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Benefits and harms of CT lung cancer screening strategies. A comparative modeling study for the U.S. Preventive Services Task Force

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Abstract

Background—The optimal screening policy for lung cancer is unknown.

Objective—To identify efficient CT-screening scenarios where relatively more lung cancer deaths are averted for fewer CT screens.

Design—Comparative modeling study using 5 independent models.

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

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

Time Horizon—Cohort followed from ages 45 to 90.

Perspective—Societal.

Intervention—576 scenarios with varying eligibility criteria (age, smoking pack-years, years quit) and screening intervals.

Outcome Measures—Benefits: lung cancer deaths averted or life-years gained; harms: CT-exams, false positives (including biopsy/surgery), overdiagnosed cases, radiation-related deaths.

Results of Best-Case—Annual screening from age 55 through 80 for ever-smokers with at least 30 pack-years and ex-smokers with less than 15 years since quitting was the most advantageous strategy. It would lead to 50% (45 to 54%) of cancers being detected at an early stage (I/II); 575 screens per lung cancer death averted; a 14% (8.2 to 23.5%) lung cancer mortality reduction; 497 lung cancer deaths averted; and 5,250 life-years gained per the 100,000-member cohort. Harms would include 67,550 false-positive tests, 910 biopsies or surgeries for benign lesions and 190 overdiagnosed cancers (3.7%; 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, and for overdiagnosed cancers between 72 and 426.

Limitations—Scenarios assumed 100% screening adherence. Data derived from trials with short duration were extrapolated to life-time 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-year exposure to smoking.

Introduction

The burden of lung cancer in the world remains extremely high: the International Agency for Research on Cancer (IARC) estimated 1.6 million new diagnoses in 2008 (12.7% of total cancers) and 1.4 million deaths (18.2% of total cancer mortality) (1). In the U.S. and Canada, incidence (per 100,000) is 48.5 for males and 35.8 for females, while mortality is 37.9 and 24.2, respectively, and cumulative risk (to age 74) of dying from lung cancer is 3% in females and 4.6% in males. In the U.S. 228,000 new cases of lung cancer and about 160,000 deaths were estimated for 2013 (2). Despite substantial reductions in smoking prevalence in the U.S., which translated into a reduction of about 32% of lung cancer

mortality between 1975–2000 at the population level (3), lung cancer remains the leading cause of cancer mortality.

Recently, the National Lung Screening Trial (NLST) demonstrated that in a volunteer population of current and former smokers aged 55 to 74 at entry, with at least 30 pack-years of cigarette smoking history and no more than 15 years since quitting for former smokers, three annual computed tomography (CT) screens reduced lung cancer-specific mortality by 20% relative to three annual chest radiography (CXR) screens at a median 6.5 years of follow up (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 between benefits and potential harms involved with alternative screening strategies (5). In this study, we estimate future harms and benefits and identify a set of possible efficient lung cancer screening policies, using five separately developed microsimulation models calibrated to the two largest randomized controlled trials on lung cancer screening. This work was initiated by the U.S. Preventive Services Task Force to inform their recommendations on lung cancer screening.

Methods

Calibration of five models to de-identified lung cancer screening data from the NLST and PLCO-trial

We used five models, calibrated to individual-level, de-identified data from the NLST (6) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) 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 three annual screens with either low-dose CT (26,722 participants) or single-view posterior-anterior chest radiography (26,730). The PLCO Trial randomized 154,901 participants aged 55 through 74 years at entry, 77,445 of whom were assigned to annual CXR and 77,456 to usual care between November 1993 and July 2001. There was no eligibility requirement concerning smoking. Although the PLCO Trial compared CXR to no screening, it provided information on the natural history of lung cancer.

Groups of investigators at the following five institutions independently developed the models: Erasmus MC in Rotterdam, the Netherlands (model E), Fred Hutchinson Cancer Research Center in Seattle (model F), the Massachusetts General Hospital in Boston (model M), Stanford University in Stanford (model S) and the University of Michigan in Ann Arbor (model U). Each model estimates screening effectiveness based on a different set of assumptions that are key in predicting the effects of earlier treatment, and each model employs different mathematical formalisms and model structure. In essence, the models all account for the individual's age-specific smoking-related risk of 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 <http://www.annals.org>).

For correct extrapolation of different possible screening scenarios, one must get the best estimates on several key parameters including the duration of the screen-detectable preclinical period (by test/age/histology/gender), sensitivity (by test/age/gender) and improvement in prognosis by earlier detection and treatment. All models were first set to mimic the design of both trials (e.g., set the numbers of screens and screening modality, ages at screening, smoking history and gender 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 cancers (by stage, histology, gender, age, type of detection, and round) and lung cancer mortality in both arms of the trials. Close calibration to the 19% (95% confidence interval 7–25%) lung cancer mortality difference between arms of the NLST at 6-years follow-up was prioritized. (See appendix figure 2 and appendix table 1, available at <http://www.annals.org>, for key similarities and differences between 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 US cohort born in 1950, using an updated version of the National Cancer Institute's (NCI) Smoking History Generator (8–11). **All models included other cause mortality to differ by gender, age, smoking status and smoking intensity.** A set of 576 programs that varied lung cancer CT screening frequency (1, 2 or 3-year intervals), ages of starting (45, 50, 55, 60) and stopping (75, 80, 85) screening (assuming including a last screen at this age), and eligibility based on smoking history (10, 20, 30, 40 pack-years; quit smoking for 10, 15, 20, 25 years) was examined, run separately for males and females.

In all scenarios, a 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 screens plus follow-up imaging examinations, number of false-positives (including surgery/biopsy), number of overdiagnosed lung cancers and number of radiation-related lung cancer deaths. Follow-up procedures were assumed to be consistent with the observed rate of exams per positive screen in the NLST; two models modeled explicit follow-up algorithms based on nodule size thresholds. False-positives are estimated as a direct proportion to the number of CT-screens, as based on the average in three rounds of the NLST, assuming that a false positive in a given round does not influence the probability of a false positive in subsequent rounds.

Overdiagnosed cases are the additional number of lung cancer cases detected in the screen scenarios, compared to the estimated cases diagnosed in the absence of screening (12). All models simulate the underlying natural history of lung cancer (separately by histology) 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, gender composition, and

potential times of other-cause death. Another way of expressing overdiagnosis is a person who has a lung cancer with its clinical detection predicted to occur 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, a cohort of persons born in 1950 was followed from ages 45 to 90. We identified “efficient” scenarios as those that prevented the greatest number of lung cancer deaths for the same number of CT screens (not including follow-up scans). Model results were compared 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, i.e. deaths averted (Y-axis) or minimizing harms, i.e. CT screens (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 the frontier (first three deciles) of at least three models. Two models (F, M) were used to estimate radiation-related lung cancers (see appendix, available at <http://www.annals.org>). All results were averaged across all five models. Finally, an advantageous scenario was selected that was efficient, and lead to a substantial lung cancer mortality reduction and life-years gained at reasonable harms. The number of screens needed was comparable to (a continuous) NLST-scenario, and to breast and colorectal cancer screening guidelines, given manpower and resources.

Results

Benefits and harms of efficient scenarios

Of the 576 possible programs, 120 were on or close to the “efficient frontier” where no alternative exists that provides more lung cancer deaths averted for fewer CT screens. 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 not among the consensus efficient programs. None of the top-ranked scenarios has a starting age of 45. For the top-ranked triennial and biennial efficient programs, the starting age is 60 years and the minimum pack-years is 40 (with one exception). Triennial screening programs lead to rather limited lung cancer mortality reductions, 4.6 to 6% in this cohort (range 1.7 to 9.5% across models). Biennial programs lead to 6.5 to 9.6% lung cancer mortality reductions (range 2.3 to 14.8% across models). When comparing the least intensive program (60-80-40-10; see Table 1 for notation key) of triennial to biennial screening, the additional percentage of lung cancer deaths averted is about 40%, at the expense of about 50% additional screenings (see also appendix figure 3, available at <http://www.annals.org>). Annual screening scenarios provide substantially more benefit, leading to 11 to 21.2% lung cancer mortality reductions (range 4.3 to 39.1% across models). In these scenarios, 48.1 to 56.9% of lung cancers are detected in stage I/II, compared to 37.4% without screening. The scenario most similar to the NLST criteria (A-55-75-30-15) leads to fewer lung cancer deaths averted but more screenings when 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 positives increase proportional to the number of CT-screens needed in each scenario, leading to 3.1 to 4.9 false positives per person screened. Decreasing the minimum pack years eligibility criteria from 30 to 20 and 10 pack years in annual scenarios provides 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 screenings (both overall and per person) and follow-up procedures, and false positives increase proportionally. Overdiagnosis ranges from 1.5 to 6.6% of all lung cancers, or 8.7 to 13.5% of screen-detected lung cancers.

Lung Cancer deaths averted and life-years gained

Clinical concerns about the potential for increased operative mortality in older individuals with heavy smoking histories, as well as increased comorbidity and reduced eligibility for surgery with curative intent at higher age limits, led us to focus on scenarios with stopping ages of at most 80 years. Figure 1 shows the impact of expanding the smoking eligibility in the age range of 55 through 80 beyond the criteria similar to NLST; for example, to 25 years since quitting (A-55-80-30-25) or even 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 screenings, but there are diminishing returns, although not at a single distinct point. The A-60-80-20-25 scenario, that extends eligibility to individuals with fewer pack-years but starting at a later age, is still efficient with respect to number of screenings and lung cancer deaths averted, but it provides fewer life-years gained than A-55-80-30-15. For the three consecutive scenarios A-55-80-30-15, A-60-80-20-25, and A-55-80-30-25, the number of screenings per lung cancer deaths averted increases progressively (550, 570, and 583), while the number of screenings per life-year gained is the highest (i.e., worst) for A-60-80-20-25 (52, 57, and 54). The A-60-80-20-25 scenario also results 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 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 an optimal 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 people born in 1950 and followed through age 90. The upper and lower bound estimates presented in the table are ranges found across the 5 different models and not confidence intervals. The table illustrates that 19,300 of 100,000 individuals would be eligible for screening at some point in their lifetime. Without screening, 5,119 will be diagnosed with lung cancer and 3,719 will die from lung cancer. Assuming 100% adherence with screening, 50.5% of lung cancers 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 suffering

advanced disease and its treatment. On the negative side, 67,550 false positives would be expected (19,300 individuals times 3.5 average false positives per individual) leading to 910 surgeries or biopsies for benign disease. There would be 1,970 persons with an earlier diagnosis of lung cancer than if they had not been screened, and about 10% of these cancers would otherwise never have been diagnosed during their lifetime (190 cases).

The same scenario for persons with 20 pack-years or more increases the number of lung cancer deaths averted by 12.9%, but means 33% more CT screens in the population with a proportional increase in false-positive test results (see table 1). Extending eligibility to 10 pack-years or more results in 8.6% more deaths averted for 23% more CT scans. Increasing the number of pack-years to 40, but extending the years since quit smoking from 15 to 25, in the age range 55–80, decreases the percentage eligible from 19.3% to 13.9%, but these individuals would on average get one more screen during lifetime, thereby increasing harms (see table 2).

Figure 2 shows the lung cancer mortality reductions for the eight (labeled) scenarios for each model group and the average of the five models. The reference scenario (A-60-80-40-25) leads to a 6.5 to 17.0% lung cancer mortality reduction, and the A-55-80-30-15 scenario to a 8.6 to 23.5% reduction. The most intensive scenario (A-55-80-10-25) leads to an estimated 12 to 34% lung cancer mortality reduction. The percentage of overdiagnosed screen-detected cases varies between 5 to 17% almost uniformly across inclusion criteria.

Discussion

Our models show that annual lung cancer screening of individuals with at least 30 pack-years of smoking from the ages of 55 through 80 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 additional 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 lung cancer screening scenario compares favorably to 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 screens (per 100,000 women) and 700 breast cancer deaths averted using the Erasmus model (20). Applying current colorectal screening guidelines translates to about 227,000 screening colonoscopies and 1,910 colorectal cancer deaths averted using 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 people in the U.S. 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 people eligible for screening and about 12,000 averted lung cancer deaths (22). Just simulating three screens as was done in NLST would, in our cohort-based approach, have led to a life-time 3.7% lung cancer mortality reduction (not shown). This is notably different from the observed mortality reduction point estimate reported at 6-years follow-up in the NLST, since only eligible persons get screened in our cohort analysis (dilution) and we modeled a life-time reduction rather than short-term follow-up.

Overdiagnosis is a general concern in screening. There are few estimates of the magnitude of overdiagnosis with CT lung cancer screening (23). We estimated overdiagnosis with CT screening to be below 17% of screen-detected cases (upper range figure 2). Although most published reports describing overdiagnosis in breast cancer screening apply to populations (i.e., multiple cohorts), our average of 10% of overdiagnosed screen-detected lung cancer cases in the advantageous scenario is equal to that for breast cancer screening in women aged 50 to 74 every 2 years in relatively low-referral programs (24) and far less than that for breast cancer screening in high-referral countries like the U.S (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 with 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 introduces uncertainty. Third, 5 models, with different structures and assumptions, showed some variability in their absolute predictions of benefits and harms (see Table 3) though the ranking of strategies was consistent across models (appendix figure 4, available at <http://www.annals.org>). Moreover, there is variance in the absolute 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, though extrapolations to the age span 75–80 seem reasonable (e.g., the oldest participants in the NLST were screened until age 78), there are still limited observational screen data in older individuals. We did note, however, that sicker individuals who were deemed less favorable candidates for possible surgical cure did not impact ranking of the strategies (data not shown).

Benefits were extrapolated from one large-scale trial in the U.S. with positive results, whereas, two 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 NEDerlands-Leuven Screening Onderzoek (NELSON-) trial with 15,822 individuals aged 50–75 and comparing CT screening to a no-screening arm (30). Preliminary analyses showed that the percentage of early detected lung cancers is more favorable than in the NLST trial (31, 32) (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 reducing the number of positive and false-positive results substantially: about 60% of referrals were false-positives, 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 “screen desirable” answers. Use of a risk-prediction model in the PLCO Trial, as compared to the NLST criteria, would have led to 41% fewer lung cancers 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 investigate possible important gender differences. In general, studies demonstrate that women are diagnosed at an earlier age, at a more favorable cancer stage, and more frequently with adenocarcinomas than are men (14, 37–41). Recently, subgroup analyses of NLST showed statistically significant lung cancer mortality reductions in persons diagnosed with adenocarcinoma (RR=0.75; 0.60–0.94), and not for other histologies. These results also showed borderline significant interaction with sex (RR=0.73 for women versus 0.92 for men, $p=0.08$) (42).

Inviting asymptomatic individuals for screening and implementing a large-scale screening program should only be considered 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 policy makers. But our predictions have some uncertainty, and are contingent on high-quality screening, 100% adherence with screening, and closely coordinated follow-up and treatment protocols. Both future providers as well as possible recipients of lung cancer screening should be fully aware of this, and only opt for screening after having been informed about these harms and benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 (A) CT screening, for programs with minimum eligibility age 55 and maximum at 80 at different smoking eligibility cutoffs and NLST scenario (A-55-75-30-15). Average number of CT screens (5 models) on X-axis.

The graph plots the average number of CT screens against the percentage of lung cancer mortality reduction for each screening scenario (vs.no screening) that was estimated for

100,000 individuals of the 1950-cohort followed from age 45 to 90. Programs are labeled: Frequency-Start Age-Stop Age-minimum Pack Years-maximum Years Since Quit. The lung cancer mortality reductions are different from the point estimate of the reduction reported at the 6.5 year follow-up in the NLST, since only eligible persons get screened in this cohort analysis (dilution) and life-time lung cancer mortality reduction is modeled. The 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 screens are small relative to the previous strategies.

Figure 2.

Estimated percentage lung cancer mortality reduction and overdiagnosed cases (of screen-detected cases) for the highlighted scenarios in Tables 1 and 2 (average number of CT-screens on X-axis) for all individual models and the average of the 5 models. Presentation of a 100,000 1950-cohort followed from age 45 to 90.

Table 1

Benefits of 26 selected efficient screening programs and a screening program most similar to NLST eligibility criteria. Numbers are per a 100,000 cohort followed from age 45 to 90 and are based on averaged estimates across the 5 models.

Frequency- start age- stop age- pack years- years quit [†]	% of cohort eligible	Number of CT screens	Screen- detected cases	Total cases (%) detected at an early stage ^{**}	Lung cancer mortality reduction (%)	Lung cancer deaths averted [^]	Life-years gained	Life-years gained per lung cancer death averted	Screens per life- year gained	Screens per lung cancer death averted
T-60-80-40-10	11.2	45,685	787	42.0	4.6	172	1,823	10.6	25	265
T-60-85-40-10	11.3	48,317	943	42.6	5.1	190	1,894	10.0	26	254
T-60-85-40-15	12.0	55,316	1,043	43.3	5.4	201	2,000	10.0	28	275
T-60-85-40-25	13.0	66,333	1,139	44.1	6.0	225	2,252	10.0	29	294
B-60-80-40-10	11.2	67,167	1,072	44.0	6.5	241	2,526	10.5	27	278
B-60-85-40-10	11.3	69,662	1,181	44.3	6.9	256	2,665	10.4	26	272
B-60-85-40-15	12.0	79,757	1,279	45.3	7.4	275	2,882	10.5	28	290
B-60-80-40-25	13.0	90,337	1,279	45.5	7.7	286	3,017	10.6	30	315
B-60-85-40-25	13.0	95,914	1,536	46.3	8.4	312	3,045	9.8	32	307
B-60-85-30-20	17.9	127,046	1,744	47.5	9.6	358	3,451	9.6	37	354
A-60-80-40-25 [†]	13.0	171,924	1,664	48.1	11.0	410	4,211	10.3	41	419
A-60-85-40-25	13.0	185,451	1,911	49.4	12.1	449	4,203	9.4	44	413
A-55-85-40-20	14.0	220,505	1,967	50.0	13.0	485	4,811	9.9	46	454
A-55-80-40-25 [†]	13.9	221,606	1,782	49.2	12.3	458	4,777	10.4	46	483
A-60-80-30-25 [†]	18.8	253,095	1,983	50.4	13.3	495	4,940	10.0	51	511
A-55-75-30-15 [*]	19.2	265,049	1,646	48.4	12.3	459	5,375	11.7	49	577
A-60-85-30-25	18.8	271,152	2,263	52.1	14.7	547	5,322	9.7	51	495
A-50-85-40-25	14.6	281,218	2,159	51.4	14.6	542	5,908	10.9	48	518
A-55-80-30-15 [†]	19.3	286,813	1,971	50.5	14.0	521	5,517	10.6	52	550
A-60-80-20-25 [†]	24.8	327,024	2,419	51.9	15.4	573	5,707	10.0	57	570
A-55-80-30-25 [†]	20.4	342,880	2,288	52.1	15.8	588	6,321	10.8	54	583
A-60-85-20-25	24.8	348,894	2,779	53.7	16.8	624	5,934	9.5	59	559
A-55-80-20-25 [†]	27.4	455,381	2,543	53.9	17.9	664	7,092	10.7	64	685

Frequency- start age- stop age- pack years- years quit [†]	% of cohort eligible	Number of CT screens	Screen- detected cases	Total cases (%) detected at an early stage ^{**}	Lung cancer mortality reduction (%)	Lung cancer deaths averted [^]	Life-years gained	Life-years per lung cancer death averted	Screens per life- year gained	Screens per lung cancer death averted
A-55-85-20-25	27.4	477,334	2,955	55.6	19.1	712	7,490	10.5	64	670
A-55-80-10-25 [†]	36.0	561,744	2,803	55.2	19.4	721	7,693	10.7	73	777
A-50-80-20-25	29.0	588,516	2,732	55.2	20.0	743	8,530	11.5	69	792
A-50-85-20-25	29.0	610,443	3,153	56.9	21.2	787	8,948	11.4	68	775

^{**} Average percentage of cases detected at an early (I/II) stage in no screening scenario was 37.4%. Incident cases in the no screening scenario was 5,119 per 100,000 persons.

[^] Average number of lung cancer deaths in no screening scenario was 3,719 (per 100,000 persons cohort).

^{*} Denotes eligibility most similar to the NLST.

[†] Seven programs highlighted are the consensus efficient, annual programs with a stop age of 80 and screen counts between 200,000 and 600,000, plus an 8th program (A60-80-40-25) with just under 200,000 screens included as a reference program.

Note, in this table the columns including lung cancer (LC) deaths averted does not include radiation-related lung cancer deaths (these are presented in Table 2). The screening programs are labeled as follows: Frequency (A=Annual, B=Biennial, and T=Triennial) - Age Start - Age Stop - minimum Pack Years (PY) - maximum Years Since Quit (YSQ). Note that these mortality reductions are different from the observed point estimate in the NLST, since in our cohort analysis only eligible persons get screened (dilution), and it is a life-time reduction compared to 6-years follow-up in the trial.

Table 2

Harms of 26 selected efficient screening programs and a screening program most similar to NLST eligibility criteria. Numbers are per a 100,000 cohort followed from age 45 to 90 and are based on averaged estimates across the 5 models.

Frequency- start age- stop age- pack-years-years- quit [†]	Number of CT screens	Total CT exams including screens	Average number of screens per person screened	Average number of false- positives (per person screened)&	Over diagnosed cases	Overdiagno- sis (% of all cases) ^{***}	Overdiagno- sis (% of screen- detected cases)	Radiation- related lung cancer deaths [^]
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

Frequency- start age- stop age- pack-years-years- quit [†]	Number of CT screens	Total CT exams including screens	Average number of screens per person screened	Average number of false- positives (per person screened)&	Over diagnosed cases	Overdiagno- sis (% of all cases) ^{**}	Overdiagno- sis (% of screen- detected cases)	Radiation- related lung cancer deaths [^]
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

^{**} Incident cases in the no screening scenario was 5,119 per 100,000 persons; LC deaths 3,719 per 100,000 persons.

[^] Average of two models. Denominator is total lung cancer deaths.

^{*} Denotes eligibility most similar to the NLST

[‡] Seven programs highlighted are the consensus efficient, annual programs with a stop age of 80 and screen counts between 200,000 and 600,000, plus an 8th program (A60-80-40-25) with just under 200,000 screens included as a reference program.

[†]The screening programs are labeled as follows: Frequency (A=Annual, B=Biennial, and T=Triennial) - Age Start - Age Stop - minimum Pack Years (PY) - maximum Years Since Quit (YSQ). Overdiagnosed cases are slightly overestimated, since all counts are up to age 90 (some early detected cases will appear clinically after age 90).

Table 3

Number of individuals having benefits and harms of annual CT screening from ages 55 through 80; current and former smokers have a minimum of 30 pack-years, and former smokers quit in the last 15 years. Numbers for 100,000 individuals from the 1950 – U.S. cohort followed from age 45 to 90; 19,300 persons eligible, assuming 100% compliance.

<i>Benefits</i>	<i>Average 5 models</i>	<i>Lower bound estimate</i>	<i>Upper bound estimate</i>
Persons no longer dying from lung cancer [^]	497	177	862
- number of life-years gained	5,250	2,020	10,153
Persons no longer needing treatment for advanced lung cancer	550	200	950
- number of 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			
<i>Harms</i>			
Times persons undergo a CT screening test	287,000	272,000	301,000
Number of false-positive test results persons experience	67,550	61,250	70,700
Times persons undergo a CT follow up test (regular dose)	43,000	23,175	50,100
Persons receiving the diagnosis of lung cancer earlier	1,970	1,370	2,845
Persons undergoing surgery/biopsy for lesions that ultimately appear benign	910	825	955
Persons diagnosed with lung cancer who would otherwise never have had the diagnosis(over-diagnosed cases)	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			

5,119 lung cancers diagnosed without screening/ 5,307 with screening; 37% screen-detected (average 5 models). 3,719 lung cancer deaths without screening.

[^] incorporates 24 radiation-related deaths.

^{^^}
(14)

The number of biopsies performed for ultimately benign lesions was based on the NLST: there were 164 surgeries and 66 needle biopsies for benign nodules out of 17,053 false positive tests or 75,126 CT screens, being 1.3% of false positive tests. Differences in the range of results reflect differences in modeling approaches, but should not be seen as formal 95% confidence intervals. We did not consider that the earlier knowledge of the diagnosis of cancer has been shown to negatively impact quality of life (15), and patients experience side-effects of treatment, anxiety for assessment, and hospital visits for a longer time, nor the possible risks of false reassurance (a false-negative screen test possibly postponing access to care) (16), or the possibility of a behavioral change (i.e., relapsing to smoking) after the screen. (17–19).