



## THE CLINICAL QUESTION

Does the reduction in lung cancer mortality in the LDCT arm in the NLST persist at extended follow-up?

## TAKE HOME MESSAGE

The originally reported reduction in lung cancer deaths in the LDCT arm vs. CXR arm was sustained at extended follow-up (median 12.3 years), with a NNS of 303.



## BACKGROUND

- The NLST reported a 20% reduction in lung cancer mortality in high-risk current and former smokers who were screened annually (3x) with LDCT vs. with CXR. The median follow-up in the NLST was 6.5 years. An additional 6 years of data are now available for mortality. This analysis of extended follow-up helps to determine whether LDCT screening just delayed lung cancer death by a few years or actually prevented it.
- The NLST also reported a statistically significant increase in lung cancer incidence in the LDCT arm, possibly suggesting over-diagnosis. An additional 5 years of data are now available for lung cancer incidence. This analysis evaluates if the increase persists at extended follow-up.

## STUDY DESIGN



- Study design: Randomized, multicenter trial
- Interventions: LDCT or single-view CXR arm, with 3 annual protocol screens for each modality
- Enrollment: 26,722 and 26,730 participants were randomized to the LDCT and CXR arms, respectively at 33 U.S. medical institutions between 2002-2004
- Primary outcomes: lung cancer mortality and lung cancer incidence

## POPULATION

### Inclusion criteria

- Patients aged 55-74 with
- At least 30 pack-years smoking history who
- Were either current smokers or had quit within the past 15 years

### Exclusion criteria:

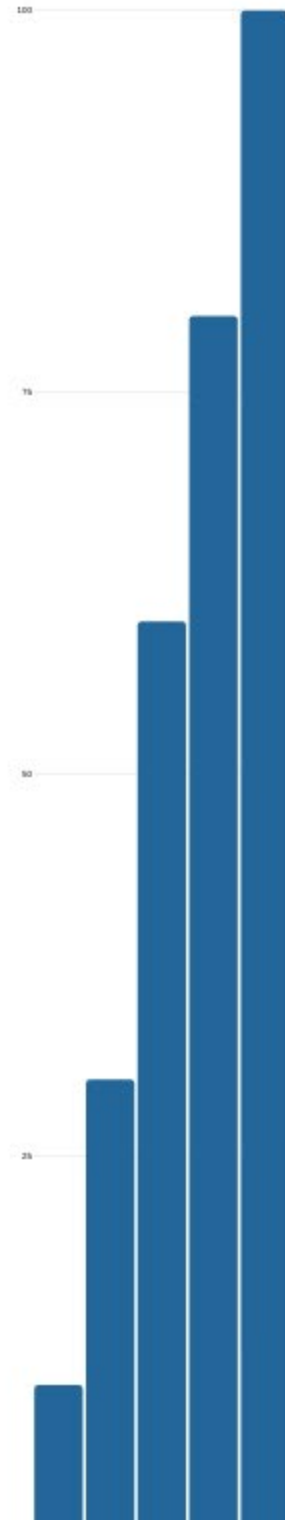
- Previous lung cancer diagnosis
- CT scan in the prior 18 months
- Unexplained 15 lb weight loss in the year before enrollment
- Hemoptysis

### Baseline characteristics

- Baseline participant demographics and smoking history were similar across arms
- Sex, male: 59%
- Age, 55-59: 42.8%
- Median pack-years: 48
- Current smoker: 48.2%



## OUTCOMES



### Primary outcomes:

For mortality, the median follow-up time was 12.3 years in each arm.

- Lung cancer mortality: 1147 lung cancer deaths with LDCT vs. 1236 with CXR (lung cancer mortality rate ratio (RR) = 0.92, 95% CI: 0.85-1.00). The difference in lung cancer deaths was 3.3 per 1000, translating into a NNS of 303. This is similar to the original NSS estimate of 320.
  - The dilution-adjusted lung cancer mortality RR was 0.89 (95% CI: 0.80-0.997). Thus, there is a significant decrease in lung cancer mortality with LDCT.

- All-cause mortality: 5253 total deaths with LDCT vs. 5366 with CXR, for a difference across arms of 4.2 per 1000 (95% CI: -2.6 to 10.9). Thus, there was no statistically significant reduction in all-cause mortality between groups.

For incidence, the median follow-up time was 11.3 years in each arm.

- Lung cancer incidence: 1701 lung cancer cases with LDCT vs. 1681 with CXR, giving a rate ratio of 1.01 (95% CI: 0.95-1.09). Thus, the lung cancer incidence was similar in both groups.

### Secondary outcomes:

There was a significant stage shift with the LDCT arm having a higher proportion of cases that were stage I and a lower proportion of cases that were stage IV.

### Adverse events:

Death and infection

## COMMENTARY

- Not all home state registries participated in the linkage effort to assist with passive follow-up.
- The use of LDCT screening after the original trial periods was not ascertained.
- The lung cancer mortality results for the NLST were based on a cut-off of a calendar date instead of a specified time period.
- Mortality rate ratio estimates in clinical trials may not be reflective of that in the general population.
- The lack of a statistically significant effect for all-cause mortality at extended follow-up may be due to the dilution effect, i.e. too long a period after screening.

## FUNDING

None



## SUGGESTED READING

1. Patz EF Jr, Greco E, Gatsonis C, Pinsky P, Kramer BS, Aberle DR. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomized, multicenter, diagnostic screening tool. *Lancet Oncol.* 2016 May;17(5):590-9.
2. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncol.* 2017 Nov;18(11):1523-31.
3. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JW, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol.* 2014 Nov;15(12):1342-50.

## ARTICLE CITATION



National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *J Thorac Oncol.* 2019 Oct;14(10):1732-42.