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Authors

Kim, E
Cenzer, I
Graham, FJ
[et al.](#)

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Peer reviewed

Time to Benefit for Lung Cancer Screening: A Systematic Review and Survival Meta-Analysis



Eliana E. Kim, BA,¹ Irena Cenzler, PhD,¹ Francis J. Graham, BA,² Jasmine Kang, MPH,^{1,2} Sei J. Lee, MD, MAS,^{1,2} Alison S. Rustagi, MD, PhD^{3,4}

Introduction: Lung cancer screening with low-dose computed tomography reduces lung cancer mortality in the long term but carries immediate risks. Guidelines recommend screening persons whose life expectancy exceeds the screening test's time to benefit, defined as the time from screening initiation to first observed benefit. This study aimed to estimate the time to benefit for lung cancer screening to prevent lung cancer mortality.

Methods: Randomized controlled trials of lung cancer screening with low-dose computed tomography were identified from two prior systematic reviews and an updated search to December 3, 2023. Studies that reported lung cancer mortality were included. For each study, independent Weibull survival curves were fitted and Markov chain Monte Carlo simulations were generated to estimate the absolute risk reduction at different time points. Time to benefit was determined as the time at which absolute risk reduction thresholds (ARR=0.0005, 0.001, 0.002) were crossed. These estimates were pooled using a random-effects meta-analysis model.

Results: A total of eight randomized controlled trials comprising 88,526 participants were included. Enrollment age ranged from age 50 to 70 years; follow-up duration ranged from 7.3 to 12.3 years. For every 1,000 persons screened, 3.4 years (95% CI 2.2, 5.1) passed before 1 death from lung cancer was prevented (ARR=0.001). The time to prevent one lung cancer death per 2,000 persons screened (ARR=0.0005) was 2.2 years (95% CI=1.4, 3.4); per 500 persons screened (ARR=0.002), it was 5.2 years (95% CI 3.7, 7.3).

Discussion: Lung cancer screening is most appropriate for older adults at high risk of lung cancer with a life expectancy greater than 3.4 years.

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INTRODUCTION

Lung cancer is the most common cause of cancer deaths in the U.S. and worldwide.^{1,2} Lung cancer screening (LCS) via low-dose computed tomography (LDCT) reduces lung cancer mortality in healthy randomized controlled trial (RCT) participants.^{3–5} However, LCS is associated with risks, including invasive diagnostic procedures following abnormal scans, procedural complications, radiation exposure, anxiety, false-positive screens, and overdiagnosis.^{6–10} While the potential harms of screening can occur soon after screening begins, its mortality benefit takes years to manifest.¹¹ Persons in poor health who are unlikely to survive to experience the delayed

mortality reductions are exposed to all of the immediate risks, with little chance of benefit.¹¹ National guidelines agree that only those in relatively good health should

From the ¹Division of Geriatrics, Department of Medicine, University of California San Francisco, San Francisco, California; ²San Francisco Veterans Affairs Health Care System, San Francisco, California; ³Division of General Internal Medicine, Department of Medicine, University of California San Francisco, San Francisco, California; and ⁴Center for Data to Discovery and Delivery Innovation (3DI), San Francisco VA Health Care System, San Francisco, California

Address correspondence to: Alison S. Rustagi, MD, PhD, Division of General Internal Medicine, Department of Medicine, University of California San Francisco, 4150 Clement Street Mail Code 111A1 T-31, San Francisco, CA 94121. E-mail: alison.rustagi@ucsf.edu.

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receive LCS, but guidelines offer varying and vague recommendations on health considerations for LCS eligibility.¹²

One approach to identify those most likely to benefit from screening is to quantify the time to benefit (TTB): the delay in time from screening to observed reductions in cancer mortality.¹³ The TTB for LCS can be defined as the time from screening onset until a clinically significant mortality benefit is observed on a population level.¹³ A reliable methodology that estimates the TTB using survival meta-analysis of RCTs has been described^{13,14} and used to estimate the TTB for colorectal and breast cancer screening.^{15–17} However, no TTB estimates for LCS have been reported to date. This study aimed to determine the TTB from LCS using LDCT to prevent mortality from lung cancer and from all causes by conducting a systematic review and survival meta-analysis of RCTs of LCS.

METHODS

Two published systematic reviews on the impact of LCS on lung cancer mortality were used to identify relevant RCTs.^{3,18} To update the search, the same search terms and databases as the Cochrane Review³ (CENTRAL, MEDLINE, Embase) from July 31, 2021 (the last search date reported by the Cochrane Review) to December 3, 2023 were used. The PRISMA reporting guidelines for meta-analyses were followed.¹⁹

The inclusion criteria were RCTs of LCS via LDCT that reported lung cancer-specific mortality in control and intervention groups either in a figure or via de-identified individual-level data.^{3,18} Studies deemed at unclear or high risk of bias (ROB) across multiple risk of bias items and studies that only included participants of age <50 years were excluded. For studies published before July 31, 2021, published ROB assessments were utilized;^{3,18} for those on or after August 1, 2021, two study team members (E.E.K., A.S.R.) assessed ROB using the Cochrane framework.²⁰ No restriction was applied on the language of publication or duration of follow-up.

To ascertain whether potentially eligible studies met inclusion/exclusion criteria, two trained reviewers (E.E.K., A.S.R.) independently screened all studies returned by the initial search criteria using the Rayyan web application.²¹ The abstractors met to review study abstracts, and, if necessary, published manuscripts for any studies that were potentially eligible. In addition, abstractors reviewed any studies in which they disagreed on eligibility. Any disagreement in study eligibility that could not be resolved was adjudicated after discussion with the full study team.

Details of TTB statistical analysis methods have been published previously.¹⁵ To calculate the TTB for each outcome (lung cancer-specific mortality and all-cause mortality), study teams were contacted to request de-identified, individual-level data. For those studies with publicly available individual-level datasets, access was requested. In the absence of de-identified, individual-level data, continuous numeric data were extracted from scanned images of published survival curves of the RCT by using the DigitizeIt software, version 2.5.9 (Germany).^{22,23}

For statistical analysis, person-level time-to-event data were reconstructed with the Stata module *ipdfc*, which yielded a dataset for each study with each individual's follow-up time from study enrollment until the end of follow-up or death.²⁴ Independent Weibull survival curves were fitted for control and treatment groups for each study, using Stata bayesian *streg* command (Appendix Figures 1 and 2). As part of the Bayesian analysis, 10,000 Markov chain Monte Carlo (MCMC) simulations were generated for individual studies, censored at 12 years of follow-up time. Absolute risk reduction (ARR) was defined as the difference in lung cancer mortality between the screening and control groups at each time point. To enhance interpretability, TTB was evaluated at three ARR thresholds corresponding to one death prevented per 2000 (ARR=0.0005), 1000 (ARR=0.001), and 500 (ARR=0.002) persons screened. For each study, MCMC simulations were used to determine absolute risk reduction (ARR) at different time points and when specific ARR thresholds (ARR=0.0005, 0.001, 0.002) were crossed for each study, that is, TTB. Finally, the ARR and TTB estimates from individual studies were pooled using a random-effects meta-analysis model. Test of heterogeneity was performed using the I^2 statistic.^{25,26} To test the impact of choosing a Weibull survival distribution, Gompertz and exponential distributions were also assessed to see if they would better approximate the trial data. To assess the impact, if any, of study bias on the TTB estimates, cumulative meta-analyses were conducted, beginning with the trial(s) deemed at the lowest ROB and then sequentially adding trials ordered in terms of ROB. This sensitivity analysis was conducted at each benefit threshold (ARR=0.0005, 0.001, 0.002) and for each outcome (lung cancer-specific mortality, all-cause mortality).

The analysis in this study involved figures from published manuscripts or de-identified data (if available). Thus, this analysis did not meet the definition of human subjects research and did not require an IRB review per the policies of the University of California, San Francisco (UCSF) IRB.

RESULTS

A total of 901 unique records were identified through the systematic electronic search from July 31, 2021, to December 3, 2023 (Figure 1). Two reviewers screened the titles and abstracts of all 901 records; of these, reviewers selected 21 records for full-text review. After full-text evaluation, both reviewers agreed that none of the studies returned from this search met inclusion criteria.

A total of 11 RCTs were identified from the 2 systematic reviews.^{3,18} Two RCTs were excluded: the French DEPISCAN trial²⁷ and the North American Jewish Hospital Lung Cancer Screening and Early Detection Study,²⁸ due to high ROB according to the Cochrane Review ROB assessment methods.^{3,20}

A total of 9 RCTs met inclusion/exclusion criteria: U. S. National Lung Screening Trial (NLST),²⁹ German Lung Cancer Screening Intervention (LUSI),³⁰ Dutch-

Belgian Netherlands-Leuven Longkanker Screenings Onderzoek trial (NELSON),⁵ UK Lung Cancer Screening trial (UKLS),¹⁸ U.S. Lung Screening Study (LSS),^{31,32} Italian Detection And screening of early lung cancer by Novel imaging TEchnology trial (DANTE),³³ Italian Lung Cancer Screening trial (ITALUNG),³⁴ Multicentric Italian Lung Detection trial (MILD),³⁵ and Danish Lung Cancer Screening Trial (DLCST).³⁶ The LSS trial met the inclusion criteria but was ultimately not included in the pooled analysis since the study publications did not report time-to-event mortality survival curves needed for TTB estimation^{31,32} and the publicly available, de-identified, individual-level dataset did not include mortality outcomes (personal communication, National Cancer Institute's Cancer Data Access System, 2024).

Data from 88,526 participants across eight clinical trials were included in the pooled analysis. Details of included trials varied slightly (Appendix Table 4). Individual, de-identified data were available for the NLST

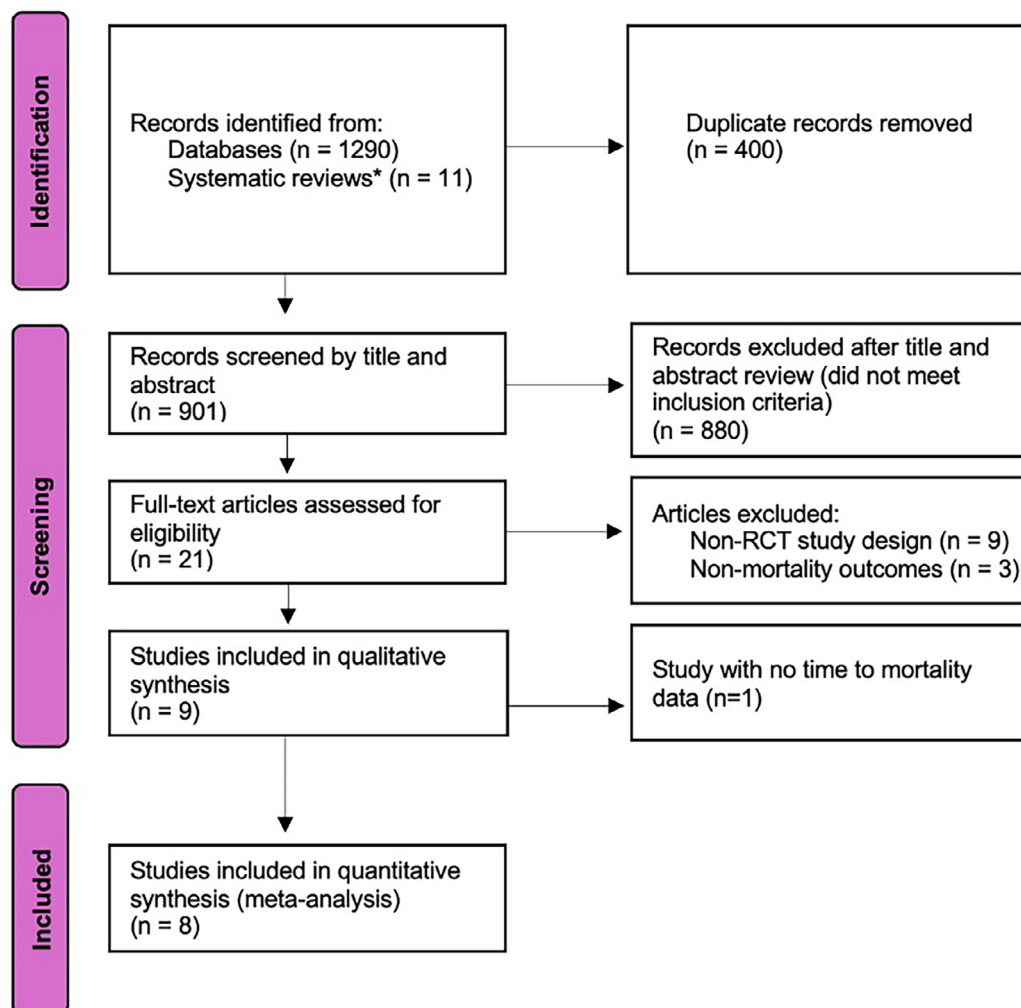


Figure 1. PRISMA study selection flow diagram. *Bonney et al.³ and Field et al.¹⁸

(n=53,452);²⁹ data extracted from published study figures were used for all other trials. The number of participants overall ranged from n=2,450³³ to n=53,452 (Appendix Table 4).²⁹ NELSON reported survival data on male participants only for the primary analysis.⁵ Enrollment age was homogenous across most studies in the 50s–70s, except DANTE which enrolled older individuals from age 60 to 74 years.³³ The median number of pack-years of smoking history varied from 35 (DLCST)³⁶ to 48 (NLST).²⁹ Screening occurred annually in all trials except NELSON in which screening occurred at 1, 2 and 2.5 years.⁵ The number of rounds of screening ranged from a single screen (UKLS)¹⁸ to 5 or more rounds (DLCST, DANTE, LUSI, MILD).^{30,33,35,36} The control arm in all included trials was no screening or usual care except NLST, which used single-view chest X-ray.²⁹

Relative risk for lung cancer mortality ranged from RR=0.65 (95% CI=0.41, 1.02)¹⁸ to RR=0.92 (95% CI=0.85, 1.00)²⁹ in studies that showed lung cancer mortality benefit with screening. Two trials, DANTE and DLCST, demonstrated minimal and nonsignificant increases in lung cancer mortality with LCS with RR=1.01 (95% CI=0.70, 1.44)³³ and RR=1.03 (95% CI=0.66, 1.60),³⁶ respectively.

Relative risk for all-cause mortality ranged from RR=0.83 (95% CI=0.67, 1.03)³⁴ to RR=1.01 (95% CI=0.82, 1.25;³⁶ 0.92, 1.11⁵⁵) in trial publications.

On average across included trials, 3.4 years (95% CI=2.2, 5.1 years) elapsed before 1 lung cancer death was prevented per 1,000 screened persons (ARR=0.001; Table 1). The time lag to prevent 1 lung cancer death per 2,000 screened persons (ARR=0.0005) was 2.2 years

(95% CI=1.4, 3.4 years), and to prevent 1 lung cancer death per 500 screened persons, the time lag was 5.2 years (95% CI=3.7, 7.3 years). There was low heterogeneity across studies with $I^2=0\%$ for TTB at each of the 3 ARR thresholds (Figure 2 for ARR=0.001, Appendix Figure 3 for ARR=0.0005; Appendix Figure 4 for ARR=0.002).

The pooled lung cancer mortality curves showed that on average, 1.9 lung cancer deaths (95% CI=0.8, 2.9) were prevented at 5 years for 1,000 screened persons (Figure 3). The average absolute survival benefit of LCS increased with longer follow-up duration. At 10 years of follow-up, 4.9 lung cancer deaths (95% CI=2.5, 7.3) were prevented per 1,000 people screened.

On average across included trials, we found that screening 1,000 persons for lung cancer prevents 1 death from any cause in 3.8 years (95% CI=1.9, 7.3 years; Appendix Table 5). Analogously, screening 2,000 persons for lung cancer prevents 1 death from any cause in 2.5 years (95% CI=1.1, 5.6 years), and screening 500 persons for lung cancer prevents 1 death in 5.8 years (95% CI=3.1, 10.8 years). There was low to moderate heterogeneity across studies for TTB with $I^2=26.34\%$ at ARR=0.001 (Appendix Figure 5); similar values were seen at ARR=0.0005 (Appendix Figure 6) and at ARR=0.002 (Appendix Figure 7).

The benefit of LCS to prevent all-cause mortality also increased in an approximately linear manner with longer follow-up duration. For example, the number of deaths from any cause prevented for 1,000 screened persons increased from 1.7 (95% CI= −0.1, 3.6) at 5 years to 4.0 (95% CI= −0.1, 8.1) at 10 years (Appendix Figure 8).

Table 1. Time to Benefit for Lung Cancer Screening at Specific Thresholds of Absolute Risk Reduction.

Trial (publication)	Time to benefit in years (95% CI)		
	ARR=0.0005 ^a	ARR=0.001 ^b	ARR=0.002 ^c
LUSI (Becker 2020)	0.7 (0.2, 12.0) ^d	1.3 (0.3, 12.0) ^d	2.8 (0.8, 12.0) ^d
UKLS (Field 2021)	1.0 (0.2, 8.4)	1.6 (0.3, 12.0) ^d	2.7 (0.8, 12.0) ^d
NELSON (De Koning 2020)	2.3 (1.3, 6.3)	3.3 (1.9, 7.3)	4.8 (3.1, 9.3)
DANTE (Infante 2015)	0.4 (0.1, 12.0) ^d	1.1 (0.2, 12.0) ^d	12.0 (0.3, 12.0) ^d
NLST (NLST 2019)	1.5 (0.8, 4.5)	2.7 (1.7, 12.0) ^d	5.1 (2.9, 12.0) ^d
ITALUNG (Paci 2017)	4.9 (0.8, 11.3)	5.3 (1.3, 11.6)	6.0 (2.3, 12.0) ^d
MILD (Pastorino 2019)	4.2 (0.7, 11.8)	4.8 (1.3, 12.0) ^d	5.8 (2.1, 12.0) ^d
DLCST (Wille 2016)	12.0 (1.3, 12.0) ^d	12.0 (2.5, 12.0) ^d	12.0 (4.6, 12.0) ^d
Summary	2.2 (1.4, 3.4)	3.4 (2.2, 5.1)	5.2 (3.7, 7.3)

Note: Boldface indicates statistical significance ($p<0.001$). NLST results were derived using individual data from the original dataset.

ARR, absolute risk reduction; NA, not applicable.

^aTime to prevent 1 lung cancer death per 2000 people screened with LDCT.

^bTime to prevent 1 lung cancer death per 1000 people screened with LDCT.

^cTime to prevent 1 lung cancer death per 500 people screened with LDCT.

^dThe upper limit of 95% CI does not exceed 12.0 years due to censoring at 12 years of follow-up.

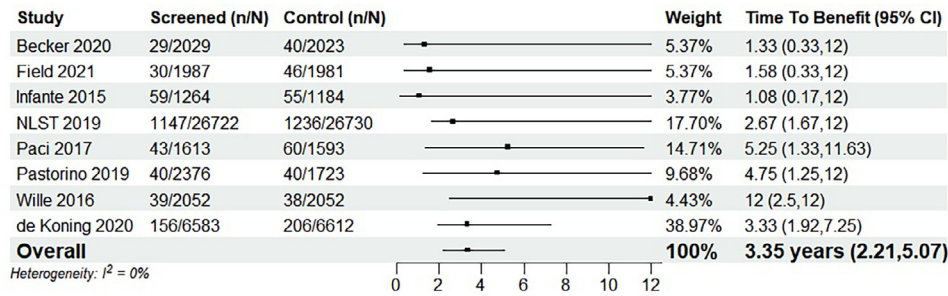


Figure 2. Time to benefit in years for lung cancer screening to prevent lung cancer death at an absolute risk reduction of 0.001. NLST results were derived using individual data from the original dataset. The upper limit of 95% CI does not exceed 12.0 years due to censoring at 12 years of follow-up.

Risk of bias assessments are available in [Appendix Table 2](#). In the cumulative meta-analysis to assess the impact of inclusion of trials with possible bias, analyses were conducted using data from the three trials deemed at lowest ROB: NLST 2019 (NLST),²⁹ Paci 2017 (ITALUNG),³⁴ and Wille 2016 (DLCST).³⁶ In sequential order, the following trials were added, then ordered from lowest to highest ROB: Becker 2020 (LUSI),²⁷ 2021 (UKLS)¹⁸ and Pastorino 2019 (MILD);³⁵ de Koning 2020 (NELSON)⁵ and Infante 2015 (DANTE).³³ There was no substantial difference between the TTB estimates when analyses were restricted to those studies with low ROB compared to TTB estimates when remaining studies were added.

There were no meaningful differences in the survival curves when alternative distributions (Gompertz, exponential) were used; all three parametric distributions yielded similar results, with slightly superior approximation from the Weibull distribution (data not shown) which we have also observed in prior work.^{37–39}

DISCUSSION

In this study, the TTB from LCS via LDCT to prevent death from lung cancer was estimated. A survival meta-analysis of 8 RCTs of LCS with a pooled sample of 88,526 participants was conducted. For every 1,000 persons screened with LDCT, 1 death from lung cancer was prevented after 3.4 years. At thresholds of 1 lung cancer death prevented per 2,000 or per 500 screened persons, the corresponding TTB was 2.2 years or 5.2 years, respectively.

When deciding whether to screen for cancer, short-term potential harms are weighed against the chance of long-term benefit.^{11,13} Harms of LCS include false positives, diagnostic procedures and associated complications, anxiety, radiation, and overdiagnosis.^{7–10} Procedural complications are perhaps the most immediate, quantifiable, and serious.^{6,10} In the NLST, 87 of 26,722 individuals, or 1 in 307 in the LDCT arm, sustained a major complication after an invasive diagnostic

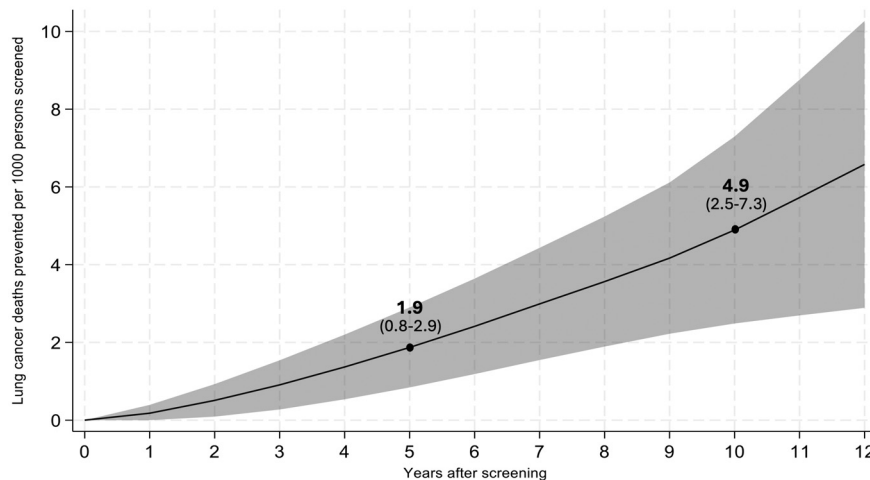


Figure 3. Absolute risk reduction in lung cancer mortality after lung cancer screening over time across 8 RCTs. Shaded areas and parenthesized numbers represent 95% CIs.

procedure following an abnormal screening exam; the majority of these ($n=75$) were later diagnosed with lung cancer, who may be more tolerant of procedural complications as a necessary step towards their cancer diagnosis.⁴ Many individuals would place a higher priority on avoiding death from lung cancer compared to avoiding a procedural complication, even one resulting in hospitalization. Conversely, due to the principle of discounting, some persons may place greater weight on the immediate risks rather than the delayed benefits of LCS,⁴⁰ and still others may recognize that procedural complications are only one of many potential harms of screening and thus opt for a higher benefit threshold to offset these aggregated harms. Given these competing considerations, an absolute risk reduction of 1 in 1,000 is a reasonable population threshold to recommend LCS. Thus, these results suggest that LCS should be recommended to most persons who meet inclusion criteria for LCS trials and have a life expectancy greater than 3.4 years.

This TTB estimate is similar to current guidelines that offer a life expectancy threshold for LCS. Both the Veterans Health Administration^{12,41} and the American Cancer Society⁴² recommend against LCS in patients with less than 5 years of life expectancy, a threshold based in part on evidence from modeling studies.⁴³ Similarly, the American College of Chest Physicians' 2021 guidelines recommend offering LCS to patients with a high net potential benefit i.e. ≥ 10 -year life expectancy, ≥ 16.2 days of life-gained per LYFS-CT calculator, and high lung cancer incidence and death risk.^{12,44} This analysis supports that patients with ≥ 10 -year life expectancy may anticipate likely benefit; however, this threshold of ≥ 10 years may discourage patients with 3.4–10 years of life expectancy to pursue LCS even though the results from this study suggest they may benefit.

In real-world clinical practice, several validated tools can also support the implementation of objective life expectancy considerations. The aforementioned LYFS-CT model provides individualized projections of benefit from screening, comparing life expectancy with versus without screening⁴⁴ and has been integrated into electronic reminders for LCS integrated into the electronic medical record.⁴⁵ The Lee Index is one of several evidence-based life expectancy tools aggregated on the ePrognosis platform (eprognosis.ucsf.edu) that is widely used in geriatric and primary care to estimate mortality risk.⁴⁶ The CAN (Care Assessment Need) score uses EHR data to predict mortality for VA primary care patients, is automatically updated weekly, and is widely integrated into clinical dashboards across specialties in the VA, including in primary care.^{47,48} These tools can help clinicians identify individuals whose life expectancy exceeds a TTB threshold.

The results of this study should not be the sole factor used to withhold or recommend LCS. Nonetheless, these results provide an important piece of information to conduct productive shared decision-making conversations. A more expansive consideration of all harms of screening (e.g. false positives, any diagnostic procedure, anxiety, radiation-induced cancers, and overdiagnosis) as well as the relative weight placed on each harm by an individual patient may lead different patients to consider different thresholds of benefit to be more appropriate for them. Thus, we present TTB across a range of benefit thresholds and at specific time intervals of 5 and 10 years.

The results of this study provide evidence that the immediate harms of LCS likely outweigh the anticipated long-term benefit of LCS for those with life expectancy of less than 2.2 years. For these individuals, the likelihood of meaningful life-year gains is minimal, and screening is unlikely to justify the associated risks. This corroborates recent work that found that those in the NLST with the highest comorbidity burden did not experience a reduction in lung cancer deaths from screening.⁴⁹ However, studies showed that primary care providers (PCPs) consider recommending LCS for those with a life expectancy as short as 6 months to 2 years⁵⁰ and acknowledge often relying on subjective clinical judgments in making their life expectancy assessments⁵¹ with significant time constraints.⁵² PCPs recognize the need for clear evidence to accurately present the risks and benefits of LCS as well as their timing to patients as a part of shared decision-making.^{50,51} This TTB analysis can be a useful tool to address this gap as it provides evidence-based estimates that can inform discussions about the timing of risks and benefits. Further, provided here are multiple levels of absolute risk reduction thresholds and the associated TTB estimates that clinicians and patients can use to tailor their decisions on LCS based on individual needs, goals, and priorities, particularly for patients with life expectancies in the range of 3.4 to 10 years where benefits may be modest but achievable.

Compared with TTB meta-analyses for other types of cancer,^{16,17} the TTB from lung cancer screening is shorter. At a threshold of one death prevented per 1,000 individuals screened, 10.3 years elapsed for screening for colorectal cancer via fecal occult blood testing and 10.7 years elapsed for screening for breast cancer via mammography, compared to 3.4 years for LCS via LDCT.¹⁶ This comparatively shorter time to benefit may further support the use of LCS in appropriately selected patients.

Lastly, while the primary focus of this study was on lung cancer-specific mortality, this study also examined the time to benefit for all-cause mortality. These

estimates should be interpreted with caution, as the CIs include zero and the results do not reach statistical significance. Nonetheless, as shown in [Appendix Figure 8](#), the data are consistent with approximately 4 deaths prevented per 1,000 individuals screened at 10 years. These findings suggest a possible signal of overall benefit, but further validation with individual-level or real-world data is needed.

Limitations

The results of this study rely on RCT data, which may not extrapolate to real-world settings. Observational analyses of real-world data suggest higher procedural complication rates after LCS,^{6,53,54} with reported rates of major complications from invasive procedures as high as one per 250 screened individuals in an analysis of data pooled across five U.S. healthcare systems.⁶ However, the rate of lung cancer detection in this cohort (1.8%) was also higher than in the baseline round of screening in the NLST (1.1%),^{4,6} suggesting that the absolute benefit and thus TTB may also differ in a real-world cohort compared to randomized settings. High-quality observational cohort studies of real-world data on benefits and harms may allow more precise estimates of real-world TTB for LCS. Second, the pooled sample in this study was predominantly male, raising questions about the generalizability of these results for women. DANTE did not enroll female participants and NELSON reported complete analyses of male participants only.^{5,33} Other trials had more male than female participants.^{18,29,30,34–36} However, the majority of individuals screened for lung cancer in the U.S. are male.⁵⁵ Third, this sample predominantly included individuals healthy enough for lung surgery due to the eligibility criteria used in the included trials.¹² Thus, the results of this study may not be generalizable to real-world populations especially to populations not well represented in the included RCTs, for example, women, those with multimorbidity, younger persons at risk of lung cancer, those of underrepresented racial/ethnic identities, or those with occupational exposures to lung carcinogens such as asbestos, silica, or radiation.

Future research can address these limitations by using individual-level data from these trials, which may permit stratified analyses by sex, age, race/ethnicity, comorbidities, or other variables that may affect the absolute benefit of early lung cancer detection. High-quality observational cohort data are also needed to assess the benefit of LCS across the full spectrum of health and outside randomized settings, and as newer technologies such as artificial intelligence,⁵⁶ biomarkers,⁵⁷ and others are applied to lung cancer detection and treatment. Such data will also allow for more precise and stratified

estimates of TTB and reduce variability in the current TTB estimates.

While the results of this study have limitations, they address a major gap by providing evidence-based timing estimates to guide LCS recommendations. Clinicians frequently navigate complex trade-offs between the immediate risks and delayed benefits of screening,¹¹ often relying on subjective judgments in the absence of standardized tools. This analysis offers important data to support these decisions, promoting greater consistency and transparency in LCS recommendations, with the flexibility to tailor decisions to individual patients by offering multiple thresholds. Although further refinement through real-world data is needed to enhance applicability across diverse populations, these results represent a valuable starting point to integrate timing into evidence-based decision-making for LCS.

CONCLUSIONS

In summary, this meta-analysis of eight randomized trials of LCS found that for every 1000 persons screened for lung cancer, one lung cancer death would be prevented after 3.4 years. This suggests that 3.4 years is a reasonable threshold of life expectancy to recommend LCS for those at high risk of lung cancer. In addition, those with a life expectancy of lower than 2.2 years are unlikely to benefit from screening.

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CREDIT AUTHOR STATEMENT

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at <https://doi.org/10.1016/j.amepre.2025.107736>.

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