Lung cancer screening in Canada
What do we know? What will we do?
by Garth Nicholas, MD, MSc, FRCPC

**ABSTRACT**

The potential value of screening for lung cancer with low-dose CT scans is currently a topic of much research and debate. This article reviews the existing trials of lung cancer screening, using chest x-ray and low-dose CT scan. Potential harms of screening, including overdiagnosis and radiation exposure, are addressed.

Lung cancer is one of the most common cancers in Canada. Incidence is comparable to breast, prostate or colon cancers, but mortality exceeds these 3 other common cancers combined. Looking at all patients with a diagnosis of lung cancer, the 5-year likelihood of survival is around 15%.

These grim statistics have detracted attention from the fact that lung cancer treatment has high success rates when patients present with early-stage disease. Patients with stage I non-small cell lung cancer (NSCLC) treated with surgical resection can expect 5-year survival in excess of 70%. With metastatic disease, however, even clinical trials enrolling the best-selected patients seldom report median survival of more than 1 year, and essentially no patients are cured.

Poor outcomes for lung cancer therefore reflect the fact that most patients present with advanced disease. Recent population-based data suggest that approximately 50% of patients present with metastatic disease, and another 25% with locally advanced disease also not amenable to surgical cure. Fewer than 20% of patients with NSCLC present at a stage where they can be offered curative surgery or ablative radiotherapy.

These facts provide a rationale for lung cancer screening. Screening is the testing of asymptomatic individuals at risk for disease in hopes of diagnosing that disease at an earlier stage. Early diagnosis is of value if the treatment of early stage disease is more successful than the treatment of late stage disease, as appears to be true for lung cancer.

Much research has been undertaken over the past 50 years to find an appropriate screening strategy for lung cancer. Early trials were based mainly on screening with chest x-ray (CXR), while more recent trials have featured low-dose computed tomography scanning (LDCT).

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**THE EVIDENCE FOR LUNG CANCER SCREENING**

**Trials using chest x-ray**

Early trials that used CXR or sputum cytology to screen patients at risk for lung cancer were not successful at demonstrating a reduction in lung cancer mortality. Many of these trials are of historical interest only.

The largest trial to study screening by CXR was the PLCO (Prostate, Lung, Colon, Ovary) screening trial, which investigated whether screening tests for several common cancers could decrease mortality from those cancers. The trial was designed to enrol 148,000 men and women between the ages of 55 and 74. Half were randomized to a multiplex screening program for prostate (prostate-specific antigen, digital rectal examination), ovarian (CA-125, transvaginal ultrasound), lung (CXR), and colorectal cancer (flexible sigmoidoscopy). The other half received standard medical care.

The lung cancer component in PLCO involved screening patients using a baseline CXR followed by 3 annual CXRs. A total of 77,464 patients were randomized to screening, and 51.4% were current or former smokers. Almost 80% of patients completed all 4 screening exams. There was a slightly increased risk of being diagnosed with cancer in the screening arm (HR 1.05, 95% CI 0.98–1.12) and screen-detected tumours were more likely to be stage I disease than non-screen detected cancers (P<0.001), however this did not result in a decrease in lung cancer mortality in the screened group (HR for death 0.99, 95% CI 0.81–1.10).

**Trials using low-dose CT scans**

In the late 1990s, interest grew in the use of LDCT for lung-cancer screening. The term low-dose refers to the radiation dose of the scan, which is roughly one-eighth the dose of a regular diagnostic CT scan. The scans are done in a single breath-hold without IV contrast.

A summary of relevant CT screening studies with reported results is presented in Table 2. These comprise 5 cohort studies14 and 6 randomized controlled trials.15-21 In aggregate, the cohort studies demonstrate the feasibility
of a CT screening program. They suggest, not surprisingly, that more cancers are detected as the screening population gets older, or has a heavier smoking history. The cohort study with the highest rate of cancer detection (in 3.4% of patients) enrolled the oldest patients (minimum age 60), while 2 studies that allowed patients in their 40s with potentially no smoking history at all had the lowest rates of detection.

In 2 of the randomized studies, the control arms received ‘standard care;’ 2 others involved an annual visit to a screening clinic; and 2 more employed CXR. In general, all studies demonstrated an increased rate of cancer detection in the LDCT arm compared to control, but in only one, the National Lung Screening Trial (NLST), did this translate to a reduction in lung-cancer-specific mortality or all-cause mortality.

The randomized studies completed to date are dominated by the NLST; this trial enrolled 53,454 patients in total, compared to 17,199 patients enrolled in all other completed randomized trials combined. The NLST is the only trial to demonstrate a survival advantage with screening. Because this trial has become central to discussion about implementing lung cancer screening programs, it is summarized in detail below.

The fact that none of the other completed randomized trials demonstrated a survival advantage is noteworthy, and requires some comment. It is likely that these trials were underpowered to detect a difference in mortality between study arms. Review of Table 1 demonstrates that, in addition to enrolling by far the largest number of patients, the NLST also enrolled patients with the greatest prior smoking history. More cancers were diagnosed, which further enhanced the statistical power of the NLST compared to the other studies.

More on the NLST
The primary outcome of the NLST was reduction in mortality from lung cancer. Eligible patients were between the ages of 55 and 74, with at least a 30-pack-year smoking history. Former smokers must have quit within the previous 15 years. Patients were randomized for screening with either CXR or LDCT scan. They were screened at randomization, and at 1 year and 2 years post-randomization. Screening results were communicated to the patient’s primary caregiver for followup as clinically appropriate, but there was no specific algorithm for managing abnormalities. The study had a 90% power to detect a 21% decrease in lung-cancer-specific mortality in the LDCT group.

The trial enrolled 53,454 patients and, of these, 26,722 were randomized to LDCT; 59% of patients were male, and 48.2% were current smokers. After a median 6.5 years of followup, there were 1060 lung cancers diagnosed in the LDCT group, compared to 941 in the CXR group. There were 356 deaths from lung cancer in the LDCT group, compared to 443 in the CXR arm, which corresponds to a 20% reduction in the rate of death from lung cancer in the LDCT screening arm (95% CI 6.8–26.7; P=0.004). In addition, there was an overall mortality reduction of 6.7% (95% CI 1.2–13.6; P=0.02). When lung cancer deaths were excluded, the all-cause mortality reduction was no longer statistically significant.

This reduction in the rate of lung-cancer mortality was obtained at the cost of very considerable investigation and medical intervention. The high frequency of nonmalignant pulmonary nodules meant that a great many patients without cancer had positive screening scans that required further workup. In the first round of screening, 7,191 of 26,722 patients (27.3%) had a screening test positive for some abnormality. These patients underwent a further 5,153 chest
There may be other harms that are not yet fully appreciated. In the Danish Lung Cancer Screening Trial, which enrolled the youngest and lowest-smoking population of any randomized trial, the relative risk (RR) for death in the screening arm was 1.46 (95% CI 0.99–2.15). This suggests that in a population at low risk for lung cancer, harms may outweigh benefits.

PRACTICAL CONSIDERATIONS FOR LUNG CANCER SCREENING PROGRAMS IN CANADA

There are many challenges to overcome before a lung-cancer-screening program can become reality in Canada. Three obvious issues include defining the population for screening, reaching that population, and cost. A fourth consideration is the relationship between screening programs and smoking cessation programs.

Defining the screening population

The definition of an appropriate population for screening is of critical importance. To respect the time commitment of patients and maximize the effectiveness of resource use, a screening program should strive to exclude patients at very low risk for cancer while capturing those most likely to be diagnosed. Relevant parameters to define the screening population include age, smoking status, and family history of lung cancer.
population include the intensity and duration of smoking, upper and lower age limits, and duration since quitting in those who no longer smoke. Table 1 summarizes how the various large clinical trials have defined their populations. Mathematical modeling may further refine the population that derives benefit.

The possibility of further refining the screening population through the use of inexpensive tests prior to LDCT scan has been studied, and was in fact one of the primary questions driving the Pan-Canadian Lung Screening Study. Publications from this trial to date have looked at the use of bedside spirometry and blood levels of pro-surfactant protein B, a biomarker proposed for NSCLC. Other authors have looked at a host of biomarkers, including sputum tests and various genetic markers. It is too soon to know which, if any, of these are strong enough predictors of lung cancer to warrant rolling use in the general screening population.

Reaching the target population
Once a target population is identified, it may be difficult to reach members of that population and convince them to participate in screening. The first difficulty relates to notification that screening is available. In screening mammography for breast cancer, many provincial screening programs send women of screening age a periodic reminder in the mail. A similar practice would be less effective and more costly for lung cancer, as there is no available roster of smokers that ministries of health could draw upon to identify potential screening subjects. Letters of invitation or phone calls directed indiscriminately to the population in the target age group would therefore reach many people who were not eligible for screening. Other options for recruitment could include media campaigns and identification of patients by family physicians and specialists.

Any plan to reach candidates for screening, no matter how comprehensive, will still run into difficulty with the population of heavy smokers who are candidates for a screening program. The demographics of smoking in Canada are such that heavy smokers tend to have lower educational attainment and are more likely to be rural than urban. Both of these factors have been associated with decreased participation in screening.

As described above, prescreening measures will be needed to assess eligibility. At the very least, this will consist of a questionnaire documenting past and current smoking history, and might optimally include additional questionnaires, spirometry and blood tests. The ability to reach appropriate participants may decline further with a complex prescreening process.

Cost
The cost of a lung cancer screening program needs to be considered. This is an obvious stumbling block in a Canadian system where many provincial governments are in financial difficulty. Compared to other screening modalities, such as Pap smears or mammograms, CT scans are relatively expensive. Noncancerous pulmonary nodules are commonly detected, and the tests required to follow them up are also relatively costly. As described above, patients in the NLST underwent thousands of additional tests to differentiate a few hundred cancers from several thousand benign pulmonary nodules. It is possible that workup might be done more efficiently if followup of abnormal results was directed to specialists dedicated to the management of pulmonary nodules. A model to differentiate malignant from benign nodules, derived from the TFRI study, might also help to decrease the frequency of followup tests.

To date, there are no published economic analyses using the primary data from screening trials. Several simulation models have been published, with most suggesting that a program similar to the NLST could be cost effective. Detailed economic data were collected for the TFRI study and, when published, will provide important information for the use of LDCT screening in the Canadian setting.

Relationship to smoking cessation programs
Another area of active discussion is twinning lung cancer screening with smoking cessation programs. In its statement in support of LDCT screening, the United States Preventive Service Task Force (USPTF) states that: “All persons enrolled in a screening program should receive smoking cessation interventions.” Indeed, it has been suggested that in the absence of smoking cessation programs, LDCT is unlikely to be cost-effective. It is uncertain whether screening promotes smoking cessation. On the one hand undergoing screening might be a ‘teachable moment,’ or cause individuals to reflect on the seriousness of lung cancer and consider cessation. On the other hand, some might interpret a negative scan as a clean bill of health and continued license to smoke.

Two European studies have published data on smoking cessation among enrolled patients. In both studies there was a higher rate of cessation in study participants than would be expected in the general population; however there was no significant difference between cessation rates in screened and unscreened patients. This suggests that volunteers for studies are perhaps more motivated to quit than smokers in the general population, but that screening itself, at least as delivered in these studies, does not alter the likelihood of cessation very much.

In the absence of strong data, it seems reasonable to acknowledge that smoking cessation is an important modality to prevent lung cancer death, and that individuals who participate in screening may be particularly likely to quit. It would be a lost opportunity if these individuals were not offered cessation interventions as part of a screening program.

CURRENT STATUS OF LUNG CANCER SCREENING PROGRAMS
Several groups have released documents supporting the value of LDCT screening for lung cancer. The most high-profile is the USPTF, and the most relevant for Canadians is the Cancer Care Ontario Program in Evidence-Based Care (CCO PEBC).

Both these statements endorse LDCT screening for an appropriate population. In terms of defining this population,
both stay close to the NLST eligibility criteria. The USPTF suggests screening asymptomatic individuals between the ages of 55 and 80 who have at least a 30-pack-year smoking history and who have quit within 15 years. Screening should be annual and stop at age 80 or once the duration of quit-time exceeds 15 years, whichever comes first. Many private insurers in the United States now reimburse this service.

The CCO PEBC guidelines suggest a similar population, though they put the upper age limit at 74 years, as did the NLST. They suggest 2 annual scans, followed by scans every 2 years for the remainder of the screening period. The CCO PEBC guidelines provide additional recommendations in areas not touched by the USPFD, including technical aspects of the scanners, and the definition and follow-up of positive scans. Finally, the CCO PEBC guidelines strongly emphasize that patients should participate in an organized screening program, rather than more ad hoc opportunistic screening.

Several Canadian provinces are currently studying the feasibility of LDCT screening. In Ontario, for instance, CCO has commenced a health technology assessment (HTA) to study LDCT. This process has several components, including modeling cost-effectiveness, evaluating communication strategies for primary-care providers and at-risk individuals, and recommended strategies for early implementation. To date, nothing has been published from this work. The report to CCO is expected in early 2015, and will inform a decision from the Ontario Ministry of Health and Long-Term Care.

CONCLUSION

A number of important messages can be drawn from research into lung cancer screening:

1. Annual CXR does not decrease the risk of lung cancer death.
2. LDCT can be effective in reducing lung cancer mortality in a population with a significant smoking history.
3. Extending LDCT to patients at lower risk for lung cancer will probably not be beneficial, and may do more harm than good.
4. Detailed economic analysis, preferably jurisdiction-specific, will be important to assure that a screening program is a cost-effective use of healthcare resources.

Although a significant public health gain might be realized by implementing a well-organized LDCT screening program, that program will have to meet the challenges of defining the appropriate screening population and encouraging that population to participate. The exact form such programs might take in a Canadian setting is the subject of ongoing study and debate.

References

30. The National Academies. Health risks from exposure to low levels of ionizing radiation. BEIR VIII phase II report.


