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Brief Communication

BRIEF COMMUNICATION

Lung Cancer Mortality in the Lung Screening Study Feasibility Trial

Maryam Doroudi, Paul F. Pinsky, Pamela M. Marcus

See the Notes section for the full list of authors' affiliations.
Correspondence to: Paul F. Pinsky, PhD, Division of Cancer Prevention, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892-9712 (e-mail: pinskyp@mail.nih.gov).

Abstract

The Lung Screening Study was a multicenter controlled feasibility trial that randomly assigned subjects to undergo two rounds of screening with either low-dose spiral computed tomography (LDCT) or chest X-ray (CXR). Long-term follow-up was performed to evaluate any differences in lung-cancer-specific and all-cause mortality between arms. In 2000, subjects were randomly assigned at six screening centers. Linkage with the National Death Index was performed to ascertain long-term mortality for subjects. Median follow-up for mortality of the 1660 and 1658 subjects randomly assigned to LDCT and CXR, respectively, was 5.2 years. There were 32 and 26 deaths from lung cancer in the two groups, respectively, corresponding to lung cancer death rates of 3.84 and 3.10 per 1000 person-years, and a risk ratio of 1.24 (95% confidence interval = 0.74 to 2.08). The risk ratio for all-cause mortality was 1.20 (95% confidence interval = 0.94 to 1.54). These findings can contribute to the overall knowledge on LDCT lung cancer screening.

Lung cancer is the leading cause of cancer-related mortality in both men and women in the United States (1). To date, several screening trials have investigated the early detection of lung cancer using low-dose spiral computed tomography (LDCT) as a method of reducing mortality from lung cancer (2–6). The National Lung Screening Trial (NLST) randomly assign more than 53 000 subjects to a LDCT vs chest radiograph (CXR) arm and showed a substantial reduction in lung cancer mortality for the LDCT arm. Four small LDCT screening trials conducted in Europe have also reported mortality outcomes. None showed a substantial reduction in lung cancer mortality, which is as expected, given their low statistical power. The results of the largest European trial, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), are scheduled to be reported soon, and may provide further evidence on the impact of this screening technology in reducing lung cancer mortality (7). Here we report the mortality results of another small screening trial, the Lung Screening Study (LSS); screening and lung cancer incidence data have been previously published for LSS, but not mortality data.

The LSS was a pilot randomized controlled trial (RCT) designed to assess the feasibility of conducting a large scale RCT of LDCT vs chest X-ray (CXR) for lung cancer screening in the United States (clinicalTrials.gov number NCT00006382) (8,9). The LSS was completed prior to the NLST being launched. LSS randomly assigned 3318 subjects at six screening centers to two annual rounds of screening, conducted from 2000 through 2001. Eligibility criteria were ages 55 to 74 years, a 30 pack-year history of cigarette smoking, and being either a current smoker or a former smoker who quit within the last 10 years (9). Note that the NLST had the same criteria, except it allowed quitting within the last 15 years. Exclusion criteria included history of a CXR or CT exam of the lungs or thorax in the previous 24 months, history of lung cancer, current treatment for another cancer other than nonmelanoma skin cancer, removal of a portion of or an entire lung, and participation in another cancer screening or cancer primary prevention trial other than a smoking cessation study (8). The Institutioanl Review Board of each center approved the trial and all participants provided informed consent.

Any noncalcified nodule 4mm in diameter or larger was considered a positive screening, as were other findings suspicious for lung cancer. Subjects with positive screenings were referred to their personal healthcare providers for diagnostic follow-up; the LSS did not specify a diagnostic algorithm. Subjects (including those with positive baseline screenings) were eligible for the year-one screening if they had not been diagnosed with lung

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Table 1. Lung cancer mortality in the lung screening study*

Outcome	Deaths	Person-years	Mortality rate (per 1000 PY)	Mortality RR (95% CI)
Lung cancer-specific mortality				
LDCT	32	8339	3.84	1.24 (0.74 to 2.08)
CXR	26	8384	3.10	
Other causes than lung cancer-specific mortality				
LDCT	107	8339	12.83	1.20 (0.90 to 1.58)
CXR	90	8384	10.74	
All-cause mortality				
LDCT	139	8339	16.67	1.20 (0.94 to 1.54)
CXR	116	8384	13.84	

*CI = confidence interval; CXR = chest X-ray; LDCT = low-dose spiral computed tomography; PY = person-years; RR = rate ratio.

cancer. Diagnostic evaluation of all positive screens was tracked by collection and abstraction of medical records.

The results of the LSS, in terms of screening compliance, screening test results, and incident lung cancers diagnosed over the two screening rounds, have been previously reported (8,9).

Several years after study completion, in 2007, a linkage analysis was performed linking LSS subjects to the National Death Index (NDI). For the linkage, participants' personally identifiable information (PII) was utilized to link LSS subjects to the NDI, with all deaths from trial entry through 2005 included. The underlying cause of death variable was used to classify deaths into lung-cancer- or non-lung cancer-related.

In this study, we report the results of this mortality linkage. We compared rates of all-cause mortality, lung cancer-specific mortality, and other-cause mortality between the two screening groups. Event rates were defined as the number of events divided by the person-years at risk for the event.

Although this trial was small, its results can contribute to the body of knowledge about LDCT screening, and can be included in future meta-analyses.

A total of 3318 subjects were randomly assigned, 1660 to the LDCT group and 1658 to the CXR group. Median follow-up time for mortality in each group was 5.2 years. There were 32 lung cancer deaths in the LDCT group as compared to 26 in the CXR group, giving rates per 1000 person-years (PYs) of 3.84 and 3.10, respectively, and a rate ratio (LDCT group compared to CXR group) of 1.24 (95% confidence interval [CI] = 0.74 to 2.08) (Table 1).

There were 139 and 116 total deaths in the LDCT and CXR groups, respectively, with corresponding all-cause mortality rates of 16.67 and 13.84 per 1000 PYs, and a rate ratio of 1.20 (95% CI = 0.94 to 1.54) (Table 1). The rate ratio for other than lung cancer death was similar, 1.20 (95% CI = 0.90 to 1.58).

In this feasibility study of lung cancer screening with LDCT, lung cancer-specific mortality rates were similar between the two arms of the trial, with a slightly higher rate in the LDCT arm, but that was not statistically significant. While LSS established the feasibility of an RCT comparing annual LDCT to CXR for lung cancer screening, paving the path for conducting the NLST, the trial was not sufficiently powered to detect statistically significant differences in mortality.

The LSS LDCT screening results were generally similar to those of NLST. For example, baseline LDCT compliance was 96% in LSS vs 98% in NLST, and the cumulative incidence of LDCT screen-detected lung cancer through the first two screening rounds was 2.3% in LSS vs 1.6% in NLST. The percentage of LDCT screen-detected lung cancers that were stage I was modestly lower in LSS (47%) than in NLST (63%) (2,8). Although the point estimate of the lung cancer mortality rate ratio went in the opposite direction in LSS as compared to NLST, the 95% CIs of the LSS estimate did include the observed NLST risk ratio.

A potential limitation of this analysis was that lung cancer deaths were based on the underlying cause of death from the death certificate and no endpoint verification (death review) was performed. However, an analysis of NLST comparing lung cancer deaths defined from death review vs those defined based on death certificates alone showed only minor differences. The lung cancer-specific mortality risk ratio was 0.80 based on death review and 0.82 based on using only death certificate data (10).

Although LSS was small, its results can contribute to the body of knowledge about LDCT screening. Currently, there are six randomized trials of LDCT lung cancer screening that have reported mortality outcomes, including this feasibility study (2–6). Of these other five, except for NLST, all were of roughly comparable in size to this LSS feasibility study (range = 2500–4100 subjects). One other trial, the NELSON trial, is on track to report its mortality findings later this year (7). For a public health intervention as important as LDCT lung cancer screening, relying on a single trial, albeit a large and well-conducted one, for evidence of effectiveness is not an optimal situation. Combining evidence from multiple RCTs conducted in various settings with different subject populations, CT readers, screen positivity criteria, and diagnostic follow-up algorithms can provide more robust evidence about the lung cancer mortality benefit, as well as harms, of LDCT screening. Using accepted criteria on trial quality and risk of bias, the results from the various RCTs of LDCT lung cancer screening can be incorporated into meta-analyses and systematic reviews as appropriate.

In conclusion, lung cancer-specific mortality rates were not found to be different between the LDCT and CXR arms of LSS.

Notes

Affiliations of authors: Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (MD, PFP); Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD (PMM).

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