Benefits and Harms of Computed Tomography Lung Cancer Screening Programs for High-Risk Populations

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Structured Abstract

Background: The National Lung Screening Trial (NLST) demonstrated that three annual computed tomography (CT) screenings reduced lung cancer-specific mortality by 20% compared with annual chest radiography screenings in a volunteer population of current and former smokers ages 55 to 74 years with at least 30 pack-years of cigarette smoking history and no more than 15 years since quitting for former smokers. To inform the updated U.S. Preventive Services Task Force recommendations on lung cancer screening, we assessed the benefits and harms of CT screening programs that varied by age, pack-year, and years since quitting criteria, as well as the frequency of screening.

Methods: Five independent microsimulation models estimated the long-term harms and benefits of screening as experienced by the U.S. cohort born in 1950. The five models were calibrated to the NLST to predict lung cancer outcomes consistent with the trial's observations. These models were also then calibrated to the lung cancer screening portion of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. We evaluated 576 scenarios with annual or less frequent screening of individuals between the ages of 45 and 85 years, for a range of minimum smoking exposure (measured in pack-years) and maximum time since quitting. Screening benefits are expressed in terms of the percentage of cancers detected at an early stage (stages I or II), percentage and absolute number of lung cancer deaths prevented, and life-years gained compared with a reference scenario with no screening. Screening harms are expressed as the number of CT screenings required (and percentage of the cohort ever screened), number of followup imaging examinations, and number of overdiagnosed lung cancers and radiation-related lung cancer deaths. We identified consensus strategies that the models identified as efficient, preventing the greatest number of lung cancer deaths for the screening examinations required. Counts and percentages reported are calculated as averages of outcomes from the five models, following a 100,000 person cohort from ages 45 to 90 years.

Results: The models ranked strategies similarly and identified a consensus set of programs. We focus in this report on 26 efficient screening scenarios that start screening at age 50, 55, or 60 years and stop screening at age 80 or 85 years. Among these 26 programs, triennial screening reduced total lung cancer mortality in the cohort by 5% to 6% compared with biennial programs that reduced mortality by 7% to 10% and annual programs that reduced mortality by 11% to 21%. When we focused on annual programs that began screening at age 55 or 60 years, ended screening at age 80 years, and required between 200,000 to 600,000 screenings per 100,000 persons, a set of seven programs remained. We added a lower-intensity reference scenario, for a total of eight programs. These eight programs include a program similar to the NLST criteria except for the stopping age: starting annual screening at age 55 years, ending at age 80 years for ever-smokers with at least 30 pack-years, and no more than 15 years since quitting for former smokers. With this program, 19.3% of the cohort would be screened at least once, requiring 287,000 CT screenings per 100,000 persons, leading to 50% of lung cancers being detected at an early stage and a 14% lung cancer mortality reduction (about 520 lung cancer deaths averted per 100,000 population), resulting in about 5,500 life-years gained per 100,000 population. These benefits must be weighed against the following harms: 330,000 CT examinations per 100,000 persons (screenings and followup CT scans), an estimated 4% overdiagnosis rate (of all lung cancers in the cohort), and 0.8% of lung cancer deaths (24 per 100,000 population) related to radiation exposure (based on two models). Important tradeoffs between the eight programs are discussed.

Conclusions: Our findings support a range of possible lung cancer screening programs, including annual lung cancer screening of individuals with at least 30 pack-years of smoking who are between the ages of 55 and 80 years, but cannot determine which tradeoff of harms and benefits is “best.” Scenarios with an older starting age (60 years) but increased maximum years since quitting (from 15 to 25 years) offer different tradeoffs of benefits and harms (depending on the minimum pack-years). Extending eligibility to individuals with fewer pack-years—although still efficient—leads to additional benefits but more additional harms. Overdiagnosis remained limited for annual screening.

Background

The National Lung Screening Trial (NLST) demonstrated that in a volunteer population of current and former smokers ages 55 to 74 years 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) screenings and subsequent treatment of early-stage lung cancer reduced lung cancer-specific mortality by 20% compared with three annual chest radiography screenings at 6.5-years followup.[1] With an additional year of followup (to 7.5 years), the lung cancer-specific mortality reduction in the NLST was 16%.[2] Albeit a significant effect, this trial does not directly address the effects of additional rounds of screening, the long-term benefits, or whether other screening policies, such as different intervals or risk groups, may result in substantial benefits. To understand the tradeoffs between benefits and important harms involved with screening, long-term outcomes must be quantified.[3]

We used five microsimulation models that were calibrated to individual-level, de-identified data from the NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (which included a wider range of smoking exposures than NLST and provides further information on the natural history of lung cancer) to estimate the long-term harms and benefits of a variety of CT screening programs.[4] In this report, we briefly summarize model calibration to NLST data and estimated future harms and benefits (averaged outcomes from all five calibrated models) of a set of 27 screening policies.

Methods

Calibration of Models to De-Identified NLST Data

The five models used were developed independently by groups of investigators at five institutions: Erasmus MC in Rotterdam, the Netherlands (Model E), Fred Hutchinson Cancer Research Center in Seattle (Model F), Massachusetts General Hospital in Boston (Model M), Stanford University in Stanford, California (Model S), and the University of Michigan in Ann Arbor, Michigan (Model U). Earlier versions of the models can be found under the model profilers at www.cisnet.cancer.gov/profiles. All five models simulate the underlying natural history of lung cancer (separated by histology) in individuals and include dose-response modules that relate a detailed cigarette smoking history over time to lung cancer risk. Initially, all models were populated with de-identified individual trial participant histories from the NLST (and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) and set to mimic the design of both trials (e.g., the number of screenings and screening modality, ages at screening, smoking history and sex of enrollees, and screening intervals). Each model estimates screening effectiveness based on a different set of equations that are key in predicting the effects of earlier treatment, but each model employs different mathematical formalisms and model structure. **Figure 1** gives a general picture of how earlier detection (followed by treatment) may have an effect in reducing serious consequences of the disease and/or increasing life expectancy. Although the five models differ substantially in their structure, they all account for the risk of lung cancer for an individual, the age and stage of lung cancer diagnosis, the corresponding lung cancer mortality, and the individual's life expectancy in the presence and absence of screening. More details of these processes will be summarized separately in a future report.

For this analysis, we prioritized the lung cancer mortality difference in the presence and absence of screening. We briefly describe how each model computes this measure. In Model E, screen-detected (and therefore earlier treated) cases experience a reduced risk of dying from lung cancer compared with the stage-specific survival if the same tumor had been diagnosed clinically, later in life. The improved prognosis in Model E is represented as a cure fraction specific to stage at detection, but if curative treatment fails, the survival of the patient will equal the survival in the case in which the tumor had been diagnosed clinically (obtained from Surveillance, Epidemiology, and End Results data). Model F estimates cure rates that depend on sex, tumor stage, and histology. Model M assumes that most patients with early-stage lung cancer would undergo resection and that (for patients without undetected distant metastases or additional primary lung cancers in another lobe) this resection is curative. For detected cancers in Model U, time to death from lung cancer is based on survival models that define cure by histology, stage, sex, and age at diagnosis. Mortality reduction due to screening is due to the earlier stage and younger age at detection. Model S estimates the probability of lethal metastases as a function of tumor size, histology, and sex. Advanced-stage lung cancer is, by definition, detected after the onset of lethal metastases, but some early-stage cases are detected before this occurs. With screening, patients are more likely to be detected at an early stage and cured of their disease following standard of care.

Figure 2 shows the cumulative lung cancer mortality ratio between the chest radiography arm and the CT arm by year of followup, indicating that the calibrated models agree with the observed lung cancer mortality reduction after 6 years of followup in the NLST.

Choosing Screening Programs and Expressing Harms and Benefits

A comprehensive set of 576 programs that varied lung cancer CT screening frequency, ages of starting and stopping screening, and eligibility based on smoking history were examined (**Table 1**) and compared with a reference scenario with no screening. To reduce the number of scenarios to consider, we first identified "efficient" programs according to each model; programs on the model's "efficient frontier" prevented the greatest number of lung cancer deaths for the same number of CT screenings. All scenarios were first run separately for men and women, and we looked for programs that were efficient for both sexes. The outcomes were then pooled to provide outcomes for both sexes combined. Modeling groups standardized input data on smoking history and nonlung cancer mortality to simulate life histories of the U.S. cohort born in 1950, using an updated version of the National Cancer Institute Smoking History Generator.[5,6] This cohort was chosen because in 2013 the individuals in this cohort will reach the same age as roughly the midrange of participants in the NLST. The cohort includes smokers and nonsmokers so that outcomes are at the population level.

Initially, all scenarios in the 90%–100% (y-axis) range of each model's efficient frontier were considered. Since there are outputs from five models for each scenario, scenarios that were evaluated as appropriately (90%–100%) efficient by at least three of the five models were considered "consensus efficient." Additionally, model results were compared using a formal approach previously described in the literature,[7] again using the consensus criterion of three or more models agreeing in their assessment. The two approaches identified similar consensus programs. In all simulated scenarios, a perfect screening adherence was assumed for individuals who met the screening eligibility criteria at any given age. A complete overview of the 576 programs and selection of consensus programs and their benefits is forthcoming.

Screening benefits are expressed as the percentage of cancers detected at an early (I or II) stage, percentage and absolute number of lung cancer deaths averted, and life-years gained (absolute and per lung cancer death prevented). Composite measures of the number of screenings per lung cancer averted and per life-year gained are also presented. Potential harms are expressed as the number of CT screenings per 100,000 persons (and percentage of the cohort undergoing at least one screening), the number of screenings plus followup imaging examinations, and the number of overdiagnosed lung cancers and radiation-related lung cancer deaths. All counts are cumulative from ages 45 to 90 years, per 100,000 persons in the cohort at age 45 years. Averages of results from all five models are presented unless otherwise noted.

A forthcoming publication based on this report will provide additional details regarding the modeling of followup examinations (the models employed varied approaches to extrapolate from NLST observations or from guidelines devised for incidentally-detected pulmonary nodules) and radiation-related lung cancers. Additional harms of screening, such as anxiety, complications, or longer periods of adverse effects of treatment, were not considered.

Results

The screening programs are labeled as follows: frequency (annual [A], biennial [B], and triennial [T]), age start, age stop, minimum pack-years, and maximum years since quitting.

We compared 26 consensus scenarios that start screening at age 50, 55, or 60 years, stop screening at age 80 or 85 years, and that are very close to or on the efficient frontier and were identified as consensus efficient using both approaches described in the Methods, as well as a 27th program that is most similar to the NLST criteria (A55-75-30-15; not among the consensus efficient programs). Of the 27 programs, four are triennial, six biennial, and the rest annual. None have a starting age of 45 years. **Table 2** shows the benefits of these scenarios and **Table 3** shows the harms. **Table 2** shows the estimated numbers of lung cancer deaths averted in this specific U.S. cohort. Without screening, 3,719 (per 100,000) persons would ultimately die from the disease. Triennial screening programs lead to rather limited lung cancer mortality reductions, on the order of 6% or less in this cohort (between 172 and 225 lung cancer deaths averted per 100,000 persons), also shown in **Table 2**. Biennial programs lead to 6.5% to 9.6% lung cancer mortality reductions. Annual programs lead to 11% to 21% lung cancer mortality reductions. When we simulated a scenario that looks most similar to the NLST design and inclusion criteria (A55-75-30-15), this cohort would experience a 12% lung cancer mortality reduction.

This 12% reduction is notably lower than the observed point estimate of 20% or the recently updated 16% in the NLST, for at least two major reasons: 1) in NLST, almost all enrolled persons in the CT arm were screened, whereas in this cohort analysis, only eligible persons (19%) in the cohort were screened (dilution effect); and 2) we assessed lifetime lung cancer mortality (compared with 6-year followup in NLST). Furthermore, in contrast to NLST, once a person’s characteristics do not satisfy the screening criteria (such as passing the limit of years since smoking cessation), that person is not invited for future screenings in our analysis, and we only considered the 1950 birth cohort instead of all NLST subjects.

For all triennial and biennial efficient programs, the starting age is 60 years and the minimum pack-years is 40 (with one exception). The first two triennial scenarios clearly show the effect of stopping at age 80 or 85 years: about 6% more screenings when stopping at age 85 years, leading to 10% more lung cancer deaths averted (**Table 2**). The next two scenarios give an indication of extending the time frame of quitting: extending the possible (quit) time from 10 years to 15 years leads to a 6% increase in deaths averted (at the expense of 14% additional screenings), and increasing to 25 years an additional 12% (at the expense of 20% additional screenings). When comparing the same eligibility criteria with triennial or biennial screening, the additional percentage of lung cancer deaths averted is about 40%, at the expense of about 50% additional screenings. The biennial comparisons generally show the same differences as discussed before with the triennial comparisons. Biennial screening scenarios are more effective, leading to 241 to 358 lung cancer deaths averted per 100,000 persons, still comprising less than 130,000 screenings. By comparing B60-85-30-20 with B60-85-40-25, we see the effect of simultaneously including lighter smokers but limiting eligibility to fewer former smokers (32% more screenings and 15% more lung cancer deaths averted).

For the annual policies, the starting ages are 50, 55, or 60 years. **Table 2** clearly shows that among the consensus efficient programs, the most intensive annual program may be substantially more effective than the most intensive biennial program (A50-85-20-25 leads to more than double the lung cancer deaths averted than B60-85-30-20). Further, the biennial or triennial strategies that emerged as consensus efficient had the strictest smoking history criteria we evaluated (40 pack-years and 10 years since quitting), leading to low numbers of screenings and less lung cancer deaths avoided. Efficient programs that screened individuals with lighter smoking histories were more likely to be annual programs. For these reasons, we focused on finding effective and efficient scenarios that screened eligible persons every year.

The scenario that resembles the original NLST criteria the most (A55-75-30-15) leads to less benefit (but more screenings) when compared with the next least intensive program (A60-80-30-25). The inclusion criteria used for the NLST are therefore not the most efficient ones for a population screening program. For example, expanding the original NLST criteria (A55-75-30-15) by 5 more years (A55-80-30-15) or beginning and stopping screening 5 years later but extending the risk group up to 25 years since quitting smoking (A60-80-30-25) are more effective and efficient; about the same number of screenings are needed, but these scenarios lead to more lung cancer deaths averted. Specifically, the NLST criteria required 577 screenings per lung cancer death averted compared with 550 and 511 screenings for the other two scenarios, respectively (**Table 2**).

When we focused on annual programs requiring between 200,000 to 300,000 CT screenings per 100,000 population, three scenarios stood out: A55-85-40-20 and two strategies with later starting ages but more inclusive cutoffs for years since quitting, A60-85-30-25 and A60-85-40-25. These scenarios lead to half (49% to 52%) of all lung cancers being detected at an early stage (compared with 37% in usual care), 12% to 15% of lung cancer deaths averted, and between 4,200 and 5,300 life-years gained (**Table 2**). Larger lung cancer mortality reductions could be reached but would require a substantial increase in the number of screenings. However, 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 these higher age limits (which the models did not address in detail in the comparative analyses), led us to focus on scenarios with stopping ages of 80 years.

The seven programs highlighted in **Table 2** and **Table 3** are the consensus efficient annual programs with a stopping 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 screenings included as a reference program.

Focusing on annual scenarios stopping at age 80 years (the highlighted scenarios) in **Table 2**, **Table 3**, **Figure 3**, and **Figure 4** shows the impact of expanding the smoking eligibility in the age range of 55–80 beyond the criteria similar to NLST; for example, to 25 years since quitting (A55-80-30-25 or even A55-80-20-25 or A55-80-10-25). Although these are still efficient scenarios per our definition (maximum lung cancer deaths averted given number of CT screenings performed), they require more CT screenings (both overall and per person) and are associated with more radiation-related lung cancer deaths, especially when expanding the eligibility criteria to less than 30 pack-years (**Table 2**).

In **Figure 3**, it is apparent that with more CT screenings, more lung cancer deaths may be averted, but there are diminishing returns, as indicated by the decrease of the slope of the line (efficient frontier) connecting the programs that yield the greatest reduction in lung cancer mortality for a given number of screenings. **Figure 4** plots the life-years gained on the y-axis. The A60-80-20-25 scenario, which extends eligibility to individuals with fewer pack-years, is still efficient with respect to number of screenings and lung cancer deaths averted but represents a noticeable tradeoff between the measures of deaths averted and life-years gained (provides fewer life-years gained). Other indications of the tradeoffs inherent in the A60-80-20-25 scenario are that for the three consecutive (in **Table 2** and **Table 3**) scenarios A55-80-30-15, A60-80-20-25, and A55-80-30-25, the number of screenings per lung cancer deaths averted keeps going up (550, 570, and 583, respectively), while the number of screenings per life-year gained is the highest (worst) for A60-80-20-25 (52, 57, and 54, respectively). Of the same three consecutive scenarios, the A60-80-20-25 scenario extends screening to the highest percentage of the cohort (19%, 25%, and 20%) but has the highest number needed to screen to prevent one lung cancer death (37, 43, and 35, respectively).

Of the efficient scenarios, annual screening in the age range of 55 to 80 years was found to have substantial benefits. The annual programs include a strategy similar to the NLST criteria: starting screening at age 55 years, ending at age 80 years for ever-smokers with at least 30 pack-years, and no more than 15 years since quitting for former smokers (A55-80-30-15). With this program, 19.3% of the cohort would be screened at least once, requiring about 287,000 CT screenings per 100,000 persons, leading to 50% of lung cancers being detected at an early stage and a 14% lung cancer mortality reduction (about 520 lung cancer deaths averted), resulting in about 5,500 life-years gained. The benefits accruing from the A55-80-30-15 program must be weighed against the following harms (**Table 3**): 330,000 CT examinations per 100,000 persons (screenings and followup CT scans), an estimated 4% overdiagnosis rate (of all lung cancers in the cohort), and 0.8% of lung cancer deaths (24 per 100,000 persons) related to radiation exposure (based on two models).

Conclusions

We conducted this study to extrapolate findings from the NLST to compare screening programs that could potentially be adopted in the general U.S. population. Of the efficient scenarios, annual screening of individuals with at least 30 pack-years of smoking who are between the ages of 55 and 80 years offers substantial benefits. Comparable scenarios (A60-80-30-25 and A60-80-40-25) offer a different tradeoff of benefits and harms. Extending eligibility to individuals with fewer pack-years—although still efficient—leads to additional benefits along with additional harms. These models cannot determine which efficient scenario is best, but are valuable tools that project the results of the trials to different screening scenarios over the course of a lifetime and show which scenarios provide the greatest benefits for a specified level of harms.

We can compare the A55-80-30-15 scenario, which required 300,000 CT screenings and yielded a 14% mortality reduction (521 lung cancer deaths averted, based on results from five models [**Table 2**], and 690 lung cancer deaths averted, as estimated solely by Model E), with the U.S. Preventive Services Task Force recommendations for breast and colorectal cancer screening by considering the number of screenings needed for each site-specific test; the breast cancer recommendation would mean about 1.1 million screening mammographies (per 100,000 women), resulting in a 30% breast cancer mortality reduction (700 breast cancer deaths averted), and the colorectal cancer recommendations would mean 225,000 screening colonoscopies, resulting in a 77% colorectal cancer mortality reduction (1,910 colorectal cancer deaths averted). These breast and colorectal cancer estimates are solely from Model E (used in prior comparative analyses[8,9]) in the 1960 birth cohort (breast) and the 1950 birth cohort (colorectal cancer), with counts per 100,000 persons followed from ages 45 to 90 years.

This comparative analysis did not quantify all potential harms from screening, including the number of false-positive results, the number of additional years a patient lives with the diagnosis of lung cancer and possible adverse effects of treatment, the possible risks of false reassurance (a false-negative result that could possibly postpone access to care), or the possibility of a behavioral (smoking) change after screening. All smokers, independent of eligibility for a screening program, should be counseled to quit and offered assistance.

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Figure 1. Schematic Depicting the Theorized Effects on Life Expectancy and Morbidity of Screening With an Effective Screening Test (b) Compared With Usual Care (a)

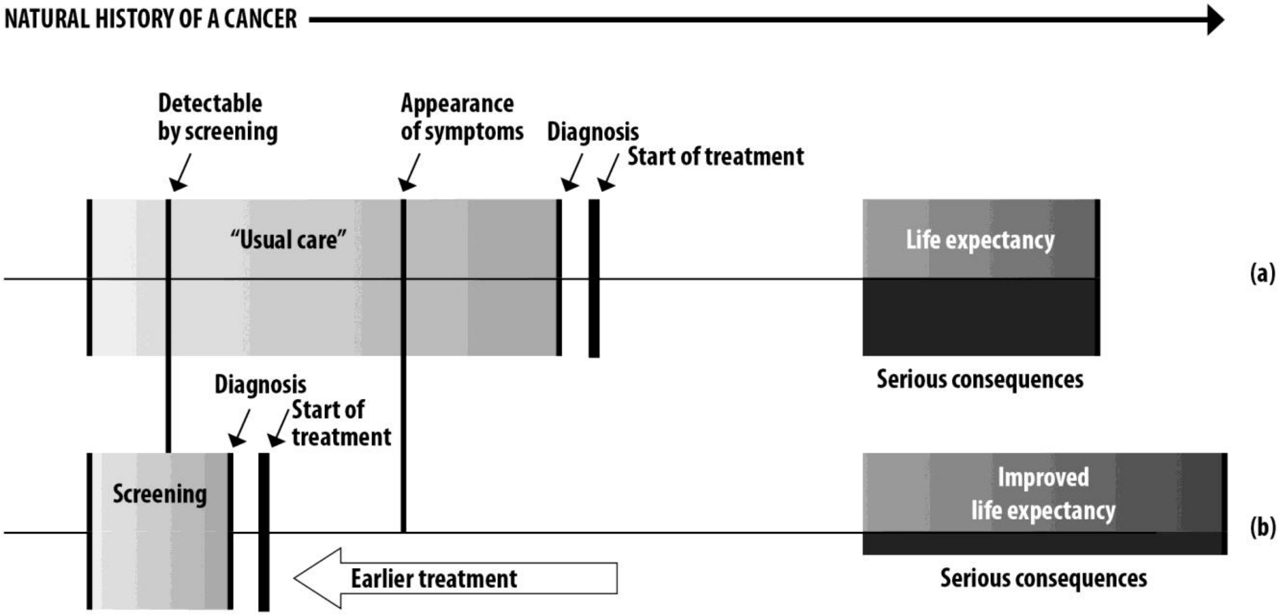
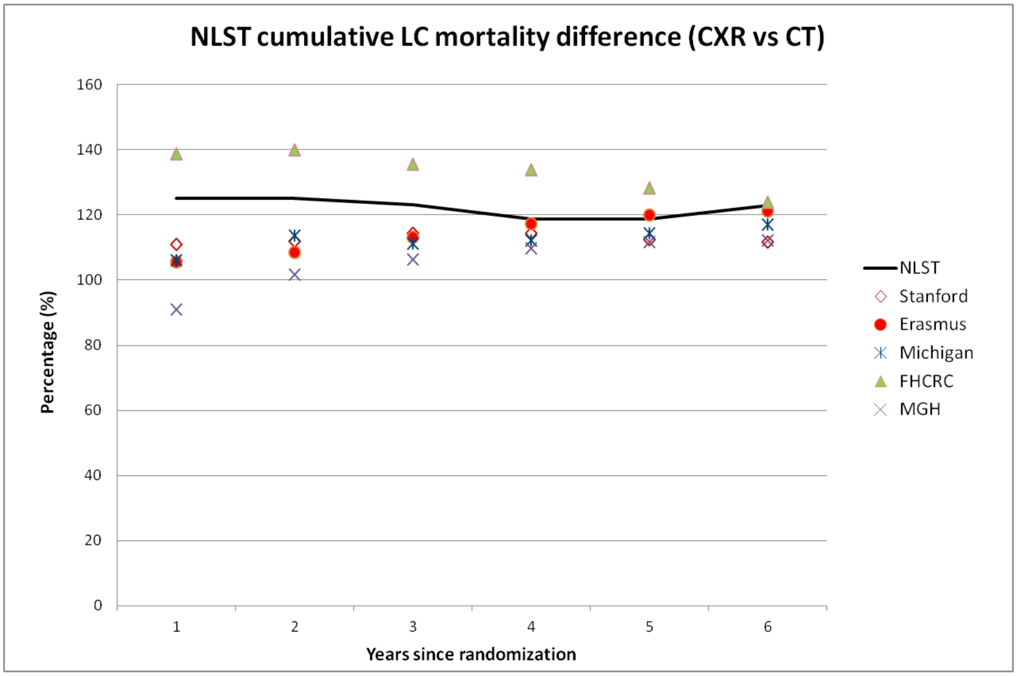
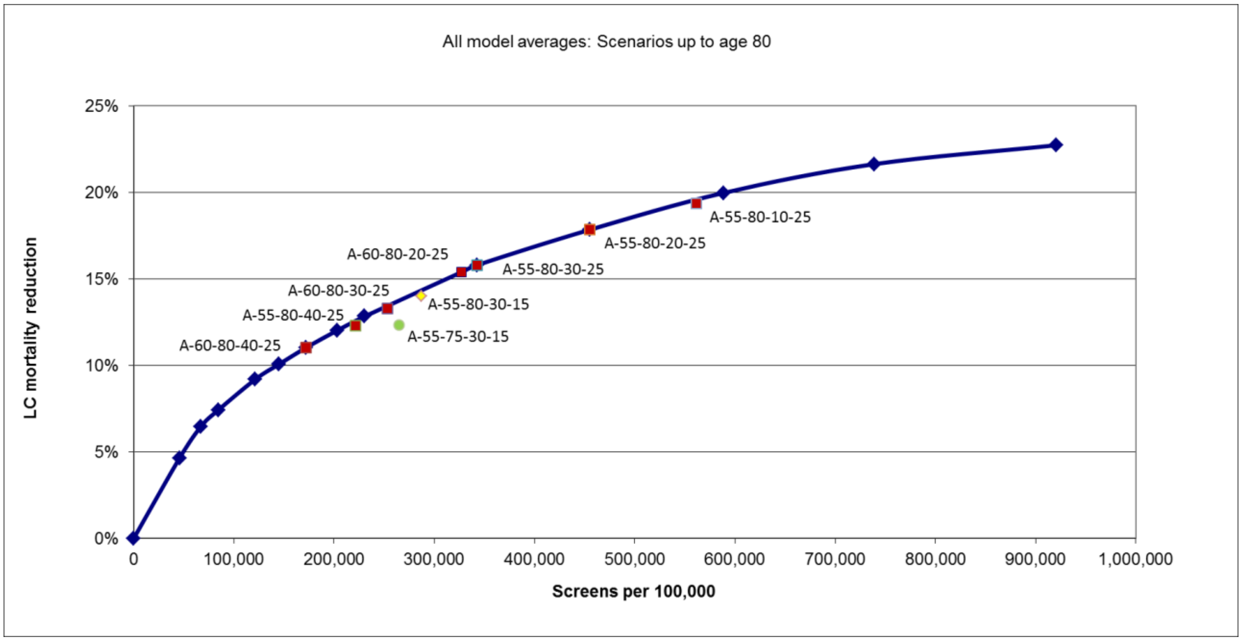


Figure 2. Percentage Difference in Cumulative Lung Cancer-Specific Mortality Between Chest Radiography and Computed Tomography, by Year of Followup: Comparison of Five Models With NLST Point Estimates*



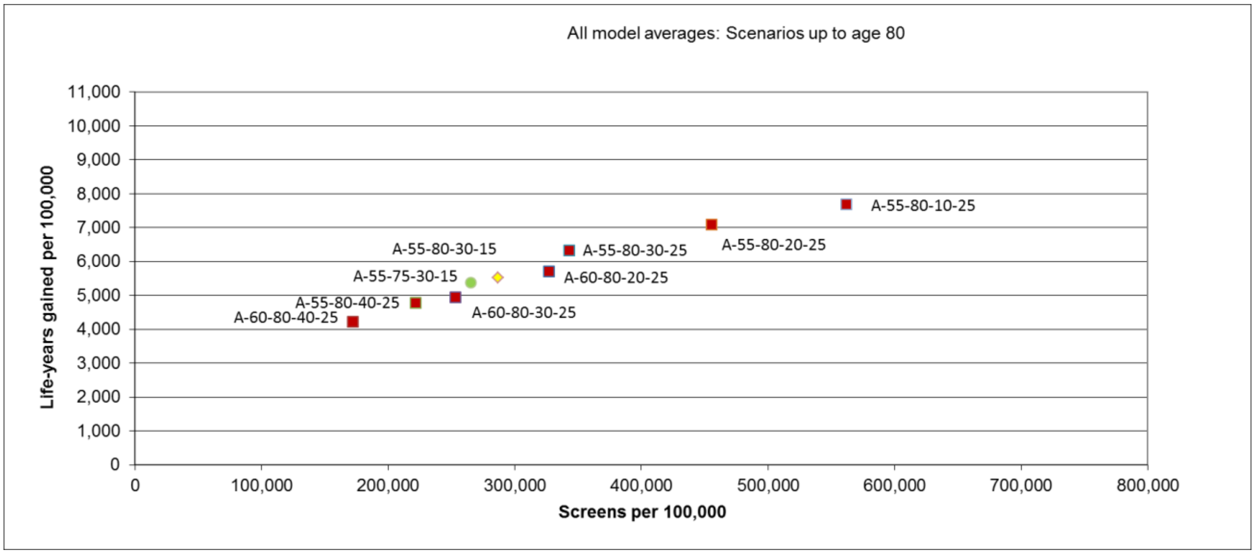
*Best fit was prioritized for year 6 since randomization.

Figure 3. Estimated Lung Cancer Mortality Reduction (Average of Five Models) From Annual Computed Tomography Screening in the 1950 Birth Cohort for Programs With Eligible Ages of 55 to 80 Years and Different Smoking Eligibility Cutoffs*



*Highlighted scenarios in Tables 2 and 3 are labeled.

Figure 4. Estimated Life-Years Gained (Average of Five Models) From Annual Computed Tomography Screening in the 1950 Birth Cohort for Programs With Eligible Ages of 55 to 80 Years and Different Smoking Eligibility Cutoffs*



*Highlighted scenarios in Tables 2 and 3 are labeled.

Table 1. Computed Tomography Lung Cancer Screening Scenarios Evaluated

Program Characteristics	Values Examined
Frequency of screening	Annual, every 2 years, every 3 years
Age at which to begin screening	45, 50, 55, 60
Age at which to end screening	75, 80, 85
Minimum pack-years for screening eligibility	10, 20, 30, 40
Maximum years since quitting for screening eligibility	10, 15, 20, 25

Table 2. Benefits of 26 Selected Efficient Screening Programs and the Screening Program Most Similar to NLST Eligibility Criteria (Average of Results From Five Models)

Scenario	Percentage ever screened	CT screenings per 100,000	Percentage of cases detected at an early stage*	Lung cancer mortality reduction	Average lung cancer deaths averted per 100,000**	Life-years gained per 100,000	Life-years gained per death averted	Relative increase in screenings compared with previous scenario (%)	Relative increase in lung cancer deaths averted compared with previous scenario (%)	Screenings per life-year gained	Screenings per lung cancer death averted	Number of persons needed to screen (ever) per lung cancer death averted
Triennial Screening												
T-60-80-40-10	11.2%	45,685	42.0%	4.6%	172	1,823	10.6			25	265	65
T-60-85-40-10	11.3%	48,317	42.6%	5.1%	190	1,894	10.0			26	254	59
T-60-85-40-15	12.0%	55,316	43.3%	5.4%	201	2,000	10.0			28	275	60
T-60-85-40-25	13.0%	66,333	44.1%	6.0%	225	2,252	10.0			29	294	58
Biennial Screening												
B-60-80-40-10	11.2%	67,167	44.0%	6.5%	241	2,526	10.5			27	278	47
B-60-85-40-10	11.3%	69,662	44.3%	6.9%	256	2,665	10.4			26	272	44
B-60-85-40-15	12.0%	79,757	45.3%	7.4%	275	2,882	10.5			28	290	44
B-60-80-40-25	13.0%	90,337	45.5%	7.7%	286	3,017	10.6			30	315	45
B-60-85-40-25	13.0%	95,914	46.3%	8.4%	312	3,045	9.8			32	307	42
B-60-85-30-20	17.9%	127,046	47.5%	9.6%	358	3,451	9.6			37	354	50
Annual Screening												
A-60-80-40-25†	13.0%	171,924	48.1%	11.0%	410	4,211	10.3	ref	ref	41	419	32
A-60-85-40-25	13.0%	185,451	49.4%	12.1%	449	4,203	9.4			44	413	29
A-55-85-40-20	14.0%	220,505	50.0%	13.0%	485	4,811	9.9			46	454	29
A-55-80-40-25†	13.9%	221,606	49.2%	12.3%	458	4,777	10.4	29%	12%	46	483	30
A-60-80-30-25†	18.8%	253,095	50.4%	13.3%	495	4,940	10.0	14%	8%	51	511	38
A-55-75-30-15‡	19.2%	265,049	48.4%	12.3%	459	5,375	11.7			49	577	42
A-60-85-30-25	18.8%	271,152	52.1%	14.7%	547	5,322	9.7			51	495	34
A-50-85-40-25	14.6%	281,218	51.4%	14.6%	542	5,908	10.9			48	518	27
A-55-80-30-15†	19.3%	286,813	50.5%	14.0%	521	5,517	10.6	13%	5%	52	550	37
A-60-80-20-25†	24.8%	327,024	51.9%	15.4%	573	5,707	10.0	14%	10%	57	570	43
A-55-80-30-25†	20.4%	342,880	52.1%	15.8%	588	6,321	10.8	5%	3%	54	583	35
A-60-85-20-25	24.8%	348,894	53.7%	16.8%	624	5,934	9.5			59	559	40
A-55-80-20-25†	27.4%	455,381	53.9%	17.9%	664	7,092	10.7	33%	13%	64	685	41
A-55-85-20-25	27.4%	477,334	55.6%	19.1%	712	7,490	10.5			64	670	38
A-55-80-10-25†	36.0%	561,744	55.2%	19.4%	721	7,693	10.7	23%	9%	73	777	50
A-50-80-20-25	29.0%	588,516	55.2%	20.0%	743	8,530	11.5			69	792	39
A-50-85-20-25	29.0%	610,443	56.9%	21.2%	787	8,948	11.4			68	775	37

* Percentage of cases detected at an early stage in no screening scenario was 37.4%.

** Average lung cancer deaths in no screening scenario was 3,719 per 100,000 persons.

† Consensus efficient annual programs with a stopping age of 80 years and screening counts between 200,000 and 600,000, plus an 8th program (A60-80-40-25) with just under 200,000 screenings included as a reference program.

‡ Denotes eligibility most similar to the NLST.

Note: All counts are cumulative, per a cohort of 100,000 persons age 45 years, followed until age 90 years. Radiation-related lung cancer deaths are not included in lung cancer deaths in Table 2 (see Table 3).

Table 3. Harms of 26 Selected Efficient Screening Programs and the Screening Program Most Similar to NLST Eligibility Criteria (Average of Results from Five Models)

Scenario	Percentage ever screened	CT screenings per 100,000	CT examinations (includes screenings) per 100,000	Average number of screenings per person screened	Overdiagnosis (percentage of all cases)*	Overdiagnosis (percentage of all screen-detected cases)	Radiation-induced lung cancer deaths per 100,000**	Average % of lung cancer deaths induced by radiation**
Triennial Screening								
T-60-80-40-10	11.2%	45,685	55,696	4.1	1.5%	10.1%	9	0.3%
T-60-85-40-10	11.3%	48,317	58,677	4.3	1.9%	10.5%	10	0.3%
T-60-85-40-15	12.0%	55,316	66,677	4.6	2.3%	11.6%	11	0.3%
T-60-85-40-25	13.0%	66,333	79,267	5.1	2.8%	13.1%	11	0.3%
Biennial Screening								
B-60-80-40-10	11.2%	67,167	80,068	6.0	2.2%	10.9%	11	0.3%
B-60-85-40-10	11.3%	69,662	82,874	6.2	2.5%	11.0%	11	0.3%
B-60-85-40-15	12.0%	79,757	94,383	6.7	3.0%	12.4%	12	0.4%
B-60-80-40-25	13.0%	90,337	106,512	7.0	2.9%	12.0%	13	0.4%
B-60-85-40-25	13.0%	95,914	112,810	7.4	3.5%	12.2%	13	0.4%
B-60-85-30-20	17.9%	127,046	148,518	7.1	3.8%	11.5%	15	0.5%
Annual Screening								
A-60-80-40-25†	13.0%	171,924	199,035	13.3	3.5%	11.2%	17	0.5%
A-60-85-40-25	13.0%	185,451	214,351	14.3	4.6%	12.9%	17	0.5%
A-55-85-40-20	14.0%	220,505	254,083	15.8	4.3%	11.6%	19	0.6%
A-55-80-40-25†	13.9%	221,606	255,398	15.9	3.7%	11.1%	21	0.6%
A-60-80-30-25†	18.8%	253,095	291,667	13.5	4.4%	11.9%	21	0.7%
A-55-75-30-15‡	19.2%	265,049	305,181	13.8	2.7%	8.7%	24	0.8%
A-60-85-30-25	18.8%	271,152	312,130	14.4	5.6%	13.5%	20	0.6%
A-50-85-40-25	14.6%	281,218	323,024	19.3	4.6%	11.5%	22	0.7%
A-55-80-30-15†	19.3%	286,813	329,809	14.9	3.7%	9.9%	24	0.8%
A-60-80-20-25†	24.8%	327,024	376,098	13.2	4.4%	9.8%	25	0.8%
A-55-80-30-25†	20.4%	342,880	393,611	16.9	4.3%	10.0%	25	0.8%
A-60-85-20-25	24.8%	348,894	400,898	14.1	6.2%	12.2%	23	0.8%
A-55-80-20-25†	27.4%	455,381	521,943	16.6	4.9%	10.4%	31	1.0%
A-55-85-20-25	27.4%	477,334	546,838	17.4	6.6%	12.2%	30	1.0%
A-55-80-10-25†	36.0%	561,744	643,001	15.6	4.9%	9.5%	35	1.2%
A-50-80-20-25	29.0%	588,516	673,103	20.3	4.9%	9.6%	38	1.3%
A-50-85-20-25	29.0%	610,443	697,962	21.1	6.5%	11.3%	37	1.3%

* Incident cases in the no screening scenario were 5,119 per 100,000 persons.

** Average of two models.

† Consensus efficient annual programs with a stopping age of 80 years and screening counts between 200,000 and 600,000, plus an 8th program (A60-80-40-25) with just under 200,000 screenings included as a reference program.

‡ Denotes eligibility most similar to the NLST.

Note: All counts are cumulative, per a cohort of 100,000 persons age 45 years, followed until age 90 years.