Lung Cancer Screening
The European Perspective

Giulia Veronesi, MD

KEYWORDS

• Lung cancer • Early-stage lung cancer • Computed tomography • Diagnostic algorithm • Survival

KEY POINTS

- European studies have contributed significantly to understanding of lung cancer screening.
- Smoking within screening, quality of life, nodule management, minimally invasive treatments, cancer prevention programs, and risk models have been extensively investigated by European groups.
- Mortality data from European screening studies have not been encouraging so far, but long-term results of the NELSON study (The Dutch-Belgian Randomized Lung Cancer Screening Trial [Dutch acronym: NELSON study]) are eagerly awaited.
- Investigations on molecular markers of lung cancer are ongoing in Europe; preliminary results suggest they may become an important screening tool in the future.

INTRODUCTION: THE EXTENT OF THE PROBLEM

Lung cancer is a leading cause of death worldwide. Incidence continues to grow among women in developed countries and across the board in developing countries.[1] Single-arm and randomized studies on early lung cancer detection with low-dose computed tomography (LDCT) without contrast have shown that the technology is highly sensitive for detecting small lung nodules, with limited radiation exposure, acceptable costs, and short examination times.[2–5]

The large randomized National Lung Screening Trial (NLST), published in 2011, recruited 53,000 high-risk smoker volunteers over 55 years of age. It demonstrated a mortality reduction of 20% in the LDCT-screened group compared with the group screened by chest radiograph.[6] Previous nonrandomized studies had also estimated a mortality reduction of between 23% and 64% compared with historical control cohorts.[7,8] The National Cancer Comprehensive Network and US Preventive Services Task Force have recommended annual LDCT screening for lung cancer in high-risk individuals.[9,10]

The contributions of European investigators to lung cancer screening are mainly in the fields of primary prevention and chemoprevention associated with screening, risk assessment models, new algorithms for nodule management, and minimally invasive and conservative treatments for screening-detected nodules. European studies on molecular markers for the early detection of lung cancer are ongoing and have produced promising results.[11,12] Several European randomized studies were underpowered and failed to demonstrate that LDCT screening could reduce mortality, whereas the largest European randomized study—NELSON—has not yet released mortality data for the 2 study arms.

In Europe, approximately 269,000 deaths from lung cancer are expected in 2014 and it now seems clear that screening and early detection can contribute to reducing lung cancer mortality. Although antismoking campaigns are having an effect and must be continued, lung cancer screening has yet to be implemented on a large scale and remains a public health priority for Europe.[12]

PRIMARY PREVENTION AND CHEMOPREVENTION IN ASSOCIATION WITH SCREENING

Primary prevention remains a cornerstone of the fight against lung cancer. Cigarette smoking causes approximately 90% of lung cancers.[13]

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Lung Cancer Early Detection Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
E-mail address: giulia.veronesi@ieo.it

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The health benefits of stopping smoking cessation are well documented and extend well beyond reducing the risk of developing lung cancer.[14] Stopping smoking proves difficult for most people, however, and cannot be achieved without determination and without help in the form of specific smoking cessation programs.

Those interested in participating in screening for lung cancer (usually heavy smokers) have, by their willingness to participate, expressed a desire for better health. They are, therefore, likely to be receptive to smoking cessation programs, which should be implemented alongside lung cancer screening, as also urged by screening guidelines.[15]

Several European studies have investigated smoking behavior in the context of screening. The effect of screening on smoking was investigated over 1 year in those recruited to the randomized Danish Lung Cancer Screening Trial (DLCST).[16] It was found that screening did not actually favor smoking cessation, emphasizing the need for an effective additional intervention to encourage cessation. A positive scan result was highly stressful, however, and did favor smoking cessation. Finally, the study found that screening did not facilitate continuation of smoking, as has been claimed by detractors of screening.

By contrast, the smoking abstinence investigation part of the NELSON randomized study[17] did not find that a positive scan result had a positive effect on stopping smoking; however, the investigators agreed that presentation of the test outcome represented an excellent opportunity for encouraging smoking cessation. One objective of the NELSON study was to assess whether a tailored self-help intervention was more effective than a standard brochure in getting long-term male smokers to stop smoking.[18] It was found that tailored smoking cessation information had no advantage over standard self-help information after 2 years of follow-up. Only a low percentage of participants, however, actually received the tailored advice. This is important information for future screening program start-ups.

Another approach to prevention is to use chemopreventive agents to block the progression of precancerous lesions and promote lung tissue repair by mechanisms, such as suppression of inflammation and growth, restoration of normal epithelial differentiation, and improving immune surveillance. All methods tested in phase III chemoprevention studies have so far proved ineffective.[19] Screening programs offer ideal populations for testing potential chemopreventive agents using new intermediate endpoints, such as disappearance/reduction of peripheral lung nodules.

To assess the effect of budesonide—a potentially chemopreventive glucocorticoid—on CT-detected nodules, the author's group performed a randomized double-blind phase IIb trial of inhaled budesonide versus inhaled placebo in current and former smokers with CT-detected target lung nodules (that had persisted for at least a year but did not require additional diagnostic ascertainment according to the COSMOS [Continuous Observation of SMOking Subjects] protocol).[20] A total of 202 individuals received inhaled budesonide, 800 mg twice daily, or placebo for 1 year. The primary endpoint was the effect of budesonide on target nodule size in a per-person analysis after 1 year. Although the per-person analysis did not show a significant difference between the 2 arms, the per-lesion analysis revealed that budesonide was significantly ($P = .02$) associated with the regression of nonsolid target nodules (**Fig. 1**). The results were confirmed after 5 years: mean nonsolid nodule diameter significantly reduced in those who had received budesonide for a year compared with controls. This study, nested in the COSMOS screening study, revealed a new endpoint: peripheral ground-glass opacities on LDCT, which are likely to be atypical adenomatous hyperplasias or adenocarcinomas in situ. These lesions will be targeted in a future study using low-dose oral aspirin. Long-term aspirin use has been associated with reduced lung cancer mortality in large meta-analyses.[21,22]

NODULE MANAGEMENT

The frequent finding of indeterminate noncalcified lung nodules remains a problem with LDCT screening for lung cancer. To reduce the number of useless investigations and consequent risk of morbidity in screened subjects, standardized algorithms for managing indeterminate lung nodules have been developed to achieve a balance between a too invasive approach and a too lax approach that risks diagnosing the cancer at a later stage. Only if lung cancer is diagnosed early does it have a reasonable chance of being cured. Single-arm studies report that approximately 80% of screening-detected cases are detected at stage I or II[23,24]—compared with 16% at this stage in historical data on unscreened individuals[25]—and the resection rate is approximately 80% to 90%. **Fig. 2** summarizes Surveillance, Epidemiology, and End Results (SEER [Statistics and Epidemiology End Results]) population-based data on the stage distribution of lung cancers at diagnosis. **Fig. 2** also shows population-based relative survival (according to SEER summary stage) for lung cancer patients.