

## Lung cancer screening, what has changed after the latest evidence?

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**Author contributions:** Trujillo-Reyes JC was involved in the study conceptualization, investigation, data visualization and writing of the original draft; Seijo L performed formal analysis, review and editing of the manuscript; Martínez-Tellez E was involved in the investigation, data visualization and review and editing of the manuscript; Couñago F participated in the investigation, data validation and writing, review and editing of the manuscript; All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** Dr. Seijo reports personal fees from Sabartech, personal fees from Esteve, personal fees from Chiesi, personal fees from Astra Zeneca, grants from Menarini, and speaking fees from Roche, outside the submitted work. Rest of authors declare no conflict of interests for this article.

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### Abstract

Lung cancer (LC) is still one of the most frequent cancers with a high related mortality. Their prognosis is directly proportional to the stage at the time of diagnosis. Seventy percent are currently diagnosed in advanced or locally advanced stage (higher than stage III), making a cure unlikely for the majority of patients. Developments in LC treatment are significant however they do not seem to be enough to reverse the current situation, at least, in a short period of time. Despite recent advances in treatment, primary prevention and early diagnosis appear to be the key to reduce the incidence and mortality of this disease. Many countries have developed LC screening programs based on the results of clinical trials published in recent years. The aim of this paper is to review the latest results of the NEDerlands Leuvens Longkanker Screenings Onderzoek and compare them with the findings of the National Lung Screening Trial. We address the question whether it is necessary to continue discussing the evidence regarding LC screening. In both trials, there is a clear impact on LC mortality but, with a modest reduction in over all mortality. Undoubtedly, the benefit of screening can be expected to grow as low-dose computed tomographs are performed over longer periods of time.

**Key words:** Lung cancer; Epidemiology; Lung cancer screening; Low dose chest computed tomography scan; Primary prevention; Molecular biomarkers

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**Manuscript source:** Invited manuscript

**Received:** March 30, 2020

**Peer-review started:** March 30, 2020

**First decision:** April 26, 2020

**Revised:** June 11, 2020

**Accepted:** July 1, 2020

**Article in press:** July 1, 2020

**Published online:** July 28, 2020

**P-Reviewer:** Neninger E, Sung WW, Zhou C

**S-Editor:** Liu M

**L-Editor:** A

**E-Editor:** Liu JH



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**Core tip:** In recent years, many publications have focused on primary prevention and Lung cancer (LC) screening. Currently, most scientific societies recommend some form of LC screening. However, implementation around the world has been slow, at least in part because of a continued controversy regarding some aspects of LC screening. The aim of this article is to analyze the recently published results of the NEderlands Leuvens Longkanker Screenings Onderzoek study and compare them to those of the American National Lung Screening Trial (NLST). There is a clear impact on LC mortality in both trials, but only the NLST revealed a reduction in overall mortality (7%).

**Citation:** Trujillo-Reyes JC, Seijo L, Martínez-Tellez E, Couñago F. Lung cancer screening, what has changed after the latest evidence? *World J Radiol* 2020; 12(7): 130-136

**URL:** <https://www.wjgnet.com/1949-8470/full/v12/i7/130.htm>

**DOI:** <https://dx.doi.org/10.4329/wjr.v12.i7.130>

## INTRODUCTION

Lung cancer (LC) is the most lethal of all cancers. It is the leading cause of death from cancer worldwide and, year after year, the number of new LC cases grows<sup>[1]</sup>.

One of the most important prognostic factors is the stage at the time of diagnosis. Most patients are asymptomatic until they develop an advanced stage making an early diagnosis challenging<sup>[2]</sup>.

Despite important advance in oncological treatments, the prevalence and persistently elevated mortality associated with lung cancer demand a paradigm shift. Primary prevention initiatives must continue, but for many current and former smokers early recognition of pulmonary nodules must be pursued. Many countries have developed laws related to primary prevention that have proven insufficient to stem the tide of lung cancer. The combination of primary prevention and LC screening could help us fight the disease before it is too late.

LC screening has become a reality in the United States following completion of the National Lung Screening Trial (NLST)<sup>[3]</sup>. The cultural gap existing between the United States and Europe and the difference between both health systems created some skepticism in the European community regarding the potential benefit of lung cancer screening programs in our continent. Results of the NEderlands Leuvens Longkanker Screenings Onderzoek (NELSON)<sup>[4]</sup> study may assuage those concerns and provide a much needed impulse for efforts regarding the implementation of LC screening in Europe. Both trials investigated the role of low dose CT as the screening tool of choice<sup>[5-8]</sup>.

## LUNG CANCER EPIDEMIOLOGY

The figures show how the global number of LC cases is increasing demonstrating that LC is the leading cause of cancer-related mortality worldwide. In 2015<sup>[9]</sup>, approximately 1.6 million new LC cases were diagnosed worldwide and, according to the World Health Organization, more than 2 million new cases were diagnosed in 2019 alone, and LC was responsible for the cancer 1.76 million deaths.

That notwithstanding, LC death rates declined 48% from 1990 to 2016 among men and 23% from 2002 to 2016 among women. The American Association for Cancer Research published in 2018 that lung cancer mortality rates among women are projected to increase by about 43 percent between 2015 to 2030.

This high mortality is related to the fact that 70% of cases are diagnosed in an advanced stage (stage III or IV disease)<sup>[10]</sup> being the 5 year-survival a 16% for stage III and 4% for stage IV<sup>[11]</sup>.

### Risk factors

Smoking continues being as the major etiological factor<sup>[11]</sup>, although occupational exposure to carcinogens such asbestos and radon<sup>[12,13]</sup>, family history of LC<sup>[14]</sup>, genetic predisposition and other concomitant diseases may also play a role.

**Tobacco use:** It is the major etiological factor. We can prevent almost 200 million people from dying before 2050 halving tobacco consumption<sup>[11]</sup>, but smoking in many countries continues to increase. In Spain, for example, the number of smokers is the same in 2017 as in 1997 despite implementation of two anti-smoking laws is even greater among the youth. Unfortunately, it is not an isolated example. It is crucial to prevent smoking in adolescence because, the patients who started smoking within this age group, have four or five-fold increased risk of developing a LC<sup>[15]</sup>. It is well known that passive smokers have a higher risk for LC when compared to nonsmokers. However, the association is too weak to be considered in a LC screening program<sup>[16]</sup>.

**Occupational exposure:** The association between LC and approximately 150 carcinogens is well known being asbestos, crystalline silica or radon<sup>[17]</sup> a few examples. It is important to note that the combination of smoking and to be exposed to these carcinogens further increases the risk of developing LC. Air pollution may also play an important role in the development of LC in urban populations.

**Pre-existing lung illnesses:** (1) Chronic obstructive pulmonary disease (COPD), Emphysema, Bronchitis: COPD and emphysema are associated with an increased LC risk<sup>[18-20]</sup>. This association may be caused by tobacco-use, however, this association is evidence in never-smokers too<sup>[21,22]</sup>; and (2) Idiopathic pulmonary fibrosis: patients who develop interstitial fibrosis also have a higher risk to develop a LC<sup>[23,24]</sup>.

**Genetic predisposition:** A systematic review of the literature performed by Matakidou *et al*<sup>[25]</sup> showed an increased risk of LC in patients with a first-degree relative with LC. A genetic locus that may be associated with a greatest risk of developing LC has been described<sup>[26]</sup>.

Identifying the presence of these risk factors could be crucial to define the population at risk and inform LC screening inclusion criteria.

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## LUNG CANCER SCREENING

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The main objective of LC screening is to detect the greatest number of people in early stage when symptoms have not yet appeared and treatment with curative intent may be possible<sup>[16]</sup>. It is important to consider that a LC screening program must take into account quality of life and life expectancy. Key elements of a successful screening program are defined in [Table 1](#).

In lung cancer screening, several questions must be addressed before implementation, but these are not easy questions to answer: What population should be screened? Is it safe and economically viable? What is the age of the population to be screened? What is the periodicity of the screening? What is the best screening tool?

In recent years several publications have attempted to address at least some of these concerns, and to provide the needed evidence to demonstrate the feasibility and efficacy of a LC screening program. Most of them used low-dose computed tomography (LDCT) as the main screening tool, however, only two randomized trials have been published using the LDCT test, NLST and recently published, NELSON trial.

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## NLST AND NELSON STUDIES

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### ***NLST, the North American evidence***

The NLST was the first large prospective randomized trial investigating the benefit of LC screening. The aim of the NLST was to determine whether screening with LDCT could reduce mortality form LC and more than 50000 individuals at risk for LC were randomized to undergo three rounds of screening with LDCT or chest radiography. Inclusion criteria were restrictive including patients between 55 and 74 years old with a high smoking habit ( $\geq 30$  pack/year).

The results of the NLST showed a reduction of more than 20% in LC mortality and 40% of LC detected were in early stage of the disease. False positive results were common demonstrating a Positive Predictive Value lower than 4% for LDCT. Part of the success was the high adherence from the study participants<sup>[3]</sup>.

Overdiagnosis was a major source of controversy surrounding the NLST, although a recent publication with long term follow up suggests that true overdiagnosis is approximately 3%.

**Table 1** Quality criteria of a screening program

Quality criteria of a screening program <sup>[6]</sup>	
False-positive	Should be low
Cost	Inexpensive
True negative	Should not be hurt
Screening test should	Improve outcome; Be scientifically validated; Be low risk; Be reproducible; Be accessible; Be cost effective

### **NELSON, the European evidence**

The NELSON trial is the largest randomized trial of LC screening, which the European health systems needed to adapt to our idiosyncrasies and population. Although, the sample size was smaller (less than 16000 participants) than the NLST's, the results confirm the reduction in lung cancer mortality<sup>[4]</sup>. Inclusion criteria and intervals were flexible reducing the rate of false positives (positive predictive value 43.5%).

The impact of both trials highlights the reduction in LC mortality with no differences in overall survival compared to the control group. **Table 2** shows details of both trials.

### **HOW TO IMPROVE LC SCREENING?**

We are aware that LDCT screening requires compromises, and no screening program is ideal. Improvement in selection criteria and nodule management may come from molecular biomarkers<sup>[27]</sup> and multiple potential candidates have been identified and studied in the context of LC screening<sup>[28,29]</sup>. Autoantibodies, complement fragments, miRNAs, circulating tumour DNA, DNA methylation, blood protein profiling, or RNA airway or nasal signatures are all promising molecular candidates. Seijo *et al*<sup>[31]</sup> defined the two clinical needs of biomarkers; the selection of individuals undergoing screening and the characterization of indeterminate nodules<sup>[27]</sup>.

The strategy has to be focused on the addition of molecular biomarkers to current screening practices.

### **CONCLUSION**

LC remains a health crisis worldwide with an increasing financial impact<sup>[30]</sup>. It is now apparent that a combination of primary prevention and LC screening may be the key to reducing the incidence of this disease and its attendant mortality. The NLST<sup>[3]</sup> has paved the way for LC screening in the United States, where it is now standard of care for those meeting the study's inclusion criteria. In Europe, a lack of evidence has been alluded to in order to delay implementation of screening. However, results of the NELSON study are now available and published confirming the benefit of LC screening for individuals at risk<sup>[4]</sup>.

In our opinion, both the NELSON and the NLST have provided sufficient scientific evidence to warrant widespread screening. Of course, both randomized trials can be criticized and we can continue discussing advantages and disadvantages of LC screening but, in our opinion, they confirm that LC screening is feasible and has a clear benefit on the population.

There is a clear impact on LC mortality but, in both trials, with a modest reduction in over all mortality. Undoubtedly, the benefit of screening can be expected to grow as LDCTs are performed over longer periods of time<sup>[31]</sup>.

LDCT is currently the test of choice. Addition of molecular biomarkers may offer a more selective approach in the future.

Table 2 Comparison between nlst and nelson

	NLST	NELSON
Age	55-74	50-74
Smoking habit	≥ 30 pack/year; ≥ 15 years since quitting	≥ 15 pack/year; ≥ 10 years since quitting
CT scan	Diameter-based	Volume-based
Sample size	53454	15822
Number of rounds	3	4
Intervals	1 yr intervals	0, 1, 2 and 2.5 yr
Adherence	95% LDCT group	87.6%
Number of cancers	1060 (645/100000 person/year)	5.58/1000 person/year
% early stage cancers	40% stage IA	50% stage IA
Positive test	24%	2.1%
PPV	3.8%	43.5%
Reduction in lung cancer mortality	20%	Higher than 20%
Population	North America	Europe

NLST: National Lung Screening Trial; NELSON: Nederlands Leuvens Longkanker Screenings Onderzoek; CT: Computed tomography; LDCT: Low-dose computed tomography; PPV: Positive predictive value.

## ACKNOWLEDGEMENTS

We would like to express our gratitude to Jose Antonio Trujillo-Reyes for his contribution and to the rest of Thoracic Surgery, Radiotherapy and Pulmonology for allowing us to continue enjoying with our job.

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