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 LDCT screening efficacy. The National Lung Screening Trial (NLST) showed that screening with low-dose CT scan (LDCT) reduces LC mortality by 20% as compared to 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 Dutch-Belgian Lung Cancer Screening Trial (NELSON) - 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 performed 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 LC 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 8 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 study [3] included only men. The age of participants ranged between 45 to 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 [4] and DLCST [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 8 studies [1-6, 12, 14]. The pooled estimates 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 allowinf fothr more frequent detection of LC cases at early stages IA and IB (RR 2.07, 95% CI 1.50-2.85), as well as 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 a 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 to a shorter duration [15]. The likely explanation is that screening with LDCT works by identifying nodules that would have been diagnosed as LC several years later: the effect of screening therefore increases with repeated tests over a prolonged period.

Replication of MILD results beyond five 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.

M Rota[1], M Pizzato[2], C La Vecchia[2]* & P Boffetta[3,4]

[1] Department of Molecular and Translational Medicine, Università degli Studi di Brescia, Brescia, Italy.

[2] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy.

[3] Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[4] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.

***Correspondence to**: (*E-mail: carlo.lavecchia@unimi.it)

Funding

MP is covered by a PhD Scholarship.

Disclosure

The authors have declared no conflicts of interest.

References

1. Pastorino U, Silva M, Sestini S et al. Prolonged Lung Cancer Screening Reduced 10-year Mortality in the MILD Trial. Ann Oncol 2019 Apr 1 [Epub ahed of print]. doi: 10.1093/annonc/mdz117.

2. Aberle DR, Adams AM, Berg CD et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. New England Journal of Medicine 2011; 365: 395-409.

3. Infante M, Cavuto S, Lutman FR et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. Am J Respir Crit Care Med 2015; 191: 1166-1175.

4. Paci E, Puliti D, Lopes Pegna A et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017; 72: 825-831.

5. Wille MM, Dirksen A, Ashraf H et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med 2016; 193: 542-551.

6. De Koning H, Van Der Aalst C, Ten Haaf K, Oudkerk M. Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. Journal of Thoracic Oncology 2018; 13: S185.

7. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

8. Tierney JF, Stewart LA, Ghersi D et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

9. Gohagan JK, Marcus PM, Fagerstrom RM et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer 2005; 47: 9-15.

10. Blanchon T, Bréchot JM, Grenier PA et al. Baseline results of the Depiscan study: A French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer 2007; 58: 50-58.

11. Field JK, Duffy SW, Baldwin DR et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess 2016; 20: 1-146.

12. Becker N, Motsch E, Gross ML et al. Randomized Study on Early Detection of Lung Cancer with MSCT in Germany: Results of the First 3 Years of Follow-up After Randomization. J Thorac Oncol 2015; 10: 890-896.

13. Yang W, Qian F, Teng J et al. Community-based lung cancer screening with low-dose CT in China: Results of the baseline screening. Lung Cancer 2018; 117: 20-26.

14. Doroudi M, Pinsky PF, Marcus PM. Lung Cancer Mortality in the Lung Screening Study Feasibility Trial. JNCI Cancer Spectrum 2018; 2.

15. Pastorino U, Rossi M, Rosato V et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. European Journal of Cancer Prevention 2012; 21: 308-315.

Table 1. Randomized trials of LDCT and lung cancer

Study	Country	Screening test & description		Age and sex of participants	Smoking status	Participants		Median length of follow-up
		LDCT	Control			LDCT	Control	
Pilot trials								
LSS **Gohagan et al. 2005 [9]** **Doroudi et al. 2018 [14]**	US	2 annual LDCT	2 annual CXR	M & F 55-74	current ≥30 pack-years, former quit <10 years	1600	1658	5.2 years
DEPISCAN **Blanchon et al. 2007 [10]**	France	Baseline LDCT	Usual care	M & F 50-75	current ≥15 cigarettes/day, former quit <15 years	330	291	Only baseline findings
UKLS **Field et al. 2016 [11]**	UK	Baseline LDCT	Usual care	M & 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. 2011 [2]**	US	3 annual LDCT	3 annual CXR	M & F 55-74	current ≥30 pack-years, former quit <15 years	26722	26732	6.5 years
DANTE **Infante et al. 2015 [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. 2015 [12]**	Germany	5 annual LDCT	Usual care	M & 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. 2016 [5]**	Denmark	5 annual LDCT	5 annual medical visits	M & F 50-70	current ≥20 pack-years, former quit <10 years	2052	2052	9.8 years
ITALUNG **Paci et al. 2017 [4]**	Italy	4 annual LDCT	Usual care	M & F 55-69	current ≥20 pack-years, former quit <10 years	1613	1593	9.3 years
AME **Yang et al. 2018 [13]**	China	Baseline LDCT	Usual care	M & 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. 2018 [6]**	Netherlands & Belgium	4 annual LDCT	Usual care	M & 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. 2019 [1]**	Italy	7 annual LDCT / 4 biennial LDCT	Usual care	M & F 49-75	current ≥20 pack-years, former quit <10 years	2376	1723	> 10 years

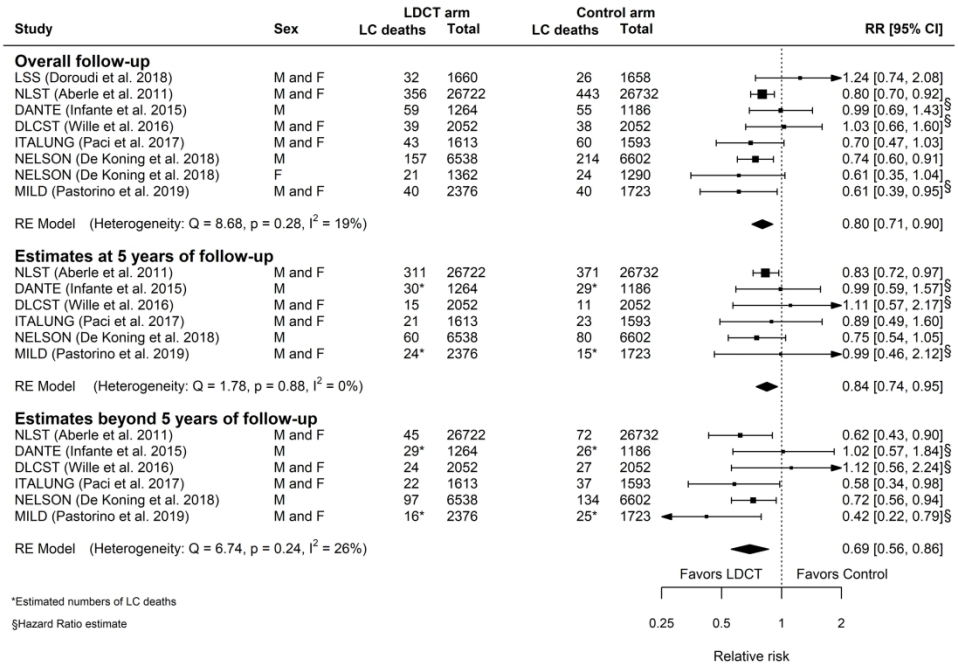

Figure 1. Forest plot of lung cancer mortality in LDCT trials

228x177mm (300 x 300 DPI)