# Editorial

## Efficacy of lung cancer screening appears to increase with prolonged intervention: results from the MILD trial and a meta-analysis

The long-term results of the Multicentric Italian Lung Detection (MILD) study [1] show a reduced lung cancer (LC) mortality at 10 years in the screened compared with the control arm [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.39–0.95); the HR for all-cause mortality was 0.80 (95% CI 0.62–1.03). Screening benefits were more evident beyond the fifth year of screening, with HRs of 0.42 (95% CI 0.22-0.79) for LC mortality and 0.68 (95% CI 0.49–0.94) for all-cause mortality.

These important findings add to our knowledge of low-dose CT scan (LDCT) screening efficacy. The National Lung Screening Trial (NLST) showed that screening with LDCT reduces LC mortality by 20% as compared with chest X-ray after a median follow-up of 6.5 years [2]. The results of the NLST were initially not replicated by smaller European trials [3–5], although preliminary results of the NEderlands Leuvens Longkanker Screenings ONderzoek (NELSON) trial—the only European trial with adequate power—showed a reduction in LC mortality at 10 years [6]. While waiting for full publication of the NELSON trial, we carried out a systematic review and meta-analysis of the currently available evidence on LDCT screening for LC, including new results of the MILD [1] and preliminary results of the NELSON [6].

We carried out a literature search in MEDLINE through PubMed and EMBASE from their inception date to 31 March 2019. Randomized controlled trials (RCTs) of lung cancer screening with LDCT as compared with other screening techniques were included. Both pilot and full RCTs were considered, without restrictions on publication type. Primary outcomes were LC mortality and all-cause mortality at the longest follow-up available, at 5 years of follow-up, and beyond the fifth year of follow-up for studies reporting long-term results. Secondary outcomes were LC incidence, detection of LC at early stages (IA and IB) and detection of lung adenocarcinoma with LDCT.

A random-effects meta-analytic model [7] of between-study variance was used to pool the estimates across studies. For LC mortality, all-cause mortality and LC incidence, we pooled together both HRs and relative risks (RRs) derived from the studies eligible for the meta-analysis. The estimates at 5 years of follow-up and those beyond the fifth year were extracted from the Kaplan–Meier curves using the methods described by Tierney et al. [8], or derived from the cumulative number of events and number of person-years at 5 years of follow-up or beyond. For detection of LC at early stages and detection of lung adenocarcinoma, the study-specific RRs were computed using as a denominator the total number of LCs detected within each study arms.

A total of 460 records were retrieved from the literature search, of which 49 were assessed for eligibility by full-text reading. Three pilot RCTs [9–11] and eight RCTs [1–6, 12, 13] were considered eligible, including a total of 51 426 subjects at high risk of LC randomized to LDCT and 50 322 to the control arm (Table 1). For the NLST trial [2] and its pilot study—the Lung Screening Study (LSS) [9]—subjects randomized to the control group underwent chest X-ray examination, while in the remaining studies [1, 3–6, 10–13] no screening was offered to subjects randomized to the control arm. The frequency (annual and/or biennial) and the number of LDCT examinations varied between studies, from three annual LDCT in NLST [2] to four annual in NELSON [6] and seven annual LDCT in MILD [1]. The DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) study [3] included only men. The age of participants ranged between 45 and 75 years. Median follow-up duration was 5.2 years in the LSS pilot study [9], 6.5 years in the NLST trial [2], 8.3 years in DANTE [3], nearly 10 years in ITALUNG (Italian Lung Cancer Screening Trial) [4] and DLCST (Danish Lung Cancer Screening Trial) [5] and above 10 years in MILD [1] and NELSON [6] studies. The German Lung Cancer Screening Intervention (LUSI) trial reported the results of the first 3 years of follow-up after randomization [12] and a Chinese community-based LC screening study only reported results of the baseline screening [13]. These studies were therefore not included in the meta-analysis.

Mortality results were reported from eight studies [1–6, 12, 14]. The pooled estimate for LC mortality was 0.80 (95% CI 0.71–0.90) (Figure 1). As also shown in MILD [1], reduction of LC mortality in the model estimate was greater beyond the fifth year of screening (RR 0.69, 95% CI 0.56–0.86). All-cause mortality was also reduced (RR 0.94, 95% CI 0.89–1.00), with a greater effect beyond the fifth year of screening (RR 0.82, 95% CI 0.71–0.95). Results for secondary outcomes showed that incidence of LC was higher in the LDCT arm (RR 1.69, 95% CI 1.30–2.19), and that LDCT screening allowed for the more frequent detection of LC cases at early stages IA and IB (RR 2.07, 95% CI 1.50–2.85), as well as lung adenocarcinomas (RR 1.20, 95% CI 1.03–1.38).

Thus, the evidence on the efficacy of LDCT as screening for lung cancer in high-risk individuals that accumulated after the publication of the NLST in 2011 [2] largely confirms the results of that landmark trial. The prolonged follow-up of the MILD, including its landmark analysis showing an HR of 0.42 beyond the fifth year of screening, provides the most convincing evidence to date of the long-term benefit of LDCT compared with a shorter duration [15]. The likely explanation is that screening with LDCT works by identifying nodules that would have been

**Table 1. Randomized trials of LDCT and lung cancer**

| Study | Country | Screening test and description | | Age and sex of participants | Smoking status | Participants | | Median length of follow-up |
|---|---|---|---|---|---|---|---|---|
| | | LDCT | Control | | | LDCT | Control | |
| Pilot trials | | | | | | | | |
| LSS: Gohagan et al. [9] and Doroudi et al. [14] | US | 2 annual LDCT | 2 annual CXR | M and F 55–74 | Current ≥30 pack-years, former quit <10 years | 1600 | 1658 | 5.2 years |
| DEPISCAN: Blanchon et al. [10] | France | Baseline LDCT | Usual care | M and F 50–75 | Current ≥15 cigarettes/day, former quit <15 years | 330 | 291 | Only baseline findings |
| UKLS: Field et al. [11] | UK | Baseline LDCT | Usual care | M and F 50–75 | 5 years lung cancer risk ≥5% according to Liverpool Lung Project risk prediction model | 2028 | 2027 | Only baseline findings |
| Trials | | | | | | | | |
| NLST: Aberle et al. [2] | US | 3 annual LDCT | 3 annual CXR | M and F 55–74 | Current ≥30 pack-years, former quit <15 years | 26722 | 26732 | 6.5 years |
| DANTE: Infante et al. [3] | Italy | 4 annual LDCT | 4 annual medical visits | M 60–74 | Current ≥20 pack-years, former quit <10 years | 1264 | 1186 | 8.4 years |
| LUSI: Becker et al. [12] | Germany | 5 annual LDCT | Usual care | M and F 50–69 | Current ≥15 cigarettes /day for >25 years or ≥10 cigarettes/day for >30 years, former quit <10 years | 2029 | 2023 | ≈5 years |
| DLCST: Wille et al. [5] | Denmark | 5 annual LDCT | 5 annual medical visits | M and F 50–70 | Current ≥20 pack-years, former quit <10 years | 2052 | 2052 | 9.8 years |
| ITALUNG: Paci et al. [4] | Italy | 4 annual LDCT | Usual care | M and F 55–69 | Current ≥20 pack-years, former quit <10 years | 1613 | 1593 | 9.3 years |
| AME: Yang et al. [13] | China | Baseline LDCT | Usual care | M and F 45–70 | Current ≥20 pack-years, former quit <15 years, family history of cancer, long history of passive smoking, occupational exposure | 3512 | 3145 | Only baseline results |
| NELSON: De Koning et al. [6] | Netherlands and Belgium | 4 annual LDCT | Usual care | M and F 50–74 | Current ≥10 cigarettes/day for >30 years or ≥15 cigarettes/day for >25 years, former quit <10 years | 7900 | 7892 | >10 years |
| MILD: Pastorino et al. [1] | Italy | 7 annual LDCT/4 biennial LDCT | Usual care | M and F 49–75 | Current ≥20 pack-years, former quit <10 years | 2376 | 1723 | >10 years |

LDCT, low-dose CT scan; CXR, chest X-Ray; LSS, Lung Screening Study; UKLS, UK Lung Cancer Screening; NLST, National Lung Screening Trial; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; LUSI, Lung Cancer Screening Intervention; DLCST, Danish Lung Cancer Screening Trial; ITALUNG, Italian Lung Cancer Screening Trial; AME, written on behalf of the AME Publishing Company Thoracic Surgery Collaborative Group; NELSON, NEderlands Leuvens Longkanker Screenings ONderzoek; MILD, Multicentric Italian Lung Detection.

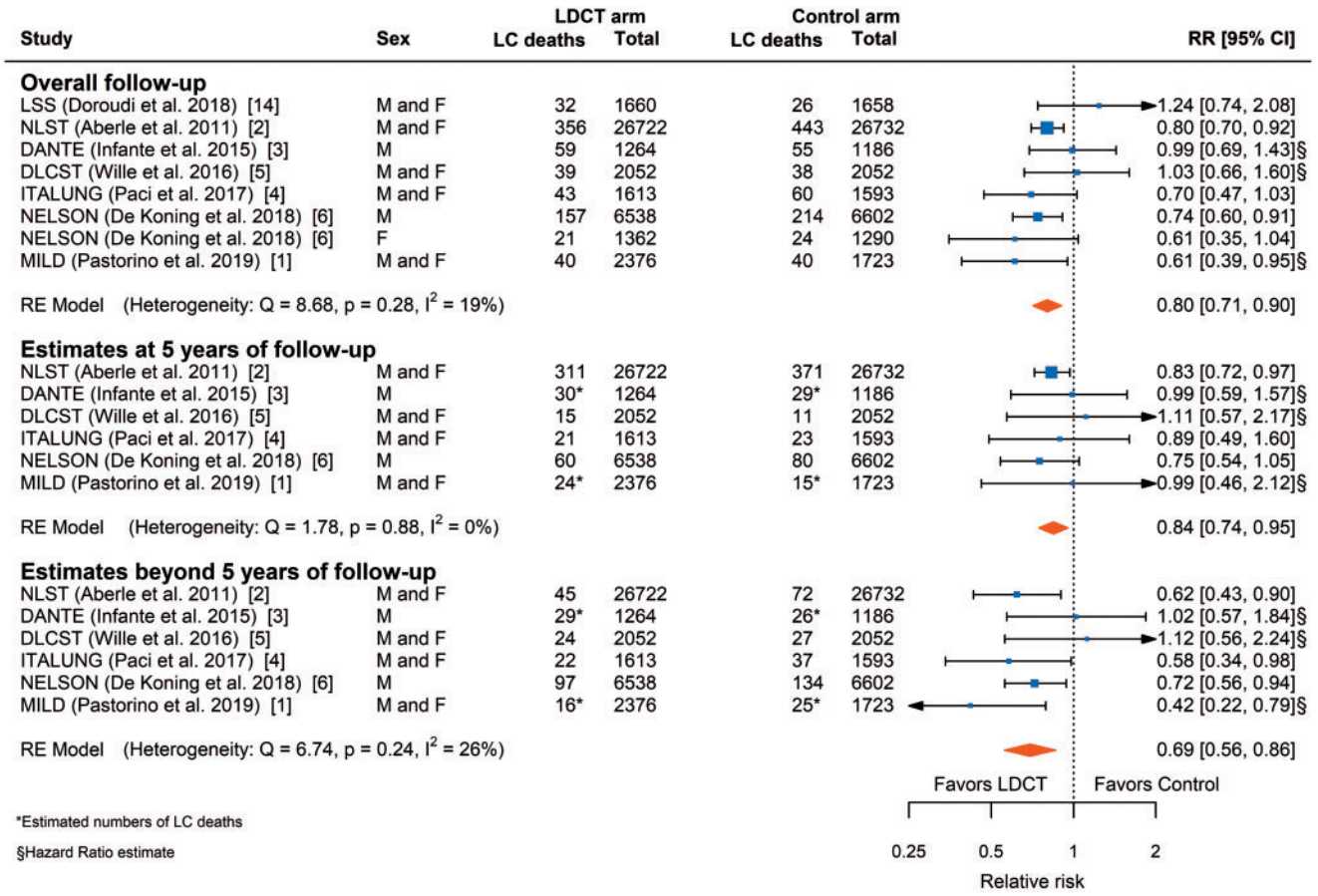


**Figure 1.** Forest plot of lung cancer mortality in LDCT trials.

diagnosed as LC several years later: the effect of screening therefore increases with repeated tests over a prolonged period. Replication of MILD results beyond 5 years of intervention and follow-up, either from NELSON [6] or from other studies, is essential to quantify the full effect of sustained LDCT screening on LC mortality and develop recommendations for long-term screening of high-risk individuals.

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## Funding

MP is covered by a PhD Scholarship (no grant numbers apply).

## Disclosure

The authors have declared no conflicts of interest.

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doi:10.1093/annonc/mdz145
Published online 2 May 2019