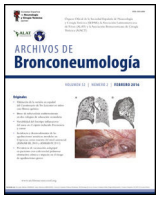
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial PRO/CON

Feasibility of Lung Cancer Screening in Europe: A Pro/con Debate

Introduction

Lung cancer (LC) is a major public health problem due to its high incidence and mortality and unfortunately will remain so for decades. Mortality is driven by the high percentage of late diagnoses, and the relatively low number of patients who benefit from immune- or targeted therapies. Approximately 50% of LC cases are diagnosed at stage IV, indicating a clear need to implement early detection. Two large, well-designed, randomized clinical trials, with different inclusion and exclusion criteria, follow-up, and comparison groups, found that LC mortality was significantly reduced for individuals offered low dose computed tomography (LDCT). The National Lung Screening Trial (NLST), conducted in the US, led the United States Preventive Services Task Force (USPSTF) to recommend coverage for this screening test.[1] With the NELSON study results (which is the largest European-based trial), including younger individuals, no screening offered to the control group and larger LC mortality reductions[2] the EU has recently recommended the coverage for LC screening, including it in the Europe's Beating Cancer Plan.[3] Despite this recommendation, there are systematic reviews from the Cochrane collaboration or the European Network of Health Technology Assessment questioning the lack of data on harms and recruitment strategies.[4,5] In this paper we will address some major pro- and con-arguments for implementing lung cancer screening, which cover basically different aspects, and conclude with opportunities ahead.

Pro

CT Screening Reduces Mortality in High-risk Individuals Substantially

The powered NLST showed an 8% LC mortality reduction for men at year 8 of follow-up, and 22% in women, and the powered NELSON trial showed a 24% reduction in men and 59% in women in the same follow-up period, likely to be a real (larger effective) difference. No detrimental effects on other causes of deaths were shown both in the NELSON[6] and the NLST, leading to an all-cause mortality reduction in the powered NLST. The smaller LUSI-trial in Germany showed a statistically significant effect in their female population.[7] In a meta-analysis, including other underpowered trials, there was a statistically significant 5% reduction in all-cause mortality (including lung cancer).[4] Modeling of the natural history of lung cancer by subtypes has learnt the chance of dying from a screen-detected stage I is being reduced by 65–85% (de Nijs, personal communication). In the Netherlands (18 million inhabitants) a rather stringent LC screening program may ultimately prevent 1000–1500 LC deaths annually,[8] which resembles the present breast cancer screening program.

Harms of CT Screening are Limited if Quality-assured

Two of the most harmful effects of screening are false-positive referrals and overdiagnosis. Overdiagnosis refers to diagnosing lung cancer in individuals that otherwise would never have had this diagnosis due to e.g., dying from another cause before the cancer would have become clinically apparent. The Cochrane group found that false positives could be limited to 1–4% when using a volumetric approach (instead of a diametric approach as in NLST) with stringent criteria for (non-) referral. For instance, the risk was found not to be elevated for nodules smaller than 100 mm compared to individuals without nodules on CT images (Lancet), and an indeterminate group was re-invited to assess (significant) growth. Overdiagnosis has been estimated to be 3–9% of screen-detected cases. This would mean that in the US for every 3 lung cancer deaths prevented, 1 individual would suffer from the consequences of an otherwise never detected lung cancer and its treatment,[9] a quite comparable ratio to high-quality breast cancer screening in the EU.[10]

Recruitment is Challenging but Successful in Several Countries

The most challenging aspects in implementation have been discussed.[11] Surely, any screening program stands or falls with succeeding in catching the 'at risk' population. Presently, the Targeted Lung Health Checks is exemplary for Europe with 360,000 baseline CT scans being performed. Cancer registry data now show that the socio-economic disparity has consequently been reduced: early stages of cancer had disproportionally less been found at higher socio-economic classes, which now has disappeared due to the substantially earlier detection of LC in more lower SES groups.[12] Selecting individuals on (past) smoking exposure through General Practitioners' (GP) registries only, is therefore promising,[13] and is also the main method in Croatia (separate digital lung module) but appears to be more difficult in other countries, due to incomplete GP records on (past) smoking exposure. The evidence on recruitment methods is still limited,[14] but successes are likely the consequence of a good governance, available digital registry systems, and a targeted recruitment method (Fig. 1). In the 4-IN-THE-LUNG-RUN trial (Netherlands centers) with a population registry, asking individuals

https://doi.org/10.1016/j.arbres.2025.03.022

Please cite this article as: A. Ruano-Ravina and H.J. de Koning, Feasibility of Lung Cancer Screening in Europe: A Pro/con Debate, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2025.03.022

Fig. 1. Recruitment method.

to self-select through an online questionnaire appeared efficacious. General invitations seem extremely cost-ineffective. The crucial question on invitation coverage[15] 'which proportion of the vulnerable high-risk group has accepted the invitation?' has not yet been answered to its full extent.

Opportunity for an Additional Smoking Cessation Offer

More than half of 'at risk' individuals have stopped smoking in the past. Nevertheless, individuals who still smoke should be encouraged to stop their habit, but in practice this is not easy. No effect was found of an increased effort of counseling in the Yorkshire Lung Cancer Screening Trial, except for ad-hoc subgroup analyses in women. Moreover, Nijs et al., found that in aged individuals at high-risk getting their CT screens was more efficacious than adding smoking cessation programs due to a low effectiveness of the latter programs.[8] We have not yet found the best approach in this respect, and feel ethically obliged to offer effective smoking cessation interventions, perhaps by standard pharmacological means.

Increasing Cost Savings in Health Care for Advanced Disease

Is it worth the money and resources? This seems an easy question if we see the enormous amounts being invested in late-stage therapy. For example, in the Netherlands, cost for LC treatment have increased by 52% over a 5-year period (compared to 5 years before),[16] so that CT screening cost may already been compensated by 80% 10 years after the introduction of screening due to savings in therapies. Screening cost could probably in the future be reduced substantially if longer intervals appear to be safe. Several studies have now shown lung cancer screening to be cost-effective.[17] The 4-IN-THE-LUNG-RUN trial, together with SUMMIT, is intended to show amongst 20,000 baseline screenees with a negative screen whether a 2-year interval is safe enough ('non-inferior'). Resources should remain limited by strongly limiting follow-up for incidental findings and can remain more limited by using AI in reading.[18]

Con

Feasibility and Resources

LC screening with LDCT has some well-known limitations such as the false-positives rate, overdiagnosis or high exposure to ionizing radiation from screening itself or check on positives.[18] Apart from them and even assuming that these limitations can be reduced to a minimum, there is the highly relevant issue of including this screening in the healthcare portfolio while making it compatible with current clinical practice in a context of limited resources. European countries provide universal healthcare coverage, much different from the US healthcare organization. Complicating this picture is the fact of a population growing older and demanding more services. Screening in Europe would be incorporated considering that CT machines have to be used for many different purposes, and that the availability of trained personnel (i.e. skilled radiologists) is limited. It has been estimated that, in Spain, 162 exclusively dedicated CT scans, working in double shift, would be needed for LC screening. This equipment should be accompanied with staff such as radiologists and technicians, all combined a quite expensive implementation.[19] Furthermore, while for breast, colorectal or cervical cancer screenings, the presence or absence of disease can be confirmed or ruled out within a relatively short timeframe,[20] this is not the case for LC screening, where positives need radiological follow-up to confirm or disregard diseases, in some cases needing periodical scans. A recent simulation study (Galicia, Spain, 2.7 million inhabitants) on the number of potential candidates for screening has shown that a range of 15 to 3 CT scanners fully dedicated to screening (all year, double shift) to attend candidates depending on how strict the inclusion criteria for screening are needed to attend a first screening.[21] This situation would change with annual screening rounds. The most frequent results of LC screening are: (1) no significant alteration, (2) finding of one or more subcentimetric nodules and eventually high suspicion of lung cancer, or (3) other findings not related with lung cancer, which include coronary artery calcifications, emphysema, bronchiectasis, COPD, or suprarenal alterations, among other findings.[22] Subcentimetric nodules require more CT tests (Lung Rads 2 or 3), and this is also the case for other findings. This increases the demand of CT equipment and staff, not only related to the image generation and interpretation, but also for other clinical specialties such as pneumology or cardiology. This has to be concealed with, i.e. cancer patients on active treatment or follow-up of survivors, needing CT control on a regular basis and in a growing number. A further aspect which complicates this landscape even more is that the EU population is older than that of the US or other countries and, per se, there is a higher need of imaging tests. So, the key questions here, are healthcare services providing universal healthcare prepared to assume LDCT LC screening without compromising the quality of care of their citizens? Do they have enough skilled personnel for such workload? And, if so, will this result in the best value for money for a universal healthcare system which has other concurrent needs?

Expected Change on the Burden of Disease

If LC screening were to be introduced, we should expect a relevant improvement in LC burden, leading to a relevant downstaging. Nevertheless, a recent study (awarded by the Spanish Society of Epidemiology), has demonstrated that, using Spanish real-world data including more than 15,000 LC patients, and applying the new screening inclusion criteria recommended by the USPSTF in 2021, 30% and 52% of all LC cases would not be detected through LDCT screening in men and women, respectively. Never-smokers, long-term ex-smokers, light smokers and those younger than 50 years or older than 80 would not be detected.[23] Small cell lung cancer has to be added, since early detection has proven ineffective.[24] Should we introduce a screening program where more than 50% of LC in women are not going to be detected?

Cost-opportunity and Tobacco Cessation

European healthcare services usually provide universal healthcare for free, but health managers have to allocate each euro to maximize the best healthcare for citizens. In this case, LDCT screening for LC has been reported as cost-ineffective in recent reports.[25] Although there is high variability between different published cost-effectiveness models, it is clear that the best way to prevent lung cancer is not smoking and abandon smoking as soon as possible. This not only reduces the LC burden but also the risk of other 11 tumors, cardiovascular and respiratory diseases, since tobacco has been classified as the most relevant cause of preventable death in Europe. In fact, in the US, lung cancer prevention through tobacco control efforts accounted for 98% of the 3.45 million deaths averted, with the remainder attributed to advances in treatment in 1975–2000.[26] A LC screening program should effectively incorporate the so-called "teachable moment" in order that current smokers stop-smoking when they enter screening. The available results show disagreement and room for improvement regarding cessation rates following LC screening. Interventions should thus be focused on preventing people from starting to smoke and on stopping smoking. Cessation smoking programs are much more cost-effective than any LC screening program, which have a much lower cost per QALY compared to LC screening. Where should we invest money? On lung cancer screening or trying to reduce tobacco consumption in EU population which is still extremely high in some EU countries such Spain?

Conclusions

Well-designed randomized controlled trials have demonstrated that LDCT screening for LC may reduce LC and all-cause mortality substantially, but there is room for improvement on the use of LDCT in screening programs, allowing the screening to be more easily assumed by the healthcare systems. The Nelson trial demonstrated how a volumetric approach may reduce false positives, and the number of work-up procedures. AI techniques possibly have a role to avoid unnecessary radiologic workload, and there is a clear opportunity to further improve screening and referral selection using biomarkers (including imaging). There are preliminary data showing that probably not all individuals would need annual screening, but RCTs are needed to show the safety of such an approach.

We do see an important (governance) role for the organizations currently managing and evaluating other cancer screening programs to increase LDCT participation and avoid health inequalities to ensure quality and reduce unnecessary referrals and harms, and establish common performance indicators and ensure evaluation.

Possibly, some other subgroups at a higher risk of lung cancer - not based on smoking exposure (i.e. occupationally or indoor radon exposed)- may also benefit from screening, but we need to generate evidence on such conditions. On the other hand, recruited individuals might benefit from interventions other than for lung cancer, especially due to their increased (but undetected) cardiovascular risk, but evidence is still limited, and it is key to clearly differentiate undetermined findings from those threatening health to avoid unnecessary overload of the healthcare system.

We need to initially start including very high-risk individuals, possibly by using smoking duration only, and also gradually implement the program. This could reduce the risk of referring too many individuals with additional findings, ensure QA and reduce unnecessary work-up. In Spain, 4-ITLR and Cassandra are the first projects to implement LC screening. Other countries are following the EU Council Recommendations to start investigating the feasibility of implementation. If recruitment is successful, we have to balance achievable benefits versus capacity, not to mention surgical capacity. Expanding the criteria to lower risk groups also increases cost and cost-effectiveness extensively.

This is the first risk-based cancer screening program where primary and secondary prevention should combine forces. The risk cohort we would like to tackle can benefit from skilled smoking cessation efforts, from cardiovascular interventions and/or other lifestyle interventions. Smoking cessation should be essential in LC screening, and smoking cessation rates should be included as an essential indicator of every CT screening program.[27] Clear governance, IT (evaluation) systems, smoking cessation offers and a successful recruitment method for LDCT screening are essential for the future of reducing the LC burden in Europe.

Conflict of Interests

The authors state that they have no conflict of interests. Q2

References

1. National Lung Screening Trial Research TeamAberle 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. 2011;365(5):395–409.
2. 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. 2020;382(6):503–13.
3. European Commission. Europe's beating cancer plan; 2023.
4. Bonney A, Malouf R, Marchal C, Manners D, Fong KM, Marshall HM, et al. Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. Cochrane Database Syst Rev. 2022;8(8). CD013829.
5. Team EOA. Lung cancer screening in risk groups. Collaborative assessment; 2020.
6. de Koning HJ, van der Aalst CM, Oudkerk M. Lung-cancer screening and the NELSON trial. Reply. N Engl J Med. 2020;382(22):2165–6.
7. Kaaks R, Christodoulou E, Motsch E, Katzke V, Wielputz MO, Kauczor HU, et al. Lung function impairment in the German Lung Cancer Screening Intervention Study (LUSI): prevalence, symptoms, and associations with lung cancer risk, tumor histology and all-cause mortality. Transl Lung Cancer Res. 2022;11(9):1896–911.
8. de Nijs K, Ten Haaf K, van der Aalst C, de Koning HJ. Projected effectiveness of lung cancer screening and concurrent smoking cessation support in the Netherlands. EClinicalMedicine. 2024;71:102570.
9. de Koning HJ, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;160(5):311–20.
10. de Gelder R, Heijnsdijk EA, van Ravesteyn NT, Fracheboud J, Draisma G, de Koning HJ. Interpreting overdiagnosis estimates in population-based mammography screening. Epidemiol Rev. 2011;33(1):111–21.
11. van der Aalst CM, Ten Haaf K, de Koning HJ. Implementation of lung cancer screening: what are the main issues? Transl Lung Cancer Res. 2021;10(2):1050–63.
12. Baldwin DR. Socioeconomic position and delays in lung cancer diagnosis: should we target the more deprived? Thorax. 2017;72(5):393–5.
13. Baldwin D, O'Dowd E, Ten Haaf K. Targeted screening for lung cancer is here but who do we target and how? Thorax. 2020;75(8):617–8.

14. Lung Cancer Policy Network. Available from: https://www.lungcancerpolicynetwork.com/.
15. Sheridan BAI, Senore C, Dimitrova N, Basu P, De Koning H, Heijnsdijk E. Prioritising performance and outcome indicators for cancer screening programs quality assessment in the EU. Public Health. 2025 [in press].
16. de Nijs K, de Koning HJ, van der Aalst C, Ten Haaf K. Medical costs of lung cancer by stage, histology and first-line treatment modality in the Netherlands (2012–2021). Eur J Cancer. 2024;208:114231.
17. Grover H, King W, Bhattarai N, Moloney E, Sharp L, Fuller L. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. Lung Cancer. 2022;170:20–33.
18. Lancaster HL, Zheng S, Aleshina OO, Yu D, Yu Chernina V, Heuvelmans MA, et al. Outstanding negative prediction performance of solid pulmonary nodule volume AI for ultra-LDCT baseline lung cancer screening risk stratification. Lung Cancer. 2022;165:133–40.
19. Ruano-Ravina A, Provencio-Pulla M, Casan Clara P. Lung cancer screening with low-dose computerised tomography. Thoughts on its use in Spain. Med Clin (Barc). 2016;147(8):366–70.
20. Ruano-Ravina A, Perez-Rios M, Casan-Clara P, Provencio-Pulla M. Low-dose CT for lung cancer screening. Lancet Oncol. 2018;19(3):e131–2.
21. Candal-Pedreira C, Ruano-Ravina A, Santiago-Perez MI, Almazan Ortega R, Gomez-Amorin A, Duran-Parrondo C, et al. Estimate of the eligible population for lung cancer screening in Galicia: an analysis of potential scenarios. Arch Bronconeumol. 2025.
22. O'Dowd EL, Tietzova I, Bartlett E, et al. ERS/ESTS/ESTRO/ESR/ESTI/EFOMP statement on management of incidental findings from low dose CT screening for lung cancer. Eur Respir J. 2023;62:2300533.
23. Candal-Pedreira C, Ruano-Ravina A, Calvo de Juan V, Cobo M, Trigo JM, Carcereny E, et al. Addressing lung cancer screening eligibility in Spain using 2013 and 2021 US Preventive Service Task Force criteria: cross-sectional study. ERJ Open Res. 2023;9(6).
24. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and outcomes of small cell lung cancer detected by CT screening. Chest. 2018;154(6):1284–90.
25. García Pérez LCMP, Hernández Yumar A, Puñal Riobóo J, Paz Valiñas L, Toledo Chávarri A, et al. Evaluación del programa de cribado de cáncer de pulmón. Ministerio de Sanidad; 2023.
26. Goddard KAB, Feuer EJ, Mandelblatt JS, Meza R, Holford TR, Jeon J, et al. Estimation of cancer deaths averted from prevention, screening, and treatment efforts, 1975–2020. JAMA Oncol. 2024.
27. Candal-Pedreira C, Ruano-Ravina A, Provencio M, Fernandez-Villar A, Perez-Rios M. Lung cancer screening quality criteria: a population perspective. Chest. 2021;160(4):e329–31.

Alberto Ruano-Ravina [a,b,c,*], Harry J. de Koning [d,*]

[a] *Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain*
[b] *CIBER de Epidemiología y Salud Pública, CIBERESP, Spain*
[c] *Health Research Institute of Santiago de Compostela (Instituto de Investigación Sanitaria de Santiago de Compostela [IDIS]), Santiago de Compostela, Spain*
[d] *Department of Public Health, Erasmus MC – University Medical Center Rotterdam, 3015 CE Rotterdam, The Netherlands*

*Corresponding authors.
E-mail address: alberto.ruano@usc.es (A. Ruano-Ravina), h.dekoning@erasmusmc.nl (H.J. de Koning).