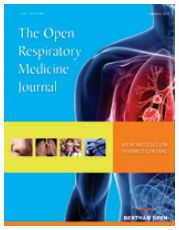

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REVIEW ARTICLE

The Journey for Lung Cancer Screening where we Stand Today

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Abstract:

Background:

Lung cancer remains a leading cause of cancer mortality worldwide with many patients presenting with advanced disease.

Objective:

We reviewed the available literature for lung cancer screening using low dose computed tomography (LDCT). We reviewed the National Lung Screening Trial (NLST), Early Lung Cancer Action Program (ELCAP) and the (Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trials. We also look at different lung cancer risk prediction models that may aid in identifying target populations and also discuss the cost-effectiveness of LDCT screening in different groups of smokers and ex-smokers. Lastly, we discuss recent guideline changes that have occurred in line with new and emerging evidence on lung cancer screening.

Conclusion:

LDCT has been shown reduce lung cancer mortality in certain groups of current and former smokers and should be considered to help in the early diagnosis of lung cancer.

Keywords: Lung cancer, Computed tomography, Screening, National lung screening trial (NLST), Evidence, Cancer.

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1. INTRODUCTION

Cancer is the second most common cause of death after cardiovascular disease and its incidence worldwide continues to increase. A recent epidemiological study revealed a 33% rise in cancer incidence between 2005 and 2015 [1]. Lung cancer remains the commonest form of cancer amongst men and carries a high mortality, accounting for approximately 1.3 million deaths per year and 28% of all cancer related deaths [2]. Late diagnosis is the foremost cause of poor outcomes in this group of patients and the data from Cancer Research UK suggest that over 70% of patients are diagnosed at stage III or IV of lung cancer [3]. Early diagnosis of lung cancer is linked with better survival and lower cost of care [4] leading to an increased emphasis globally to develop screening modalities for early detection. In this article, we look at the major studies that have been conducted for lung cancer screening as well as the recommendations of different societies based on this evidence. Almost all of these studies have looked at people who currently smoke or were heavy smokers.

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1.1. Background

Initial studies of lung cancer screening centered around use of chest X-ray(CXR) as a screening but failed to show reduction in mortality [5]. In the 1980s, The National Cancer Institute conducted a randomized trial, using sputum cytology and annual CXRs for the early detection of lung cancer but found no evidence to support the use of either modality [6]. The Prostate, Lung, Colorectal and Ovarian (PLCO) trial published in 2011 recruited and randomized more than 150,000 patients to either have CXR at baseline and then annually for 3 consecutive years versus standard care. Study participants were followed up for 13 years (or until December 31 2009 - the study end date) and as before, no mortality benefit was found using CXR for screening [7].

With the advent of CT scanning and its wider availability in the 90s, the use of low-dose computed tomography (LDCT) as a lung cancer screening tool was considered the logical next step by several research groups that assessed its use in this setting [8 - 11]. The most important early studies were performed by the Early Lung Cancer Action Program (ELCAP) [9, 10].

1.2. ELCAP

In this prospective study of 1000 current and ex-smokers, The ELCAP group recruited patients aged 60 and over with a minimum 10 pack-year smoking history. All study subjects had an LDCT and CXR at baseline and repeat screening was performed at 12 months. Results revealed non-calcified nodules (NCNs) in 233 (23.3%) participants with LDCT and only 68 (6.8%) with CXR. 27 and 7 cases of lung cancer were diagnosed with LDCT and CXR, respectively (2.7% *vs* 0.7% p = 0.0005). Moreover, in the LDCT group, 23 cancers (85%) were stage 1 as compared to only 4 cases (15%) in the CXR group. Based on these results, ELCAP investigators predicted a possible cure rate of 80% (a lung cancer fatality rate of 20%) for high-risk subjects who continued annual screening with LDCT.

The encouraging results from the ELCAP study lead to the formation of international early lung cancer action program (I-ELCAP) [12]. The I-ELCAP group screened 31,567 at-risk patients with LDCT between 1993- 2005, with a repeat scan 7-18 months later. There were 484 cancer diagnoses in the study, with 412 (85%) being stage I. The estimated 10-year survival in this group was 88% rising to 92% in the subgroup treated with surgical resection within a month of diagnosis.

I-ELCAP was the first study to show the effectiveness of lung cancer screening and also to reveal a possible "stage shift", with more curable lung cancers being detected through LDCT as opposed to usual care.

Following the success of I-ELCAP, a larger trial called "The National Lung Screening Trial" (NLST) was undertaken in the United States [13].

1.3. NLST

NLST was a large prospective randomized controlled trial conducted across 33 centres and recruited 53,454 subjects between 2002-2004.

The participants were aged 55-74 years with minimum 30 pack-year smoking history and were randomized to LDCT or CXR group. In total, the participants had 3 LDCTs, one at baseline and two further two in consecutive years. Subjects were considered "screen positive" if they had NCN >4mm, pleural effusion or lymphadenopathy. LDCT group had 24.9% participants screen positive as opposed to only 6.9% in the CXR group. The rate of cancer detection was calculated to be 645 per 100,000 person-years in the LDCT arm and 572 per 100,000 person-years in the CXR study arm, while cancer-related mortality was projected as 247 *vs* 309 per 100,000 person-years in LDCT and CXR group respectively. The results reveal a 20% cancer-related mortality reduction ($p<0.05$) using LDCT as a screening tool [13].

In conclusion, 320 patients needed to be screened over the study period to prevent one cancer-related death and an absolute reduction in cancer-related death from 1.66% to 1.33% was achieved through LDCT screening, meaning 3 fewer deaths per 1000 study participants in the LDCT group. The NLST was terminated early after the independent data and safety board determined that the primary endpoint of the study was already reached.

Subsequently, in 2013, the U.S Preventive Services task Force (USPSTF) recommended annual LDCT screening for adults aged 55-80 years with a minimum of 30 pack-years smoking history and ex-smokers with similar previous smoking history who had quit within the past 15 years. The task force recommended stopping screening for those who had not smoked for 15 years or had developed a health problem that limited their life expectancy. Screening could also be discontinued for the participants who were no longer willing or able to pursue curative surgery if diagnosed with early-stage cancer [14].

More recently, the results of "Netherlands-Leuven Longkanker Screening Network" (NELSON) trial with 15,822 participants have been published, confirming the utility of LDCT screening for the detection of early-stage lung cancer [15].

2. NELSON

The NELSON study that started in the year 2000 was another large randomized controlled trial that recruited 15,792 participants (13,195 men,2594 women) and was powered to demonstrate a $\geq$ 25% reduction in lung cancer mortality using LDCT in the at-risk population at 10-year follow up. The study subjects were current or ex-smokers (quit <10 years ago) and were randomized to undergo screening at baseline and years 1, 2 and 2.5 versus no screening. At randomization, the median smoking pack-year count was about 38 in each group.

Amongst men, 467 (2.1%) LDCTs were test-positive, leading to 203 screen-detected cancers, resulting in a positive predictive value of 43.5%. However, only 59% (203 of 344) of all lung cancers were detected through screening. Importantly, the screen-detected lung cancers were more likely to be stage IA or IB (58.6%), whereas in the control group, only 14.2% of cancers were at similar early stage. On the other hand, in the control group, about half the cancers were stage IV compared to only 9.4% in the LDCT group. Overall, the rate ratio of death from lung cancer at 11 years of follow-up among male participants was 0.78 (95% CI 0.63-0.95) when compared to controls. However, only about 50% of participants in the NELSON trial met the eligibility criteria of the NLST. Among the subgroup of men who would have been ineligible per NLST criteria (age 50-54 years), the rate ratio of death from lung cancer was not significantly lower than controls at 0.85 (95% CI 0.48 to 1.5).

An important difference between NLST and NELSON was that positive baseline screening was noted in 24% of NLST participants but only 2.1% of NELSON participants (positive predictive values 3.8% and 43.5%, respectively). This is most likely because the NLST trial sites included geographical areas known to be endemic for histoplasmosis, coccidioidomycosis and blastomycosis, all common causes for non-malignant lung nodules. This is an important consideration for policy-makers in implementing a national screening program as areas with a higher incidence of non-malignant lung diseases will probably have high false-positive rates on the screening LDCT.

In summary, the NELSON trial showed that among asymptomatic adult males, screening led to a 26% (0.09 to 0.41 95% CI) reduction in lung cancer deaths over 10 years of study

follow-up (86% compliance). In a smaller subset of female patients, the rate-ratio of dying from lung cancer varied between 0.39 and 0.61 in different years of follow-up. The study was not powered to show an all-cause mortality difference and none was found [16].

2.1. Lung Cancer Risk Stratification

The NLST survival advantage came at the cost of a large number of false-positive tests. Therefore, Kovalchik and colleagues [17] developed a prediction model for lung cancer deaths to help refine lung cancer screening. The risk factors included in their prediction model included age, body mass index, family history of lung cancer, pack-years of smoking, years since smoking cessation and emphysema diagnosis. Using these variables, they created 5 quintiles of patients according to their calculated risk of lung cancer. The 5-year risk of lung cancer was as noted to be 0.15 to 0.55% in quintile 1, 0.56 to 0.84% in quintile 2, 0.85 to 1.23% in quintile 3, 1.24 to 2.00% in quintile 4 and more than 2.00% in quintile 5. In this cohort, 60% of participants were stratified into the group with the highest lung cancer risk (quintile 3 through 5). These patients constituted 88% of the screening-prevented lung cancer deaths. On the other hand, 20% of patients were in the lowest risk group (quintile 1). These patients accounted for only 1% of prevented lung cancer deaths. The results encouraged other research groups to look at risk based stratification of patients for lung cancer screening using clinical and demographic variables. Tammemagi and colleagues [18] developed a validated model (PLCO $_{M2012}$) using data from the PLCO control and intervention groups of people with a smoking history. They compared the accuracy of their PLCO $_{M2012}$ criteria with those of the NLST criteria. The study variables included age, education level, body mass index (BMI), family history of lung cancer, chronic obstructive pulmonary disease (COPD), CXR in the previous 3 years, as well as patients' smoking status, history of smoking and quit date. They observed that when compared to NLST, PLCO $_{M2012}$ had greater sensitivity (83% *vs* 71% $p < 0.001$) and positive predictive value (4.0% *vs* 3.4% $p < 0.01$), without loss of specificity (62.9% *vs* 62.7% p=0.54). Also 41.3% fewer lung cancers were missed using PLCO $_{M2012}$.

Sanchez-Salcedo and colleagues [19] looked at NLST criteria in 2 different lung cancer screening studies from the United States and Europe and found that only 36% and 59% of participants in the two studies, respectively would have met NLST criteria. However, the use of NLST criteria alone to screen for malignancy missed 39% of lung cancers. They deduced that a simple way to increase the detection rate would be to annually screen those patients who either met NLST criteria or had "presence of emphysema". Doing so resulted in the detection of most lung cancers (95% in the United States cohort and 88% in the European cohort).

Other risk prediction models developed in recent years include the two stage clonal expansion (TSCE) model [20], the Liverpool Lung Project (LLP) model [21], the Knoke model [22], the Bach model [23], the Hoggart model [24] and the Spitz model [25, 26]. Please see Table **1** for an overview of these different models.

Although the predictive models contain several discrepancies in terms of their performance, the PLCO$_{M2012,}$ Bach and TSCE models have been shown to be more sensitive than NLST criteria in predicting 6 year lung cancer incidence in the chest X ray arm [27]. Moreover, Tamemagi's PLCO$_{M2012}$ model has been shown to have greater sensitivity, better positive predictive value and cost-effectiveness for detecting lung cancer compared to NLST criteria [18].

Although the LLP model was used prospectively in the UK lung screen trail [28], it is important to note that at this time, evidence of superiority of most risk models comes mainly from retrospective or micro-simulation modelling analyses. Hence, more data from prospective studies are needed before the risk models can be used in LDCT screening programs.

Table 1. Lung Cancer Risk Prediction Models

	Models						
Model Name	**Bach [23]**	**TSCE* CPS* [20]**	**LLP [21]**	**Spitz [24, 25]**	**Knoke [22]**	**Hoggart [24]**	**PLCOm2012 [18]**
Database	Carotene and Retinol Efficacy Trial (CARET)	Two ACS* Cohorts & British Doctors Cohort	Liverpool Lung Project (LLP)-case control	MD Anderson Database	ACS first cancer prevention study (CPS-1)	European Prospective Investigation into Cancer and nutrition (EPIC)	Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO)
Sample Size	18,172	Multiple Cohorts	4,055	3,852	174,993	169,035	115,185
Age of cohort in years	50-69 +45-69[*1]	Three different cohorts	50-75	20-80 (no age restriction)	40-80	40-65	55-74
Risk Factors							
Age	x	x	x	x	x	x	x
Gender	x	x	x	x	x		
Smoking characteristics	x	x	x	x	x	x	x
Race							x
Education							x

(Table 1) contd.....

Models							
Model Name	**Bach [23]**	**TSCE* CPS* [20]**	**LLP [21]**	**Spitz [24, 25]**	**Knoke [22]**	**Hoggart [24]**	**PLCOm2012 [18]**
BMI*							x
COPD/Emphysema			x	x			x
H/O Cancer			x				X
F/H of Cancer			x	x			X
H/O Pneumonia			x				
Asbestos Exposure	x		x				
Dust Exposure				x			

* TCSE = Two-Stage Clonal Expansion; CPS = Cancer prevention Study; ACS = American Cancer Society; BMI= Body mass Index

*1 = CARET had two cohorts of different ages.

X = Parameter was used in risk calculation score

2.2. Lung Cancer Screening among Never or Light Smokers

Both NLST and NELSON trials focused exclusively on current or former heavy smokers only. However, a significant number of patients developing lung cancer are light smokers or have never smoked. Pinsky *et al*. [29] applied NLST criteria for lung cancer screening to data from the Surveillance, Epidemiology and End Results (SERS), the 2010 census and the National Health Interview survey. They found that doing so only captured 27% of total lung cancers and the results highlight that almost three fourth of lung cancers would have been missed if the NLST criteria alone were used for screening. However, the investigators were able to capture 68% of all lung cancers when they broadened the age range (50-79 years) and changed smoking status to include participants who had smoked at any time irrespective of pack years.

Lung cancer in nonsmokers is more common in the Asian population and studies from Japan have suggested a higher proportion of lung cancer among women and also among light or never smokers when compared to western populations [30]. Currently a randomized control trial of non-/light smokers is being conducted in Japan [31]. Once the results of this trial are available more can be deduced about the efficacy of LDCT screening in non-Caucasian, non-smokers and light-smokers.

Presently, none of the guidelines recommend LDCT screening in light smokers, but LDCT may be considered on a case by case basis in patients who have emphysema and or a significant family history of lung cancer, recognizing that this is not standard practice.

2.3. Costs of LDCT Screening

One of the most important considerations to look at before LDCT can be implemented on a national level is the cost of the program. Data from the NLST (which was performed in the United States) estimated the screening cost effectiveness of LDCT to be $52,000 per quality adjusted life year (QALY) gained versus $81,000 for Chest X rays [32]. Other systemic reviews have also looked at the cost-effectiveness of LDCT programs and have come up with a wide range of potential costs, from $18,452 to $66,480 per life year gained [33, 34]. In developed countries, this cost may be considered acceptable, for example, in the United States, a test that is below the threshold of $100,000 is considered acceptable, considering the size of their economy and the resources they can allocate for healthcare. However, these same costs may be prohibitive in countries with substantially fewer resources. In order to determine if an intervention is cost-effective for a particular country, the World Health Organization (WHO) has suggested that any intervention that costs less than three times the national annual per capita gross domestic product (GDP) can be considered being cost effective [35].

The cost-effectiveness of any screening test such as LDCT will be impacted by a number of factors, including the prevalence of the disease in that country as well as the rate of false positive results. Hence an ideal solution would be for each country to develop its own specific lung cancer risk model that has been developed using LDCT screening in its particular population. Such an approach will allow healthcare planners to see if LDCT screening for lung cancer is cost effective in its respective population. This is particularly true for non-Caucasian populations, and for women since the majority of patients in both NLST and NELSON trials were Caucasian men.

2.4. New USPSTF Recommendations

Pinsky *et al*. [36] looked at the PLCO cohort (which included 18,114 ex and 12,243 active smokers) to assess lung cancer risk among smokers with a 20-29 pack year history of smoking. They noted that lung cancer risk for current smokers with a 20-29 pack year history was similar to that of former smokers with a greater than 30 pack year history of smoking. Additionally, reducing the screening threshold to 20 pack years would result in a greater proportion of women and minorities being screened. A fact that was confirmed by Aldrich and colleagues [37] who demonstrated that expanding the inclusion criteria for LDCT scanning to 20 pack years would considerably increase the screening sensitivity for African American individuals.

We mentioned earlier that the USPTF had in 2013 recommended LDCT screening for patients greater than 30 pack year history of smoking. However, based upon the findings mentioned above the USPTF investigators [38] performed a comparative simulation modelling study for individuals born from a 1950 and 1960 US birth cohort. Using this model they were able to compare a total of 288 risk factor based screening scenarios and compare them with reference screening or no screening. They placed special attention on consensus-efficient scenarios leading to a mortality reduction of at least 9%. When they looked at scenarios for 20 pack years

of smoking, mortality reductions of 12.1% to 14.4% were observed, as opposed to a mortality reduction of 9.8% if the 2013 USPTF recommended strategy had been used. They also looked at risk model-based strategies and observed that although they averted more lung cancer deaths than risk factor-based strategies, the difference in life-years gained was less pronounced.

In light of the above-mentioned evidence supporting LDCT screening in patients with 20-30 pack year history of smoking, the USPTF recently updated their guidelines in March 2021 [39]. They now recommend annual screening with LDCT for patients aged 50 to 80 years with a 20-pack year smoking history and who currently smoke or quit within the past 15 years. They observed that these new guidelines would not only allow for a greater lung cancer related mortality reduction but would also reduce disparities in eligibility by race/ethnicity and gender, by allowing for more women and African Americans to be screened at an earlier stage.

2.5. Harms and Challenges of LDCT

A major concern when performing LDCT is radiation exposure from the multiple rounds of screening scans that patients would receive in their lifetime. At the time of the NLST trial the cumulative radiation dose for three rounds of screening was calculated to be 4.5 mSv. However, further radiological tests to investigate worrisome findings were often performed, leading to an estimated radiation dose per patient of 8 mSv over three years. It has been postulated that this exposure would lead to one radiation induced malignancy per 2500 participants [40]. However, present day CT scanners are now able to perform LDCTs using ultra low dose of radiation (well below 1 mSv) [41]. Hence the risk of radiation induced cancers is considerably low these days.

Another problem in implementing a national lung cancer screening program would be the shortage of trained radiologists who can read LDCT scans [42]. This remains a problem in many countries and efforts are being made to overcome this. One initiative has been an LCS (lung cancer screening) certification program from the European Society of Thoracic imaging which is based on online learning and workshops followed by a final examination. However, it has become evident that moving forward, if LCS is to be adopted at a national level, artificial intelligence (AI) will have to be used to help deal with the sheer volume of scans that are generated. Validation studies are underway to determine the role of deep learning AI software in LCS programs, either as a second, concurrent or first reader [42].

Overdiagnosis has also been another concern for implementation of LCS programs. The overdiagnosis rate in the NLST trial was estimated at 18.5% for screen detected lung cancers, but approximately 80% for screen detected lepidic adenocarcinoma [43]. In contrast, the NELSON trial calculated an overdiagnosis rate of 19.7%, which dropped to 8.9% when extending their follow up to 11 years [16]. The ERS statement paper recommends the following potential strategies to reduce overdiagnosis; 1) development of risk models for multidimensional stratification of patients and nodules; 2) a more conservative approach when managing sub-solid nodules; 3) quantification of the volume doubling time; and 4) longer interval of screening. Adoption of such strategies would also mean fewer LDCTs and eventually a reduction of false-positive findings undergoing referral, thus reducing overtreatment [42].

Lastly the psychosocial consequences of false positives and overdiagnosis need to be considered. At this point this remains an area where further research is needed, however because of this possibility in most screening programs a "shared decision-making model" has been implemented where the patient is informed about the potential false positives rates and adverse effects prior to enrollment in the program.

CONCLUSION

In summary, the NLST and NELSON trials have clearly demonstrated that LDCT scanning resulted in a reduction in Lung cancer mortality in a select group of smokers and ex-smokers. At the moment, a few countries have developed national guidelines and some societies have published their own guidelines based on available evidence. For physicians who are working in countries where national guidelines do not exist, we would recommend using a lung cancer risk calculator (our preference would be the $PLCO_{M2012}$ model. This can be calculated online through the website www.shouldIscreen.com). Once a patient's risk has been calculated, shared decision making should be done based on the patient's risks and desires. If a decision is made to continue with screening, then we would recommend annual LDCT scans.

LIST OF ABBREVIATIONS

LDCT	=	Low Dose Computed Tomography
NLST	=	National Lung Screening Trial
ELCAP	=	Early Lung Cancer Action Program
NELSON	=	Nederlands–Leuvens Longkanker Screenings Onderzoek

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

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REFERENCES

[1] Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017; 3(4): 524-48. [http://dx.doi.org/10.1001/jamaoncol.2016.5688] [PMID: 27918777]

[2] Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.

[http://dx.doi.org/10.1002/ijc.29210] [PMID: 25220842]

[3] Lung cancer incidence statistics. Cancer Research UK. 2015. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence

[4] Sheehan DF, Criss SD, Chen Y, *et al.* Lung cancer costs by treatment strategy and phase of care among patients enrolled in Medicare. Cancer Med 2019; 8(1): 94-103. [http://dx.doi.org/10.1002/cam4.1896] [PMID: 30575329]

[5] Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. Am J Respir Crit Care Med 2015; 191(1): 19-33. [http://dx.doi.org/10.1164/rccm.201410-1777CI] [PMID: 25369325]

[6] Berlin NI, Buncher CR, Fontana RS, Frost JK, Melamed MR. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: Introduction. Am Rev Respir Dis 1984; 130(4): 545-9. [PMID: 6548343]

[7] Oken MM, Hocking WG, Kvale PA, *et al.* Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011; 306(17): 1865-73. [http://dx.doi.org/10.1001/jama.2011.1591] [PMID: 22031728]

[8] Swensen SJ, Jett JR, Hartman TE, *et al.* CT screening for lung cancer: five-year prospective experience. Radiology 2005; 235(1): 259-65. [http://dx.doi.org/10.1148/radiol.2351041662] [PMID: 15695622]

[9] Henschke CI, McCauley DI, Yankelevitz DF, *et al.* Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354(9173): 99-105. [http://dx.doi.org/10.1016/S0140-6736(99)06093-6] [PMID: 10408484]

[10] Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, *et al.* Early lung cancer action project: initial findings on repeat screenings. Cancer 2001; 01;92(1): 153-9. [http://dx.doi.org/10.1002/1097-0142(20010701)92:1<153::AID-CNCR1303>3.0.CO;2-S]

[11] Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. N Engl J Med 2005; 352(26): 2714-20. [http://dx.doi.org/10.1056/NEJMcp042630] [PMID: 15987920]

[12] Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006; 355(17): 1763-71. [http://dx.doi.org/10.1056/NEJMoa060476] [PMID: 17065637]

[13] Aberle DR, Adams AM, Berg CD, *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365(5): 395-409. [http://dx.doi.org/10.1056/NEJMoa1102873] [PMID: 21714641]

[14] Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160(5): 330-338. [http://dx.doi.org/10.7326/M13-2771] [PMID: 24378917]

[15] van Iersel CA, de Koning HJ, Draisma G, *et al.* Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007; 120(4): 868-74. [http://dx.doi.org/10.1002/ijc.22134] [PMID: 17131307]

[16] de Koning HJ, van der Aalst CM, de Jong PA, *et al.* Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020; 06;382(6): 503-13.

[17] Kovalchik SA, Tammemagi M, Berg CD, *et al.* Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013; 369(3): 245-54. [http://dx.doi.org/10.1056/NEJMoa1301851] [PMID: 23863051]

[18] Tammemägi MC, Katki HA, Hocking WG, *et al.* Selection criteria for lung-cancer screening. N Engl J Med 2013; 368(8): 728-36. [http://dx.doi.org/10.1056/NEJMoa1211776] [PMID: 23425165]

[19] Sanchez-Salcedo P, Wilson DO, de-Torres JP, *et al.* Improving selection criteria for lung cancer screening. The potential role of emphysema. Am J Respir Crit Care Med 2015; 191(8): 924-31. [http://dx.doi.org/10.1164/rccm.201410-1848OC] [PMID: 25668622]

[20] Hazelton WD, Clements MS, Moolgavkar SH. Multistage carcinogenesis and lung cancer mortality in three cohorts. Cancer Epidemiol Biomarkers Prev 2005; 14(5): 1171-81. [http://dx.doi.org/10.1158/1055-9965.EPI-04-0756] [PMID: 15894668]

[21] Raji OY, Duffy SW, Agbaje OF, *et al.* Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med 2012; 157(4): 242-50. [http://dx.doi.org/10.7326/0003-4819-157-4-201208210-00004] [PMID: 22910935]

[22] Knoke JD, Burns DM, Thun MJ. The change in excess risk of lung cancer attributable to smoking following smoking cessation: an examination of different analytic approaches using CPS-I data. Cancer Causes Control 2008; 19(2): 207-19. [http://dx.doi.org/10.1007/s10552-007-9086-5] [PMID: 17992575]

[23] Bach PB, Kattan MW, Thornquist MD, *et al.* Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003; 95(6): 470-8. [http://dx.doi.org/10.1093/jnci/95.6.470] [PMID: 12644540]

[24] Hoggart C, Brennan P, Tjonneland A, *et al.* A risk model for lung cancer incidence. Cancer Prev Res (Phila) 2012; 5(6): 834-46. [http://dx.doi.org/10.1158/1940-6207.CAPR-11-0237] [PMID: 22496387]

[25] Spitz MR, Hong WK, Amos CI, *et al.* A risk model for prediction of lung cancer. J Natl Cancer Inst 2007; 99(9): 715-26. [http://dx.doi.org/10.1093/jnci/djk153] [PMID: 17470739]

[26] Spitz MR, Etzel CJ, Dong Q, *et al.* An expanded risk prediction model for lung cancer. Cancer Prev Res (Phila) 2008; 1(4): 250-4. [http://dx.doi.org/10.1158/1940-6207.CAPR-08-0060] [PMID: 19138968]

[27] ten Haaf K, Jeon J, Tammemägi MC, *et al.* Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 2017; 14(4): e1002277. [http://dx.doi.org/10.1371/journal.pmed.1002277] [PMID: 28376113]

[28] Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011; 66(4): 308-13. [http://dx.doi.org/10.1136/thx.2010.152066] [PMID: 21317179]

[29] Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen 2012; 19(3): 154-6. [http://dx.doi.org/10.1258/jms.2012.012010] [PMID: 23060474]

[30] Sagawa M, Sugawara T, Ishibashi N, Koyanagi A, Kondo T, Tabata T. Efficacy of low-dose computed tomography screening for lung cancer: the current state of evidence of mortality reduction. Surg Today 2017; 47(7): 783-8. [http://dx.doi.org/10.1007/s00595-016-1438-x] [PMID: 27815717]

[31] Sagawa M, Nakayama T, Tanaka M, Sakuma T, Sobue T. A randomized controlled trial on the efficacy of thoracic CT screening for lung cancer in non-smokers and smokers of <30 pack-years aged 50-64 years (JECS study): research design. Jpn J Clin Oncol 2012; 42(12): 1219-21. [http://dx.doi.org/10.1093/jjco/hys157] [PMID: 23042771]

[32] Black WC, Gareen IF, Soneji SS, *et al.* Cost-effectiveness of ct screening in the national lung screening trial. N Engl J Med 2014; 371(19): 1793-802. [http://dx.doi.org/10.1056/NEJMoa1312547] [PMID: 25372087]

[33] Raymakers AJN, Mayo J, Lam S, FitzGerald JM, Whitehurst DGT, Lynd LD. Cost-effectiveness analyses of lung cancer screening strategies using low-dose computed tomography: A Systematic Review. Appl Health Econ Health Policy 2016; 14(4): 409-18. [http://dx.doi.org/10.1007/s40258-016-0226-5] [PMID: 26873091]

[34] Puggina A, Broumas A, Ricciardi W, Boccia S. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: A systematic literature review. Eur J Public Health 2016; 26(1): 168-75. [http://dx.doi.org/10.1093/eurpub/ckv158] [PMID: 26370440]

[35] van der Aalst CM, ten Haaf K, de Koning HJ. Lung cancer screening: Latest developments and unanswered questions. Lancet Respir Med 2016; 4(9): 749-61. [http://dx.doi.org/10.1016/S2213-2600(16)30200-4] [PMID: 27599248]

[36] Pinsky PF, Kramer BS. Lung cancer risk and demographic characteristics of current 20–29 pack-year smokers: Implications for screening. JNCIJ 2015; 107(11): djv226.

[37] Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. Evaluation of USPSTF Lung Cancer Screening Guidelines Among African American Adult Smokers. JAMA Oncol 2019; 5(9): 1318-24. [http://dx.doi.org/10.1001/jamaoncol.2019.1402] [PMID: 31246249]

[38] Meza R, Jeon J, Toumazis I, ten Haaf K, Cao P, Bastani M, *et al.* Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: a collaborative modeling study for the u.s. preventive services task force. Rockville (MD): Agency for Healthcare Research and Quality 2021. Available from:

http://www.ncbi.nlm.nih.gov/books/NBK568586/

[39] Krist AH, Davidson KW, Mangione CM, *et al.* Screening for Lung Cancer. JAMA 2021; 325(10): 962-70. [http://dx.doi.org/10.1001/jama.2021.1117] [PMID: 33687470]

[40] Bach PB, Mirkin JN, Oliver TK, *et al.* Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012; 307(22): 2418-29. [http://dx.doi.org/10.1001/jama.2012.5521] [PMID: 22610500]

[41] Huber A, Landau J, Ebner L, *et al.* Performance of ultralow-dose CT with iterative reconstruction in lung cancer screening: limiting radiation exposure to the equivalent of conventional chest X-ray imaging. Eur Radiol 2016; 26(10): 3643-52. [http://dx.doi.org/10.1007/s00330-015-4192-3] [PMID: 26813670]

[42] Kauczor HU, Baird AM, Blum TG, *et al.* ESR/ERS statement paper on lung cancer screening. Eur Respir J 2020; 55(2): 1900506. [http://dx.doi.org/10.1183/13993003.00506-2019] [PMID: 32051182]

[43] Patz EF Jr, Pinsky P, Gatsonis C, *et al.* Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014; 174(2): 269-74. [http://dx.doi.org/10.1001/jamainternmed.2013.12738] [PMID: 24322569]