Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography

Alexandre Sadate, Bob Occean, Jean-Paul Beregi, Aymeric Hamard, Takieddine Addala, Hélène de Forges, Pascale Fabbro-Peray, Julien Frandon

Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography

Alexandre Sadate (1), Bob V. Occean (2), Jean-Paul Beregi (1), Aymeric Hamard (1), Takieddine Addala (1), Hélène de Forges (1), Pascale Fabbro-Peray (2), Julien Frandon (1)

1 Department of Radiology and Medical Imaging, CHU Nîmes, Univ. Montpellier, EA2415, Nîmes, France

2 Department of Biostatistics, Epidemiology, Public Health and Innovation in Methodology (BESPIM), CHU Nîmes, Univ. Montpellier, Nîmes, France

Correspondance to:

Dr Alexandre Sadate, Département d'Imagerie Médicale, CHU Nîmes, 4 rue du Professeur-Robert-Debré, 30029 Nîmes cedex 9, France.

Mail : alexandre.sadate@chu-nimes.fr

ABSTRACT

Introduction. Lung cancer (LC) has the highest cancer mortality worldwide with poor prognosis. Screening with low-dose computed tomography (LDCT) in populations highly exposed to tobacco has been proposed to improve LC prognosis. Our objective was to perform a systematic review and meta-analysis to evaluate the efficacy of screening by LDCT compared to any other intervention in populations who reported tobacco consumption for more than 15 years on LC and overall mortality.

Methods. We searched randomized controlled trials (RCTs) studying screening by LDCT compared with any other intervention in a population who reported an average smoking history greater than 15 pack-years from inception until the 19th February 2018 using Medline and Cochrane Library databases. Publication selection and data extraction were made independently by two double-blind reviewers.

Results. Seven RCTs were included in the meta-analysis which corresponds to 84558 participants. A significant relative reduction of LC-specific mortality of 17% (RR= 0.83, 95% CI: 0.76-0.91) and a relative reduction of overall mortality of 4% (RR= 0.96, 95% CI: 0.92-1.00) was observed in the screening group compared with the control group.

Conclusion. In populations highly exposed to tobacco, screening by LDCT reduces lung cancer mortality.

Keywords

Lung cancer; screening; low-dose computed tomography; meta-analysis

List of abbreviations

CI: Confidence Interval

CXR: Chest X-ray

LC: Lung Cancer

HAS: National Authority for Health

LDCT: Low-Dose Computed Tomography

NLST: National Lung Screening Trial

OR: Odds Ratio

PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

p-yrs: person years

RCT: Randomized Controlled Trial

RR: Risk Ratio

Yrs: years

Introduction

Lung cancer shows the highest cancer mortality worldwide and a poor prognosis with a 5–year survival rate of 16% in the United States (1). It is the fourth most common cancer in France; around 30 000 lung cancer specific deaths in 2012 for around 40 000 diagnosed diseases (2). The incidence rates have been stable among men whilst they are rising rapidly in women in France and Europe. One cause may be that the main risk factor of lung cancer is tobacco consumption, that increases in women yet decreases in men (3,4). This confirms the promotion of smoking cessation is the most effective strategy to reduce LC mortality. One major issue is early detection, as nearly half of patients are diagnosed at an advanced stage, with various prognosis depending on cancer stage at diagnosis (5).

Two main trials have evaluated the benefits of chest radiography with or without sputum cytology, the PLCO Cancer Screening Trial and the Mayo Lung Project, with no efficacy in reduction of cancer-specific mortality (6,7). Several years later, a Japanese trial showed that low-dose computed tomography (LDCT) was superior to chest radiograph for the detection of peripheral lung cancer in a population highly exposed to tobacco (8). The Early Lung Cancer Action Project (ELCAP) program then showed that LDCT not only detected more lung cancers than chest radiography but also at an earlier and more resectable stage, which could potentially reduce cancer-specific mortality (9).

Radiation risk is one of the main obstacles preventing a more wide-spread lung cancer screening in populations highly exposed to tobacco. However, LDCT allows dose reduction without altering image quality (10), thanks to tube voltage and current reduction and iterative reconstructions.

Based on these results, several randomized controlled trials (RCT) were launched to evaluate the efficacy and cost effectiveness of a potential lung cancer screening in high-risk populations.

Following the results of a large randomized American trial, the National Lung Screening Trial (NLST) (11), which demonstrated a significant relative reduction in all-cause and lung cancer-specific mortality, the US Preventive Services Task Force recommended screening with LDCT all adults between 55 and 80 years with a 30 pack-year smoking history (12). Other international guidelines have also published recommendations supporting lung cancer screening in various eligible populations (13).

The objective of our systematic review and meta-analysis was to evaluate the efficacy of lung cancer screening by LDCT in populations highly exposed to tobacco on cancer specific- and overall mortality.

Materials and methods

The systematic review protocol was registered with PROSPERO on March 27th, 2018 (CRD42018091720). Results are reported here following the PRISMA Equator Network guidelines (14).

Search strategy

The search was made using the Medline and Cochrane Library databases. The research terms were covering lung cancer, screening by LDCT compared with any other intervention, randomized controlled trials (RCT) and their synonyms, from inception until the February 19th, 2018, as follows: *((((("Lung Neoplasms"[Mesh] OR lung neoplasm*[TIAB] OR pulmonary neoplasm*[TIAB] OR bronchopulmonary neoplasm*[TIAB] OR broncho-pulmonary neoplasm*[TIAB] OR bronchial neoplasm*[TIAB] OR lung cancer*[TIAB] OR pulmonary cancer*[TIAB] OR bronchopulmonary cancer*[TIAB] OR broncho-pulmonary cancer*[TIAB] OR bronchial cancer*[TIAB] OR lung carcinoma*[TIAB] OR pulmonary carcinoma*[TIAB] OR bronchopulmonary carcinoma*[TIAB] OR broncho-pulmonary carcinoma*[TIAB] OR bronchial carcinoma*[TIAB] OR bronchogenic carcinoma*[TIAB] OR lung blastoma*[TIAB] OR pulmonary blastoma*[TIAB] OR bronchopulmonary blastoma*[TIAB] OR broncho-pulmonary blastoma*[TIAB] OR bronchial blastoma*[TIAB] OR lung tumor*[TIAB] OR pulmonary tumor*[TIAB] OR bronchopulmonary tumor*[TIAB] OR broncho-pulmonary tumor*[TIAB] OR bronchial tumor*[TIAB])) AND ("Mass Screening"[Mesh] OR "Early Detection of Cancer"[Mesh] OR screen*[TIAB] OR test[TI] OR testing[TI] OR detection*[TI])) AND (random*[TI] OR randomly[TIAB] OR randomized[TIAB] OR placebo[TIAB] OR Random*

Allocation[MH] OR Double-Blind Method[MH] OR Single-Blind Method[MH] OR Cross-Over Studies[MH] OR randomized controlled trial[PT] OR controlled clinical trial[PT])))

It was completed by a Medline search with the names of the trials identified, the reference list of the eligible articles, a clinicaltrials.gov database search, a free-text Internet search and a regular update Medline search. The search was limited to articles published in English and French. The initial search was updated on February 12th, 2020.

Study selection criteria

Inclusion criteria for the systematic review and meta-analysis were topics about lung cancer screening, RCT study design, LDCT compared to any other intervention, population who reported an average smoking history over 15 pack-years (corresponding to the lowest criteria of the European RCTs on lung cancer screening) and the report of data on all-cause mortality or lung cancer-specific mortality.

Two double-blind reviewers (AS, QD) selected the publications by screening the titles and abstracts first, and then on the full-text articles. Discrepancies were resolved by consensus between the two readers. If a consensus was not made, an epidemiologic expert (PFP), it was consulted.

Quality assessment and data extraction

The critical appraisal of each eligible RCT was made by two reviewers (AS, JF) using a CONSORT checklist including random assignment, complete diagnostic work-up planned, respect of inclusion criteria, valid measurement of mortality and blinded outcomes assessment. The contents of the checklist and the inclusion or exclusion of each study for the meta-analysis were then discussed with two epidemiologic experts (PFP, BO). Data were collected and managed using REDCap electronic data capture tools.

The extraction of the data for the meta-analysis was made independently by two double-blind reviewers (AS, JF), and the differences were resolved by an epidemiologic expert (PFP). When several articles were available for a single study, data from the most recent publication were used, unless unique data was found in a previous publication. The following data were extracted: title of the article, sample size,

participants, characteristics (age, sex, smoking history), type of intervention in the control arm, median follow-up, number of screening rounds, time between rounds, number of any-cause and lung cancer-associated deaths.

Statistical analysis

Results on all-causes and lung cancer-specific mortality of the studies included were combined for meta-analysis. In the collection of studies considered the effect size and the true effect size were estimated. A general model was then specified by both standard and random effects models to incorporate the between-study variance (15). The inverse variance weighting method was used for pooling, on the hypothesis of common "effect size" normality and weights assigned to individual studies. This method allows maximizing the accuracy of the estimate of the common effect, minimizing the variance of the pooled result. The binary outcome data as mortality rate was extracted in a 2X2 table for all selected studies. A relative risk and 95% confidence interval (95% CI) were used as summary statistics. The heterogeneity between trials was taken into account using chi-square tests. I^2 statistic was used to estimate the percentage of total variation across studies arising from heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% represented a low, moderate or substantial heterogeneity (16). The reasons for substantial heterogeneity were explored and subgroup analyses were performed to consider possible variations across studies. Supplementary analyses excluding studies with heterogeneity and low contribution to the overall effect, then including only those with the highest weighting, were performed. A subgroup analysis was performed to take into account variability across studies during follow-up. Possible publication biases were explored through visual analysis of funnel plots. Statistical analysis was performed using General Package for Meta-Analysis "meta" v4.9-1 with R software v3.5.1.

Results

Study selection

Of the 891 publications identified with the search strategy in the Medline and Cochrane Library databases, 799 were excluded on titles and abstracts because of topic or study design: 449 were not related to lung cancer screening, 142 reported results of lung cancer screening without using LDCT, 40 were not RCTs and 168 were systematic review or general considerations. The additional search identified 22 other publications which were added to the 92 studies. Reading the full-text of these 114 publications, 107 studies were excluded: 11 were pilot study, 31 did not report mortality data in the control group, 59 did not assess mortality as primary endpoint, and 6 presented intermediate results. A total of 7 RCTs were finally included, including a total of 84,558 patients (Figure 1) (17–23).

Study characteristics and quality assessment

The characteristics of the 7 RCTs included are detailed in Table 1. For all studies included in the meta-analysis, randomization was performed at inclusion. The intervention in the control arm was chest X-ray (CXR) at inclusion followed by annual clinical examination in the DANTE study, annual CXR in the NLST study, primary prevention for smoking cessation in four RCTs (NELSON, LUSI, ITALUNG, MILD) and annual clinical examination for the Danish Randomized Lung Cancer CT Screening Trial (DLCST). Five studies included both men and women; the DANTE and NELSON studies only included men.

All 7 trials presented a complete diagnostic work-up planned in the protocol with well-described and respected inclusion criteria. Validity of mortality measurement was checked in all studies. Quality assessment results of all 7 RCTs are shown in Table 2.

Overall and lung cancer-specific mortality

Two trials reported statistically significant results on mortality data. The NLST trial showed a relative reduction of lung cancer-specific mortality of 20% (95% CI: 6.8- 26.7; p=0.004) and a relative

reduction of overall mortality of 6.7% (95% CI: 1.2-13.6) in the LDCT group compared to the control annual CXR group. The NELSON study reported a relative reduction of lung-cancer-specific mortality of 24% (95% CI: 6- 39; *p*=0.01) compared with standard primary prevention; there was no difference of overall mortality in the two groups.

The final results of the ITALILUNG, DANTE, MILD and LUSI trials did not find any difference for both overall and lung cancer-specific mortality in the LDCT groups compared to the control groups.

Publication biases

The risk of publication bias was evaluated using a funnel plot (Figure 2). The symmetric distribution of the relative risk across the global effect paired with the standard deviation of the screening effect confirmed the studies included did not present major biases.

Results of the meta-analysis

A total of 84,558 participants were included in the meta-analysis. There was no heterogeneity in the data (I^2=0%, tau^2=0, *p*=0.67). A relative reduction of overall mortality of 4% was observed in the experimental screening group *versus* control group (RR=0.96, 95% CI: 0.92-1.00) (Figure 3). Concerning lung cancer-specific mortality, a significant relative reduction of 17% was observed in the experimental screening group (RR=0.83, 95% CI: 0.76-0.91) (Figure 4). To prevent one lung-cancer related death, 294 patients needed to be screened.

Discussion

Our meta-analysis on the impact of lung cancer screening using LDCT is, to our knowledge, the first meta-analysis including the final mortality results of the recently published NELSON, DLCST, ITALUNG, MILD and LUSI studies (18–20,22,23). Our results show a significant relative reduction of lung cancer-specific mortality of 17% in the screening group compared to the control group, but no significant difference in the mortality of all causes.

A previous meta-analysis (24) based on the pooled analysis of four RCTs (DANTE, MILD, NLST and the intermediate results of DLCST) showed a significant decrease of lung cancer-specific mortality in the control group (OR=0.84 [0.78, 0.96]); no difference was reported for overall mortality between the two groups (OR=1.04 [0.72, 1.51]). However, this pooled analysis included RCTs with both short (intermediate results of MILD with a 4.4-year follow-up) or long follow-up (DANTE: 8.3-year follow-up), one reason of the heterogeneity of the study (Q test p-value = 0.13). In our meta-analysis, we have included more studies as recent RCTs have been published since, including the final results of the MILD study, *i.e.* we included only final results for the RCTs included, and thus mostly long follow-up studies.

One major issue regarding lung cancer risk and screening is defining target populations at risk. Among studies included in the meta-analysis, only the NLST study included older participants with higher smoking history. Subgroups analyses divided the population into quintiles according to the risk of lung-cancer associated death (25). Lung-cancer specific mortality increased significantly with each quintile and the proportion of false positive results decreased significantly. Overall, 88% of the prevented lung cancer-associated deaths in the LDCT group corresponded to the 60% of participants within the highest risk subgroups, whereas 1% of the prevented lung cancer deaths accounted for 20% of participants in the lowest risk subgroups. Furthermore, the number of screened patients required to prevent one death from lung cancer decreased from 5276 in the lowest risk subgroup to 161 in the highest risk subgroup of patients. Another study with post-hoc analysis of the targeted population was published on the DLCST cohort (24). In the highest risk subgroup (patients with chronic obstructive pulmonary disease and a smoking history of more than 35 pack-years), there was a non-significant a 20% decrease

in the hazard ratio for LC mortality in the LDCT group was reported although it did not reach significance (26). The recent NELSON study included patients with relatively small smoking history (less than 36 packs.years) as compared with other studies and especially the NLST study (23). Overall, these results suggest the screening program may be restricted to patients with the highest risk, *i.e.* patients with a significant smoking history.

Our meta-analysis included the eagerly awaited recent NELSON study (23). This well-designed study, the biggest European study, reported results after a long follow-up (10 years). The results were significant regarding the specific overall mortality, but did not show any difference between the two groups for the all-causes mortality. This was explained by the authors by the study design, as the study included around 13,000 patients, a number, although consequent, which was not sufficient to show a difference. Also, a strength of the NELSON study was the very low number of false-positive (1.2% only). This may be due to the study design and the fact that the positive screening tests were assessed by nodule volume and not size as many other studies.

One strength of our meta-analysis is the design and quality of our study; we conducted a systematic review following the PRISMA guidelines with two double-blind independent reviewers to avoid missing publications. Quality assessment of each eligible trial and data extraction were also made by two double-blind independent readers to prevent data errors. Other strengths included inclusion in our meta-analysis of only controlled randomized studies with precise inclusion and exclusion criteria. Also, the studies included had long-term follow-up and we only included final analyses results (no intermediate or preliminary results). The symmetric distribution of the relative risk in the funnel plot confirms the minimal publication bias among the studies included. Last, our meta-analysis included a large final total number of patients (n=84,558).

Limitations of our study include the partial heterogeneity of the protocols studied, in particular the interventions in the control arm, either prevention or clinical examination in all the studies except the NLST (annual CXR), and DANTE (CXR at inclusion) studies. Also, heterogeneity among studies concerned the smoking history of patients included, much higher in the NLST study than in other RCTs included.

Conclusions

Our meta-analysis is the first systematic review to include all recent RCTs including the recent NELSON study. Our results confirm that of the NELSON study, showing an impact of lung cancer screening on lung cancer-specific mortality, reduced in the LDCT group. No impact of such screening on all-cause mortality was reported.

Acknowledgements

We would like to thank Sarah Kabani for valuable editorial assistance and Quentin Durand for the study selection. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest statement

None declared

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. févr 2012;62(1):10-29.

2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 1 mars 2015;136(5):E359-386.

3. Réseau Francim, Service de biostatistique des Hospices civils de Lyon, Institut de veille sanitaire, Institut national du cancer, Binder-Foucard F, Belot A, et al. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Étude à partir des registres des cancers du réseau Francim. Partie 1 – Tumeurs solides. Saint-Maurice; Boulogne-Billancourt: INVS; INCA; 2013.

4. Bray FI, Weiderpass E. Lung cancer mortality trends in 36 European countries: secular trends

and birth cohort patterns by sex and region 1970-2007. Int J Cancer. 15 mars 2010;126(6):1454-66.

5. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. juin 2013;68(6):551-64.

6. Gohagan JK, Prorok PC, Hayes RB, Kramer BS, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials. déc 2000;21(6 Suppl):251S-272S.

7. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. J Occup Med Off Publ Ind Med Assoc. août 1986;28(8):746-50.

8. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology. 1 déc 1996;201(3):798-802.

9. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet Lond Engl. 10 juill 1999;354(9173):99-105.

10. Macri F, Greffier J, Pereira FR, Mandoul C, Khasanova E, Gualdi G, et al. Ultra-low-dose chest CT with iterative reconstruction does not alter anatomical image quality. Diagn Interv Imaging. nov 2016;97(11):1131-40.

11. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 4 août 2011;365(5):395-409.

12. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 4 mars 2014;160(5):330-8.

13. Shen H. Low-dose CT for lung cancer screening: opportunities and challenges. Front Med. févr 2018;12(1):116-21.

14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for

systematic reviews and meta-analyses: the PRISMA statement. BMJ. 21 juill 2009;339:b2535.

15. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 15 juin 2002;21(11):1539-58.

16. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993;2(2):121-45.

17. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, 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. 15 mai 2015;191(10):1166-75.

18. Wille MMW, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med. 1 mars 2016;193(5):542-51.

19. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax. 2017;72(9):825-31.

20. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged Lung Cancer Screening Reduced 10-year Mortality in the MILD Trial. Ann Oncol Off J Eur Soc Med Oncol. 1 avr 2019;

21. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer. 15 nov 2013;119(22):3976-83.

22. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening - results from the randomised German LUSI trial. Int J Cancer. 4 juin 2019;

23. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 06 2020;382(6):503-13.

24. Fu C, Liu Z, Zhu F, Li S, Jiang L. A meta-analysis: is low-dose computed tomography a superior method for risky lung cancers screening population? Clin Respir J. mai 2016;10(3):333-41.

25. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of

low-dose CT screening according to the risk of lung-cancer death. N Engl J Med. 18 juill 2013;369(3):245-54.

26. Turner SR, Isbell JM. Lung Cancer Screening in the Post-National Lung Screening Trial Era: Applying Screening in the Real World. Semin Thorac Cardiovasc Surg. 27 nov 2017;

Figure and Table legends

Table 1: Details of the 7 Randomized Clinical Trials included

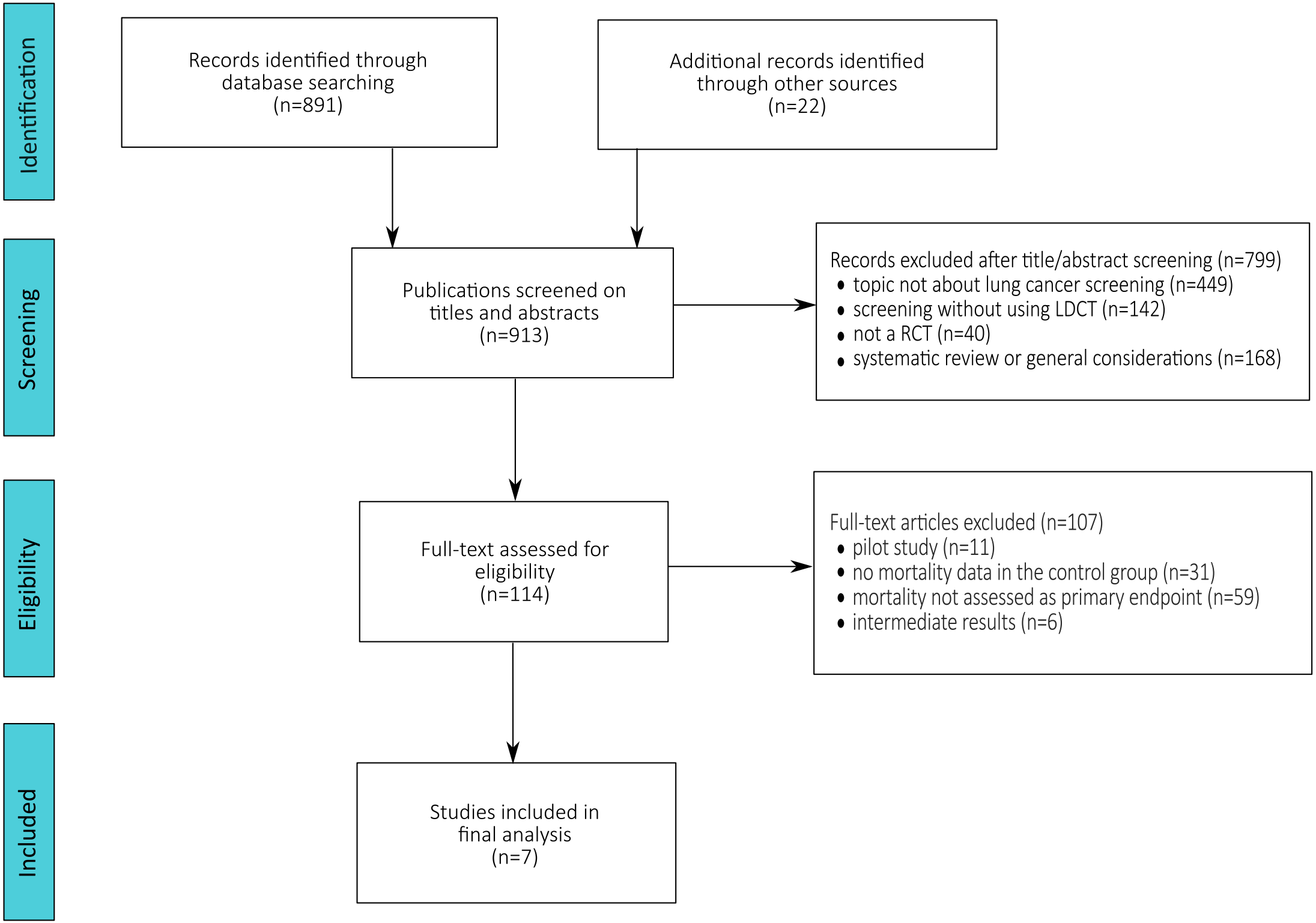
Table 2: Quality assessment results

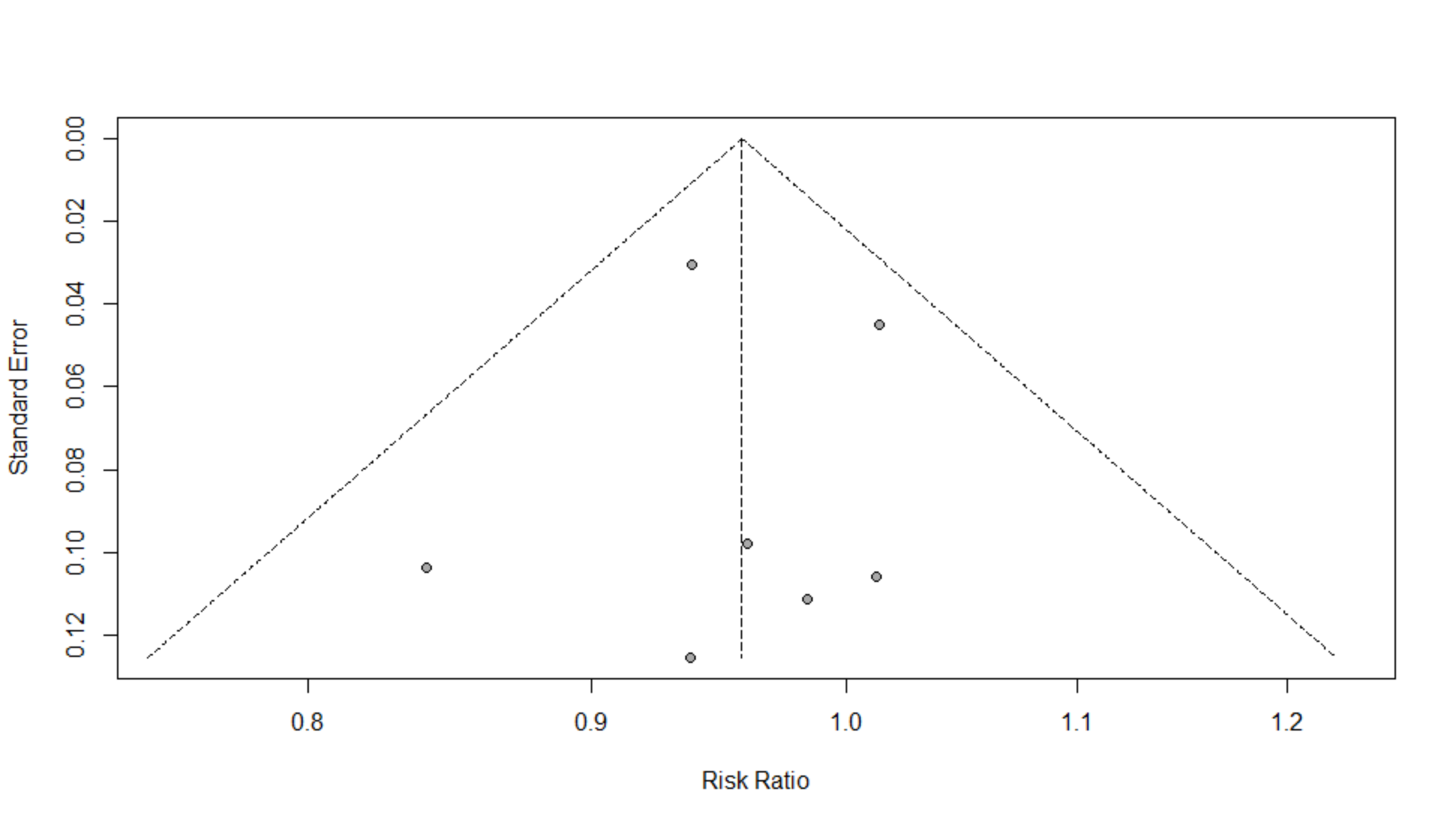
Figure 1: PRISMA flowdiagram of the meta-analysis

Figure 2: Funnel plot reporting relative risk for overall mortality

Figure 3: Forrest plot of relative risk for overall mortality

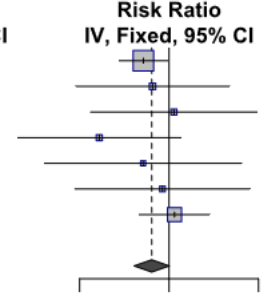
Figure 4: Forrest plot of relative risk for lung cancer specific mortality


Identification
Screening
Eligibility
Included
Records identified through database searching (n=891)
Additional records identified through other sources (n=22)
Publications screened on titles and abstracts (n=913)
Records excluded after title/abstract screening (n=799)
• topic not about lung cancer screening (n=449)
• screening without using LDCT (n=142)
• not a RCT (n=40)
• systematic review or general considerations (n=168)
Full-text assessed for eligibility (n=114)
Full-text articles excluded (n=107)
• pilot study (n=11)
• no mortality data in the control group (n=31)
• mortality not assessed as primary endpoint (n=59)
• intermediate results (n=6)
Studies included in final analysis (n=7)


Standard Error
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.8
0.9
1.0
1.1
1.2
Risk Ratio

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
NLST - 2013	1912	26722	2039	26730	53.5%	0.94 [0.88-1.00]
DANTE - 2015	180	1264	176	1186	5.2%	0.96 [0.79-1.16]
DLCST - 2015	165	2052	163	2052	4.5%	1.01 [0.82-1.25]
ITALILUNG - 2017	154	1613	181	1593	4.7%	0.84 [0.69-1.03]
MILD - 2019	137	2376	106	1723	3.2%	0.94 [0.73-1.20]
LUSI - 2019	148	2029	150	2023	4.0%	0.98 [0.79-1.22]
NELSON - 2020	868	6583	860	6612	24.9%	1.01 [0.93-1.11]
Total (95% CI)		**42639**		**41919**	**100.0%**	**0.96 [0.92-1.00]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.02$, df = 6 (P = 0.67); $I^2 = 0\%$



Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
NLST - 2013	469	26722	552	26730	55.6%	0.85 [0.75-0.96]
DANTE - 2015	59	1264	55	1186	6.4%	1.01 [0.70-1.44]
DLCST - 2015	39	2052	38	2052	4.2%	1.03 [0.66-1.60]
ITALILUNG - 2017	43	1613	60	1593	5.6%	0.71 [0.48-1.04]
MILD - 2019	40	2376	40	1723	4.4%	0.73 [0.47-1.12]
LUSI - 2019	29	2029	40	2023	3.7%	0.72 [0.45-1.16]
NELSON - 2020	160	6583	210	6612	20.1%	0.77 [0.62-0.94]
Total (95% CI)		**42639**		**41919**	**100.0%**	**0.83 [0.76-0.91]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.11$, df = 6 (P = 0.66); $I^2 = 0\%$

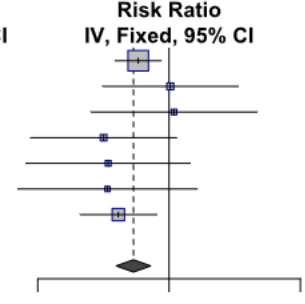


Table 1 Randomized Controlled Trials included in the meta-analysis

Characteristics	DANTE 2015 (1)	DLSCT 2015 (24, 29)	ITALILUNG 2017 (4)	MILD 2019 (5)	LUSI 2019 (6,7)	NLST 2013 (8–10)	NELSON 2020 (11)
Country	Italy	Denmark	Italy	Italy	Germany	USA	Belgium / Netherland
Control arm	CXR at inclusion	Annual clinical examination	Primary prevention for smoking cessation	Primary prevention for smoking cessation	Primary prevention for smoking cessation	Annual CXR	Primary prevention for smoking cessation
Total sample size	2450	4104	3206	4099	4052	53452	13195
LDCT arm	1264	2052	1613	2376	2029	26722	6583
Control arm	1186	2052	1593	1723	2023	26730	6612
Age, yrs	60-74	50-70	55-69	≥49	50-69	55-74	50-74
Men, %	100	55	65	66	65	59	100
Median follow-up, yrs	8.35	Intermediate: 4.8 Final: 9.8	9.3	4.4	3	6.5	10
Screening, p/yr	10875	19439	14658	6449.5	/	144103	/
Control, p/yr	10104	19547	14247	5556.7	/	143368	/
Smoking history	Mean [95% CI]:	Mean [95% CI]:	Mean:	Median:	NR	Mean:	Mean:
LDCT, pack-yrs	47.3 [45.7 – 49]	36.4 [23 – 49.8]	40	39		56.04	38.0 [29.7–49.5]
Controls, pack-yrs	47.2 [45.5 – 49]	35.9 [22.5 – 49.3]	38	38		55.93	38.0 [29.7–49.5]
Current smoker, n (%)	1395 (57%)	3124 (76%)	2077 (65%)	3176 (77%)	2506 (62%)	25779 (48%)	7254 (55%)
Former Smoker, n (%)	1055 (43%)	980 (24%)	1129 (35%)	923 (23%)	1545 (38%)	27677 (52%)	5941 (45%)
Screening rounds, n	5	5	4	5 or 3[i]	5	3	4
Time between rounds, yrs	1	1	1	1 or 2	1	1	1-2-2.5
Definition of positive screening test	Nodule ≥ 10 mm	Nodule ≥ 5 mm	Nodule ≥ 5 mm	Nodule volume ≥60mm³	Nodule ≥ 5 mm	Nodule ≥ 4mm	Nodule volume ≥50mm³

CXR: Chest X-ray / 95% CI: 95% confidence interval / NR: not reported

[i]5 for the annual arm and 3 for the biennial arm; p-yr: person years; yrs: years

Table 2: Quality assessment (CONSORT Check List) of the seven randomized controlled trials included in the meta-analysis.

Quality criteria	DANTE	DLSCT	ITALILUNG	MILD	LUSI	NLST	NELSON
Recruitment Strategies well defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete diagnostic work-up planned	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random assignment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Inclusion criteria described and respected	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Measure of all-cause mortality	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Measure of specific mortality	Yes	Yes	Yes	Yes	No	Yes	Yes
Valid measurement of mortality	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinded of outcome Assessment	Yes	NR	Yes	Yes	NR	Yes	Yes
Long enough follow-up	Yes	Yes	Yes	No	Yes	Yes	Yes

NR : not reported