**Timing of screening benefit for lung cancer with low-dose computed tomography**

**Short title: Timing of screening benefit for lung cancer with LDCT**

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**Ethics statement**

This study has obtained ethical exemption from the Xi’an Jiaotong University Health Science Centre institutional review board (MC-KYLLSL-2023-005) because this was a secondary data analysis based on publications and anonymised de-identified data.

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**Abstract:**

**Background**

Increasing evidence supports lung cancer screening with low-dose computed tomography (LDCT). However, the benefits of LDCT screening for lung cancer may not be immediate, making it unlikely to benefit patients with limited life expectancy.

**Research Question**

What is the time to benefit (TTB) from LDCT screening for individuals at high risk for lung cancer?

**Study Design and Methods**

Population-based, randomized controlled trials of lung cancer screening using LDCT and reporting mortality outcomes were systematically searched in PubMed. TTB was estimated for the National Lung Screening Trial (NLST) and the pooled data from four trials using our established analysis framework.

**Results**

Our analysis included four trials encompassing 64,105 individuals. In the NLST trial(N=53,452), to prevent one death from lung cancer, 2,000 individuals would need to be screened over 1.78(95% confidence interval, 0.60-5.27) years. On average, it took 2.87 (1.31- 6.32), 4.66 (2.64-8.21) and 8.87 (5.12-15.37) years before one death from lung cancer was prevented for every 1000, 500 and 200 individuals screened, respectively. These findings didn't vary when added to other trials.

**Interpretation**

The clinical benefits of LDCT screening may not be appropriate for individuals with limited life expectancy. Integrating TTB estimates into patient selection criteria could help maximise the benefits of LDCT screening.

**Keywords:** clinical benefit, Lung cancer, low-dose computed tomography, screening

**Abbreviations**: absolute risk reduction (ARR), confidence interval (CI), hazard ratio (HR), Kaplan-Meier (KM),low-dose computed tomography (LDCT), time to benefit (TTB).

Lung cancer remains the leading cause of cancer mortality worldwide,1 resulting in an estimated 1.8 million fatalities in 2020, which represents 18% of all cancer-related mortality.2 Over the past decade, numerous substantial clinical trials have shown that screening with low-dose computed tomography (LDCT) reduces lung cancer mortality. This reduction is primarily attributed to the early diagnosis and treatment at earlier disease stages.3-8 Consequently, LDCT screening has gained recommendations as a promising strategy to curtail lung cancer mortality for high-risk individuals in the US,9 Canada10 and Korea.11

Despite the widespread adoption of the LDCT-based screening programme across diverse health systems, 12,13 it is essential to acknowledge that the clinical benefits of screening intervention are not immediately realized. The time delay in observing the advantages such as reduction in cancer mortality, poses a unique challenge. Specifically, patients with a life expectancy shorter than the time required to achieve these benefits face immediate risks with little chance that they would survive long enough to benefit.14,15

Previous randomized controlled trials have primarily focused on assessing the magnitude of benefits rather than determining when these benefits manifest.3-8 As a result, it is unclear how long a patient needs to live to potentially gain survival benefits from LDCT screening for lung cancer. This analysis aims to estimate the time to benefit (TTB) of LDCT screening, drawing upon individual participant data from completed randomized clinical trials. Our approach employed an established analysis framework.16,17 distinct from previous methods that visually identify the point at which outcome curves diverge to estimate the timing of treatment benefit onset.18,19

**Study Design and Methods**

**Data Source and Searches**

Two reviewers independently conducted an extensive search for clinical trials related to lung cancer screening with LDCT. Initially, published trials were identified through prior systematic reviews and meta-analyses. Additionally, a thorough search for the most recent publications was performed, extending up to June 11, 2023.

The search strategy encompassed MeSH headings and text-word searches, combining various terms related to lung cancer, LDCT, screening, diagnosis, trials, systematic reviews, and meta-analysis. These searches were specifically limited to English-language publications. The search strategy can be found in **eTable 1.**

In our study, we only included randomized clinical trials that (1) compared LDCT screening with non-LDCT screening methods, such as no screening, screening with chest radiograph(CXR) and sputum cytology examination; (2) provided follow-up data on lung cancer mortality; and (3) provided vector Kaplan-Meier (KM) curves that enabled us to reconstruct individual participant time-to-event data if original individual data was inaccessible.

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**Outcome**

The primary outcome in this analysis was lung cancer mortality. While the collection of vital status varied among the included trials, a panel, which was blinded to group assignments, was consistently employed in each trial. This approach was designed to prevent any potential bias stemming from distinguishing between a death directly caused by lung cancer and one resulting from the diagnostic evaluation or treatment of lung cancer. The secondary outcome was all-cause mortality.

**Data extraction and reconstruction**

We emailed the trial authors to request individual data to facilitate our analysis. However, only the National Lung Screening Trial (NLST) provided us with these data, utilizing the application from NCI's Cancer Data Access System (CDAS). In cases where patient-level data were not accessible, we rebuilt the time-to-event data at the individual level based upon the published KM curves. This method, along with the algorithm, has previously been developed and validated,20 and adopted in our previous publications.16,17 In essence, we employed the DigitizeIt software application- a tool designed for extracting numerical data from graphical images -to extract survival probabilities at the corresponding time points from the published KM curve. Subsequently, we utilized a Stata command*ipdfc*to reconstruct the survival data, incorporating information about the number of patients at risk whenever such data was available. Notably, the reconstructed KM curves closely resembled the published curves (**eFigure 1**)

**Statistical analysis**

Cumulative event rates at various time points were estimated through KM curves. Additionally, the hazard ratio (HR) and its corresponding 95% confidence interval (CI) were calculated using the Cox proportional hazards model. This analysis was stratified by each individual trial to account for any potential trial-specific variations. A forest plot with combined HRs (with 95% CIs) for mortality benefit of LDCT vs non-LDCT screen was also constructed using fixed-effects meta-analysis.

We fitted Weibull survival curves for both the LDCT and non-LDCT groups in each trial. This approach allowed us to calculate the absolute risk reduction (ARR) and estimate the time required to reach specific ARR thresholds (i.e., 0.0005, 0.001, 0.002, and 0.005). Statistical inference for the model to calculate the TTB was performed by the frequentist method with Monte Carlo simulations to derive the CIs. The details of the calculation have been described in our previous publication.17 The TTB calculation was conducted in R version 3.4.0 (R Project for Statistical Computing), while other analyses in this study were performed in Stata version 15.0 (StataCorp).

**Results**

A total of 508 articles were initially identified through the electronic database search in PubMed. Following the screening of titles and abstracts, 475 records were excluded, leaving us with 33 systematic reviews and meta-analyses that represented 178 individual trials. In addition, we identified an additional 27 trials up to June 11, 2023, and after excluding 205 duplications, we proceeded to assess 66 trials in full text. Among these, four trials met the eligibility criteria, while the remaining 62 were excluded, with detailed reasons provided in **Figure 1**.

Collectively, the four eligible randomized controlled trials enrolled a total of 64,105 individuals, with participant numbers ranging from 2,450 to 53,452 across the trials. The inclusion and exclusion criteria were notably similar among these four trials, with an overlapping age range of 45 years and above. Furthermore, all trials required a substantial smoking history, defined as at least 20 pack years or more, as a part of their inclusion criteria. The primary intervention in these trials was chest LDCT, although the frequency and duration of LDCT screenings varied. Notably, no screening was conducted in the control arms of all trials, except in the case of the NLST trial, where chest radiography was employed (**Table 1**).

The KM curve generated from the pooled trial data revealed that individuals undergoing LDCT screening consistently exhibited a lower cumulative incidence of lung cancer mortality when compared to those in the control group (HR, 0.85 [95% CI, 0.76-0.95]; *P* < .001) (**eFigure 2A**). This finding was further validated by a meta-analysis conducted at the study level, which also indicated an HR of 0.85 (95% CI, 0.76-0.94) (**eFigure 2B**).

In our analysis of determining the TTB at various clinically meaningful thresholds from LDCT screening, we observed that to prevent one death from lung cancer, 2,000 individuals would need to be screened over 1.78 years (95% CI, 0.60-5.27). Similarly, the time required to prevent one lung cancer death was 2.87 years (95% CI, 1.31- 6.32) for every 1000 individuals screened, 4.66 years (95% CI, 2.64-8.21) for every 500 individuals screened, and 8.87 years (95% CI, 5.12-15.37) for every 200 individuals screened in the NLST trial (**Figure 2**).

Overall, our TTB estimates remained relatively stable even after progressively adding the trials, starting from NLST to the MILD trial (**Table 2**). For instance, when considering an ARR threshold of 0.002, the TTB was estimated to be 4.66 years (95% CI, 2.64-8.21) for the NLST trial, and it eventually reached 5.16 years (95% CI, 3.13-8.49) after incorporating the MILD trial. Similarly, with an ARR threshold of 0.005, the TTB was 8.87 years (95% CI, 5.12-15.37) for the NLST trial and extended to 9.29 years (95% CI, 5.90-14.63) after the inclusion of the MILD trial.

In addition, our further analysis for TTB in all-cause mortality indicated that it required 3.23 years before preventing one death for every 2,000 people screened and 3.89 years before preventing one death for every 1,000 people screened (**eFigure 3**).

**Discussion:**

This analysis, to the best of our knowledge, is the first to offer consolidated and quantified estimates of the TTB for lung cancer screening with LDCT, based on data from randomized clinical trials. Our analyses provide valuable insights beyond the standard Number Needed to Screen (NNS)—the number of individuals who need to be screened to prevent one lung cancer death. Specifically, to prevent one death from lung cancer, screening 2,000 individuals is required over 1.78 years, 1,000 individuals over 2.87 years, 500 individuals over 4.66 years, and 200 individuals over 8.87 years.

These findings highlight the time and scale considerations in the context of LDCT screening for lung cancer and contribute to a more comprehensive understanding of its impact.

Screening tests are medical examinations conducted on individuals who are either asymptomatic or at a high risk of specific medical conditions, with the aim of detecting life-threatening diseases at a stage where they can still be effectively treated. A previous microsimulation study has indicated that high-risk patients may not experience a net benefit from LDCT screening if their life expectancies are not sufficiently long (<10.5 years). 21 Another modelling study suggested that excluding individuals with limited life expectancies (<5 years) from screening retained the life years gained by screening while reducing overdiagnosis,22This finding aligns with the study conducted by Iakovos et al. 23 Recognizing these critical issues, certain healthcare providers, such as the Veterans Health Administration and the United States Preventive Services Task Force (USPSTF), require careful assessment of life expectancy when determining eligibility for high-risk individuals to undergo screening. 9 24,25

Similar to various medical interventions, LDCT screening entails benefits and harms. Healthy individuals who undergo LDCT screening may encounter downstream harms including radiation risk, psychological stress, unnecessary additional testing such as biopsies, and treatment costs associated with overdiagnosis or false-positive results. 26,27 As a result, it is crucial to assess the TTB and carefully weigh it against the potential harm related to the detection and treatment of tumours that would have never progressed. Clearly, for patients with a life expectancy shorter than the TTB, especially for those with coexisting chronic illness, such as advanced chronic obstructive pulmonary disease (COPD), or cardiovascular disease. 28 LDCT screening exposes this group to immediate risks, with limited prospects of living long enough to experience the benefits. Given the benefit-to-harm ratio, the potential harms—such as radiation exposure, false positives, and overdiagnosis—may outweigh the benefits for individuals with a shorter life expectancy, emphasizing the need for careful patient selection. Consequently, there is a growing argument for incorporating TTB into shared decision-making processes.14-17 By doing so, the target population can derive greater benefits from screening, especially for those with limited life expectancy.14,15 This approach aims to ensure that the potential benefits of screening outweigh the associated risks and uncertainties for each individual.

The most reliable metric to quantify TTB of cancer screening tests is to leverage data derived from clinical screening trials. Historically, randomized controlled trials of screening have primarily focused on the magnitude of benefits rather than when those benefits occur. In our study, we presented a spectrum of TTB at various specific thresholds of ARR. This approach facilitates tailored decision-making across a broad spectrum of patients with varying preferences and life expectancies. The timing of clinical benefits may differ depending on different perspectives concerning the trade-off between the probability of mortality benefit and the immediate risks and burdens associated with screening. For example, it's advisable to encourage patients with a life expectancy exceeding 10 years to undergo LDCT screening if an ARR of 0.002 is considered a reasonable screening policy. Conversely, individuals with life expectancies less than three years (i.e., less than the time lag of 8.87 years for achieving an ARR of 0.005) may not be suitable candidates for screening, as the potential benefits are unlikely to outweigh the associated risks in their case.

Our findings were subject to some limitations. Firstly, our summary of TTB results only provides an average estimate of lung cancer mortality with LDCT screening, and individualized decision-making should account for patient preferences and values to maximize benefits and minimize risks. Patients should have the opportunity to make informed choices that align with their specific circumstances (e.g., coexistent diseases affecting life expectancy) and priorities. Secondly, we performed a systematic search but our pooled analysis could include all the screening trials due to data availability(e.g., missing NELSON trial). Nonetheless, our analysis indicated that the TTB estimates remained relatively stable as we sequentially added trials. Thirdly, it's important to acknowledge that the landscape of cancer screening is continuously evolving. Current strategies for cancer screening are being refined to maximize the detection of lung cancers through screening while minimizing the issue of overdiagnosis. Consequently, uncertainties surrounding our TTB estimates may exist, given that our analysis heavily relies on data from older trials and focuses on mortality benefits rather than patient-reported outcomes, such as quality of life. As screening practices and technologies advance, the TTB may vary, and ongoing research is essential to refine our understanding of the benefits and risks associated with LDCT screening for lung cancer.

**Interpretation**LDCT screening is less likely to provide substantial benefits to individuals with limited life expectancy, primarily because the benefits of screening are not realized immediately. For example, our analysis estimates that individuals with life expectancies less than three years may not be suitable candidates for screening as it needs 8.87 years to achieve an ARR of 0.005 in mortality benefit. Therefore, it is crucial to offer the public a clear and dependable estimate of the TTB to ensure that the targeted population can derive the maximum advantages from such screening after considering their specific circumstances and preferences.

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**Take Home Points:**

**Study Question:** What is the time to benefit (TTB) from LDCT screening for individuals at high risk for lung cancer?

**Results:** To prevent one death from lung cancer, it would take 1.78 years when screening 2,000 individuals, 2.87 years for 1,000 individuals, 4.66 years for 500 individuals, and 8.87 years for 200 individuals

**Interpretations:** The clinical benefits of LDCT screening may not be appropriate for individuals with limited life expectancy. Integrating TTB estimates into patient selection criteria could help maximize the benefits of LDCT screening.

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None declared.

**Figure**

**Figure 1** Flowchart of the Search, Selection, and Inclusion of the Studies

**Figure 2** Pooled cancer mortality curves by groups for NLST trial.

Values are the time to benefit at different absolute risk reductions (ARR).

One death from lung cancer was prevented per 2000 people screened (ARR=0.0005), per 1000 people screened (ARR=0.001), per 500 people screened (ARR=0.002) and per 200 people screened (ARR=0.005).