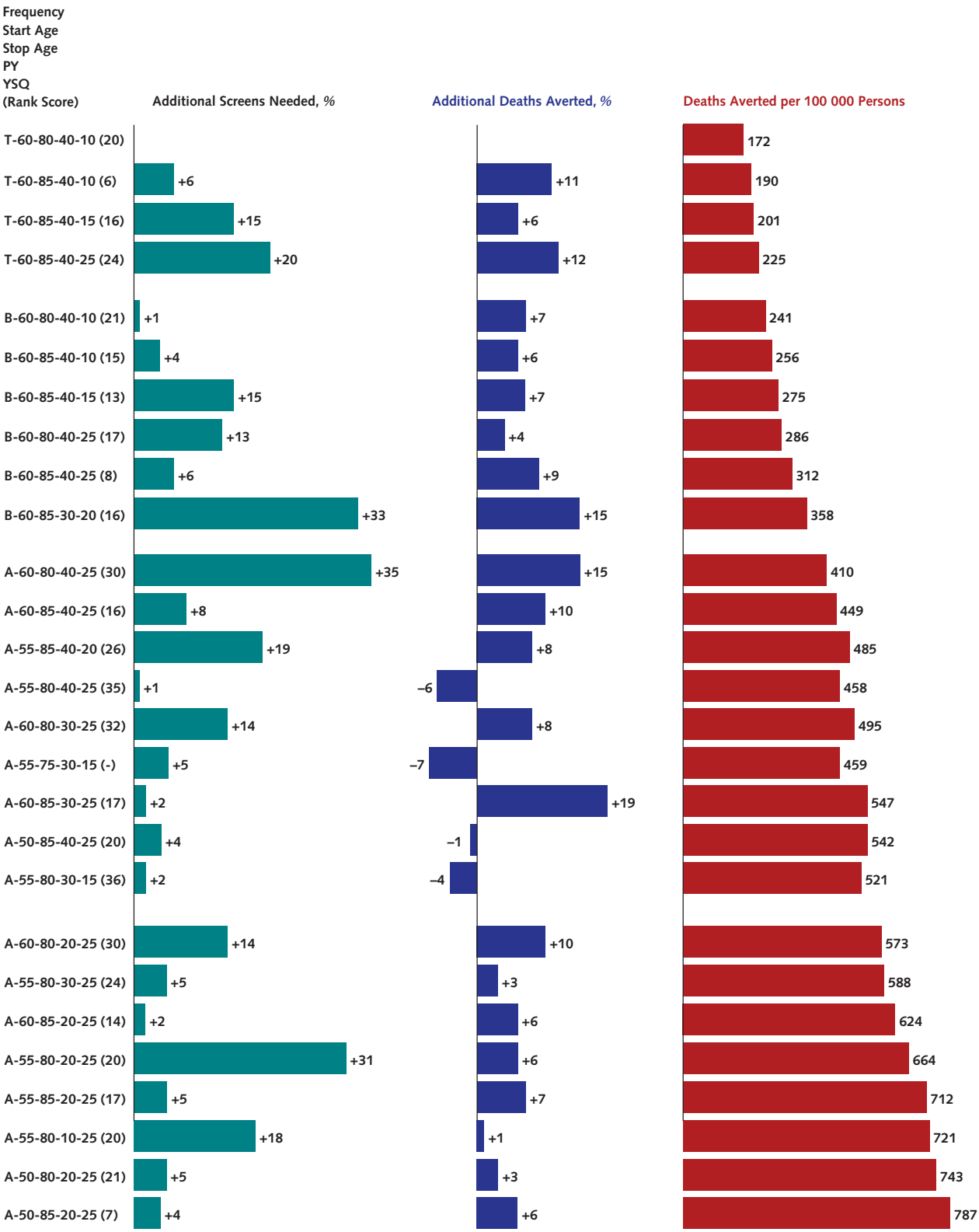
* If applicable, numbers per 100 000-person 1950 cohort followed from ages 45 to 90 years. Key parameters relate to the diagram in **Appendix Figure 1**.

† There is no direct comparison with observed data for this specific 1950 cohort.

‡ Numbers are arranged as follows: Frequency (A = annual)–age start–age stop–minimum pack-years–maximum years since quitting.

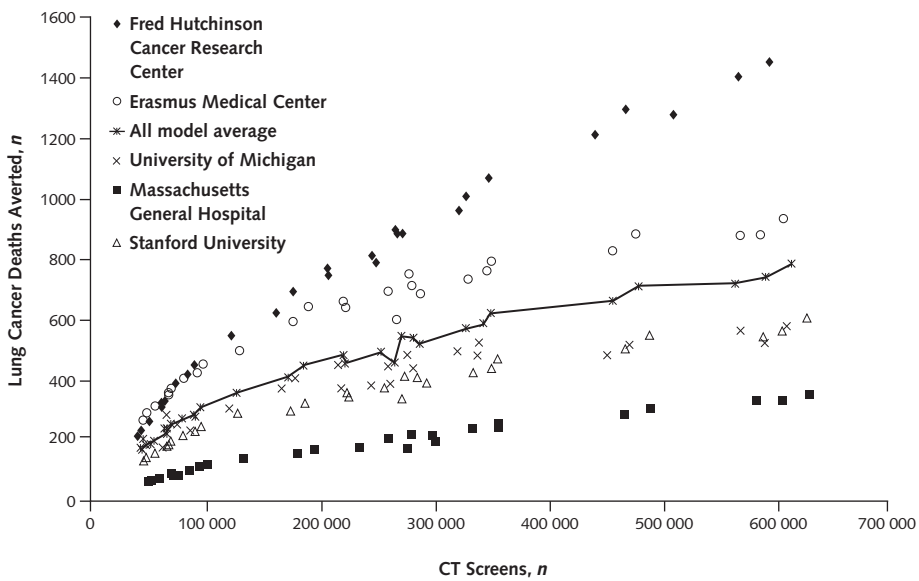
§ Data obtained from Pinsky (personal communication). Model estimates of relative risks were obtained from reference 45.

Appendix Figure 3. **Twenty-seven screening scenarios in order of increasing number of CT examinations needed, with the relative increase in screening examinations and lung cancer deaths averted (compared with the prior scenario), and the average number of lung cancer deaths averted in each scenario, for a 100 000-person 1950 cohort followed from ages 45 to 90 years.**



Number of CT scans is given in **Table 1**. The bars show the absolute number of lung cancer deaths averted in 27 screening scenarios and the percentage increases in both screening examinations and deaths averted when inclusion criteria are relaxed. The first 2 triennial scenarios show the effect of stopping through age 80 or 85 years: about 6% more screenings when stopping through age 85 years, leading to 11% more lung cancer deaths averted (compared with stopping through age 80 years). Extending the maximum (quit) time from 10 years to 15 years leads to a 6% increase in deaths averted (at the expense of 15% additional screening examinations), and extending it to 25 years yields an additional 12% in lung cancer deaths averted (at the expense of 20% additional screening examinations). Decreasing the minimum patient-year eligibility criteria from 30 to 20 and to 10 patient-years in annual scenarios shows relatively large increases in additional CT scans needed compared with additional lung cancer deaths averted. The scenario's rank score among 576 possible scenarios (that is, the average distance to the efficient frontier for the 5 models) is shown in parentheses. A = annual; B = biennial; CT = computed tomography; PY = minimum pack-years; T = triennial; YSQ = maximum years since quitting.

Appendix Figure 4. **Absolute number of lung cancer deaths averted for the scenarios in Table 1, for all model groups separately and the average of 5 models.**



Presentation of 100 000 individuals of the 1950 cohort followed from ages 45 to 90 years. The *x*-axis shows the number of CT screening examinations. Ranking of strategies is similar across models. There is no direct comparison with observed data for this specific 1950 cohort. CT = computed tomography.