

Computed tomographic screening for lung cancer

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International Early Lung Cancer Action Program Investigators; Henschke CI, Yankelevitz DF, Libby DM, Pastmantier 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.

Research question

Can annual spiral computed tomographic (CT) screening detect lung cancer that is curable?

Type of article and design

Multicentre case-series study

Relevance to family physicians

In 2006, 22700 Canadians were diagnosed with lung cancer, and 19300 died from this cancer.¹ It remains the most common cause of cancer death. Yet, lung cancer is one of the most treatable cancers if diagnosed early; therefore, detecting this cancer at an earlier point could greatly reduce the mortality of this devastating disease. Unfortunately, tools for screening lung cancer (chest radiology and sputum cytology) have been found to be less effective in reducing the mortality rate than a standard history and physical examination.²

In the early 1990s, low-dose computed tomography (LDCT) was introduced. Low-dose computed tomography produced high-quality images at dosage levels much lower than standard diagnostic CT; therefore, the potential of LDCT for screening purposes was raised. Though observational studies have investigated the effects of LDCT screening on lung cancer detection, mature results from rigorous trials on its effect on mortality are absent. This large collaborative study has offered health care providers, health insurers, and millions of high-risk patients the hope that many cancers could be detected before they become clinically evident and incurable.

Overview of study and outcomes

This study by the International Early Lung Cancer Action Program Investigators (I-ELCAP) assessed 31 657 men and women with risk factors for lung cancer between 1993 and 2005 in the United States, Europe, Israel, China, and Japan. "High-risk" patients were defined as asymptomatic, 40 years of age and older, any history of smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to second-hand smoke. In addition, 27 456 repeat screenings were performed at 7 to 18 months after the baseline assessment. Any new

nodule was considered a positive finding. A centralized protocol for review of images and pathology was established, including a 5-member pulmonary pathology review. In addition, a specific management algorithm was also provided. The median age was 61 years and the median number of pack-years was 30. The median tumour size was 13 mm at baseline and 9 mm at the annual repeat CT scan.

Results

Lung cancer was diagnosed in 484 patients; 405 were diagnosed at the baseline screening and 74 at the repeat screening. The authors estimated the 10-year survival rate for all the patients to be 80% (95% confidence interval [CI], 74%-85%). There were 412 (85%) stage I cancers discovered. This subgroup had an estimated 10-year survival of 88% (95% CI, 84%-91%). Of these 412 patients, 39 died of cancer; 375 underwent resection; 29 had radiation, chemotherapy, or both but no surgery; and 8 received no treatment. All 8 patients who had no treatment died within 5 years of diagnosis. For patients whose tumours were excised, the 10-year survival rate was 94%.

Analysis of methodology

This study highlights the rigour general practitioners must use to evaluate screening tools that are possibly costly or harmful to society and to patients. For example, the cost of LDCT is approximately \$400 and the operative mortality in a large cooperative study was 1%.³ This does not include the cost of further tests to address abnormalities found on screening, of recruitment and reminders to attend screening, and of the unnecessary referrals to specialists to identify and manage false-positive results.

A review of the literature finds little evidence from randomized trials that early intervention is effective in reducing mortality.⁴ Based on the *Journal of the American Medical Association* guidelines to evidence-based medicine,⁵ several methodological points should be addressed. Assessments using primary and secondary guides determine the validity of the study. The primary guide is used to assess whether there was an independent, blind comparison with a reference standard.

This study had no independent comparison group. It was a case series and, without a comparison group, the possibility of bias is introduced. Therefore, the study must address whether the sample included an appropriate spectrum of patients. This study included a relatively

heterogeneous sample, including 20% of patients recruited from a Japanese screening program. Of these patients, 50% had never smoked compared with 6% of patients accrued from the United States, Europe, Israel, and China. In addition, centres were allowed to specify their own criteria for enrolment. In other words, the definition of "high risk" might be difficult to apply to our own practices. Secondary guides include a description of the test procedures and equipment that permits replication. The authors have addressed this issue in detail in other publications,⁶ but the specific equipment used and technical performance was not described in this study. Protocols for diagnosis and workup were rigorous and explicit. In addition, central review, interpretation criteria, and quality-assurance procedures were put in place.

Application to clinical practice

Should and can a single non-randomized study change practice? About 6 of 10 people with lung cancer die within 1 year of finding out they have lung cancer.⁷ Yet the 5-year survival rate for cancer diagnosed early (stage I) is more than 70%. This study demonstrates an impressive sensitivity of 98% and specificity of 88%. These results are equal to, if not better than, commonly accepted screening tools. The sensitivity and specificity of the Papanicolaou test are 30% to 87% and 86% to 100%, respectively.^{8,9} Although there are no randomized controlled trials, there is good evidence from cohort studies that this test can reduce mortality from cervical cancer by up to 80%.⁹ Randomized controlled trials of mammography have consistently shown high sensitivity and specificity, with a meta-analysis¹⁰ reporting ranges of 83% to 95% and 94% to 99%, respectively.

The United States Preventive Services Task Force found fair evidence that screening with LDCT, chest x-ray, or sputum cytology can detect lung cancer at an earlier stage than lung cancer would be detected in an unscreened population.² This study by Henschke et al is one of the strongest to suggest that screening for lung cancer with LDCT decreases mortality. Regrettably, the tests and treatments that are inevitably ordered after a positive result are invasive and pose substantial risk. Without a comparison group, it is difficult to determine the balance between the benefits and harms of LDCT screening for lung cancer. The comparison group could allow health care providers to evaluate the efficacy of treatment for lesions detected by screening and the effect of finding these small lesions early. These lesions might have gone undetected in an unscreened control population and remained indolent for long periods. Furthermore, the possibility of a high number of false-positive results (as high as 90% in the baseline sample calculated by the authors of this review) raises concern that the balance might tip toward harm. The definition of a positive result was very inclusive (for example, any


BOTTOM LINE

- This study is a provocative non-randomized study that is consistent with observational data previously published, but demonstrates a probable survival benefit for screening with low-dose computed tomography.
- Lead-time bias, overdiagnosis, and cost-effectiveness issues are not resolved; therefore, this single study is not sufficient to recommend computed tomographic screening for lung cancer.
- Ongoing randomized trials addressing screening should be supported.

POINTS SAILLANTS

- Cette provocante étude non randomisée corrobore les données d'observation déjà publiées, mais démontre un bienfait probable d'un dépistage avec tomodensitométrie à faible dose au chapitre de la survie.
- Les questions reliées à la partialité afférente au délai, au surdiagnostic et à la rentabilité ne sont pas résolues; par conséquent, cette étude à elle seule n'est pas suffisante pour recommander le dépistage du cancer du poumon par tomodensitométrie assistée par ordinateur.
- Il faudrait encourager la réalisation d'études randomisées sur une base continue concernant le dépistage.

≥5-mm nodules were considered for the investigation algorithm).

From a population perspective, the substantial increase in LDCT use could increase wait times for these limited diagnostic and treatment resources. Lead-time bias and overdiagnosis are concerns that are not addressed adequately by this case series.¹¹ General practitioners are "gatekeepers" and need to apply evidence-based tools to determine the value of screening tests. And despite a probable increase in requests for LDCT screening by our high-risk patients due to this publication, this single paper is insufficient to change practice. 

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Competing interests

None declared

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