CANADIAN PARTNERSHIP AGAINST CANCER | PARTENARIAT CANADIEN CONTRE LE CANCER

SCREENING PORTFOLIO

Lung Cancer Screening

Expert Panel: Summary of Existing and New Evidence

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ANTICIPATORY SCIENCE

a summary of existing and new evidence

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Summary Statement of the Panel

The National Lung Screening Trial (NLST) conducted by the U.S. National Cancer Institute is the first randomized trial of adequate sample size and follow-up to evaluate the efficacy of low dose computed tomography (LDCT) screening to reduce lung cancer mortality in heavy smokers. The trial found a significant 20% reduction in lung cancer mortality, after three annual LDCT screens.

Although the NLST results are encouraging, more investigation is needed in the areas of: over-diagnosis; net benefit versus harm; at risk population to screen; frequency and duration of LDCT screening; the most appropriate diagnostic work-up of screen detected abnormalities; and implications for public policy.

While not all issues have identified and/or resolved in this document, broader discussion is necessary to guide policy and planning initiatives. An immediate next step will be taken by the Canadian Partnership Against Cancer to organize national forums to facilitate these and other considerations in lung cancer screening. The first forum is tentatively planned for Fall 2011.

Purpose

The purpose of this document is to review the current evidence regarding lung cancer screening using LDCT, to assist health professionals and policy-makers in making an informed decision on lung cancer screening in Canada. This document synthesizes the mortality outcome results from the NLST trial.[1] Several screening studies have already been published evaluating lung cancer screening. In addition to the NLST trial, the U.S. randomized Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is expected to publish its results shortly while the NELSON Trial in the Netherlands and Belgium is still ongoing. A précis of these studies along with the historical context of lung cancer screening trials is included in this document.

In addition, this summary document gives background epidemiology information on lung cancer. It outlines the principles of screening and the management of the disease if abnormalities are detected. This document also addresses knowledge gaps and research needs in the area of lung cancer screening which should be considered before lung cancer screening is adopted on a population basis.

This document is not intended to provide definitive answers or clinical and/or policy recommendations. The views expressed herein represent the views of the Lung Cancer Screening Expert Panel.

Canadian Partnership Against Cancer, Lung Cancer Screening Expert Panel. Lung Cancer Screening Expert Panel: Summary of Existing and New Evidence. Toronto: Canadian Partnership Against Cancer; 2011.

Background and Lung Cancer Epidemiology

Importance, Mortality and Incidence

Lung cancer is the leading cause of cancer death in North America[2,3] and the world.[4] Worldwide in 2002, there were an estimated 1.2 million lung cancer deaths[4] and this number is on the rise.[5] It is estimated that in Canada in 2011, there will be 20,600 lung cancer deaths (11,300 in men and 9,300 in women),[2] accounting for about 28.3% of all cancer deaths during that period. The age-adjusted mortality rate (standardized to the 1991 Canadian population) will be 46 per 100,000 overall, 56 per 100,000 in men and 39 per 100,000 in women. Lung cancer is the second most common cancer in both men and women in Canada.[2] For 2011, the estimated number of new cases of lung cancer in men is 13,200 and in women is 12,200, and the corresponding age-adjusted incidence rates in men and women are 65 and 51 per 100,000[2] respectively.

The incidence and mortality rates for lung cancer in men and women follow cigarette-smoking trends with an approximate 20–30 year lag. In Canadian men, incidence and mortality rates levelled off in the mid-1980s and have been declining since. In women, lung cancer incidence has been increasing since 1980 but is now levelling off and is predicted to start declining in the near future.[4]

Incidence and mortality rates of lung cancer begin to increase between the ages of 40–44 in both men and women, and rise progressively until age 75 (Figure 1 and Figure 2).

Figure 1: Lung cancer incidence rates by age group and gender[6]

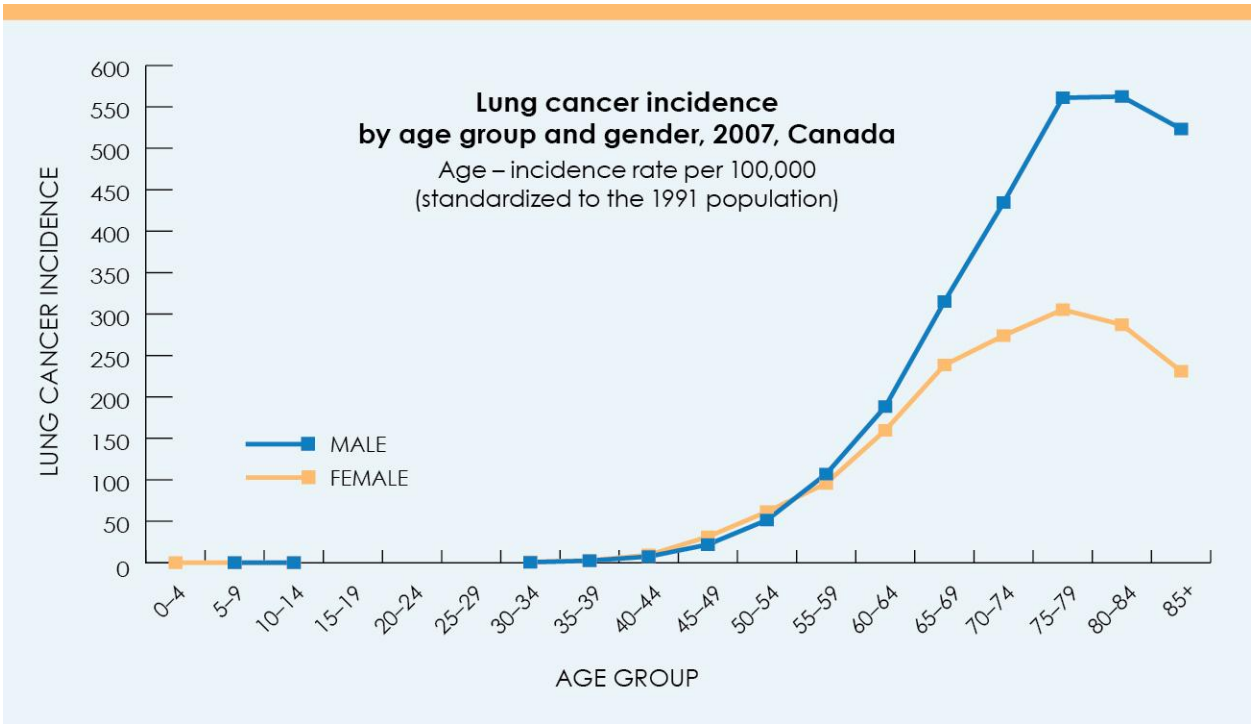
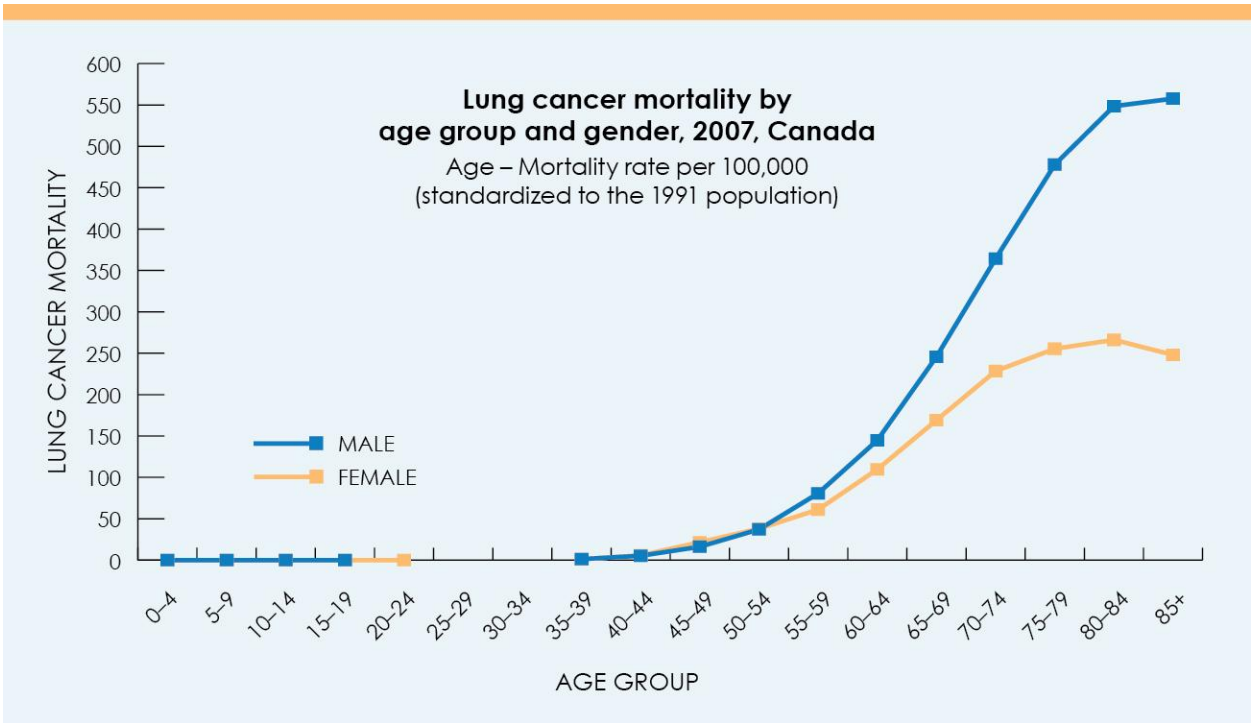


Figure 2: Lung cancer mortality rates by age group and gender[6]



Survival

Lung cancer incidence and mortality rates are similar because lung cancer is a highly fatal disease. In Canada, for the 2002–2004 period, the proportion of men surviving five years was 13% and for women it was 17%.[7] Recent Canadian Cancer Registry data (2005–2007) suggest a five-year lung cancer survival of 17.7%.[8] The statistics indicate a small gradual improvement in five-year survival over the last 30 years.

The majority of lung cancers are detected at an advanced stage when they have a very poor prognosis. In the United States, Surveillance Epidemiology and End Results registry data (1995–2000) indicated that lung cancers were diagnosed with localized, regional, distant and unknown stages in the following proportions: 16.4%, 20.3%, 53.0%, and 10.3%, respectively; and these stages had the following five-year survival proportions: 48.8%, 22.8%, 3.3% and 8.7%.[9]

Histological Distribution and Trends

Lung cancers can be divided into two major types by their histological appearance and biological behaviour: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The majority of lung cancers today are NSCLCs (approximately 82%), and the most common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Prior to the 1970s, squamous cell carcinoma was the most common histological type, but since that time, the proportion of adenocarcinoma has increased and has now become the most common type. Squamous cell carcinomas and SCLCs are often located in the central airways, whereas adenocarcinomas are usually more peripherally located.

Stage at Diagnosis

For the purposes of guiding treatment and determining prognosis, NSCLCs are grouped into stages by the local extension of the tumour and extent of its local and distant spread. NSCLC stages include 0 (carcinoma *in situ*, no invasion past the epithelium has occurred), I, II, III and IV (metastases of cancer to distant sites has occurred). Alternatively, NSCLC stages are sometimes simplified into local, regional and distant categories. SCLCs tend to spread early and historically were categorized in two stages: *limited* (confined to one lung and possibly local lymph nodes) and *extensive* (the cancer has spread beyond the primary lung site to the other lung, lymph nodes on the other side of the chest or to distant organs). The most recent (7th) edition of the lung cancer staging manual now suggests using the same staging system in SCLC and NSCLC.[10]

Localized NSCLCs can be treated surgically with curative intent. When the cancer has spread and surgery with curative intent is not possible, then treatment with chemotherapy or radiation therapy or both can be offered. In patients with regional nodal disease, treatment often involves pre-operative chemotherapy and radiation or post-operative chemotherapy. That five-year survival proportions can approach 70% in stage IA NSCLCs (small local cancers that have not spread to lymph nodes) suggests that early detection of such lung cancers through screening might reduce lung cancer mortality.[11]

Risk Factors

The vast majority of lung cancers (85–90%) are associated with cigarette smoking. Preventing the onset of smoking and bringing about successful smoking cessation in current smokers will most effectively achieve primary prevention of lung cancer. Exposure to second-hand smoke is the second most common risk factor for lung cancer. Pooled evidence comparing non-smokers living with smokers indicates that second-hand smoke is associated with a 20–30% increased risk in lung cancer, after controlling for some potential biases and confounding factors.[12,13]

Other risk factors for lung cancer, predominantly environmental and occupational, include exposure to air pollution, arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon and radon decay products.[14] In addition, fumes from cooking stoves and biomass fires are associated with increased risk in some developing countries.

Family history of lung cancer has been frequently found to be associated with lung cancer even after careful adjustment for smoking.[15] Genome-wide association studies have identified inherited susceptibility variants for lung cancer on three chromosomal loci.[16-23] Several additional factors have been associated with lung cancer, but the findings have not been consistent. For example, several studies have suggested that diets rich in fruits and vegetables are protective. Generally, the associations between non-smoking factors and lung cancer are substantially smaller than the association between cigarette smoking and lung cancer and therefore the principal target group for screening should be smokers and those who have quit after substantial periods of smoking.

Smoking Trends – Prevalence Data

During the years 1999–2009 smoking among Canadians 15 years of age and older declined overall from 25% in 1999 to 18% in 2009.[24] However, in spite of the reduction of smoking in North America, lung cancer is expected to continue to be a major public health concern for decades to come, because long-term heavy smokers carry a residual risk of lung cancer after smoking cessation. Former smokers make up more than 50% of the lung cancers diagnosed now.[25,15]

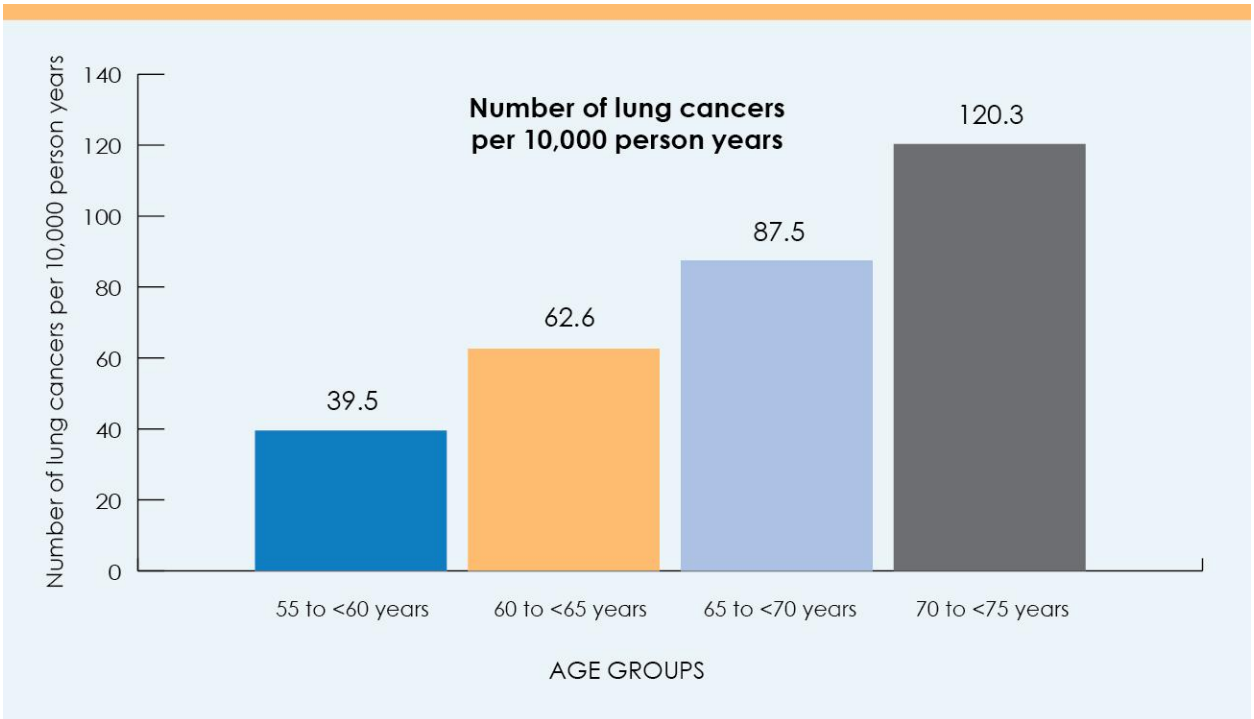
In the NLST, which found that LDCT lung screening significantly reduced lung cancer mortality by 20%, the sample had been selected to be at elevated risk for lung cancer. The NLST enrolled individuals with a smoking history of 30 or more pack-years and former smokers who had smoked regularly within the last 15 years. These two criteria are referred to in this text as the NLST criteria. Data are not available in Canada to

identify what proportion of the general population would fit this high-risk category or what their lung cancer risk would be. To provide a sense of the magnitude of these numbers, however, data and statistics were generated by applying the NLST criteria to the PLCO control arm (statistics prepared by Dr. Tammemagi, with permission). The PLCO attempted to carry out population-based sampling in the United States from 10 geographical areas. Although participants generally were of a higher socioeconomic status than average,[26] the NLST/PLCO statistics presented here may provide an estimate of what might be anticipated in Canada. Details of the PLCO and NLST are provided later in this report.

In the PLCO control subjects (N = 70,949) the proportion of individuals who met the NLST criteria broken down by their age category at study onset was 16.7% in the 55 to <60 age group, 18.2% in the 60 to <65 age group, 16.6% in the 65 to <70 age group, and 12.9% in the 70 to <75 age group. The probability of meeting the NLST criteria decreased with age (odds ratio per year = 0.985, 95% CI 0.986–0.989; $p < 0.001$) and was twice as high in men (odds ratio men vs. women = 2.04, 95% CI 1.96–2.12; $p < 0.001$). Figure 3 presents the estimated number of lung cancers in the four age groups of individuals meeting the NLST criteria.

The age-gender specific rates of meeting the NLST criteria and the lung cancer incidence rates for these groups as observed in the PLCO trial were applied to the Canadian 2010 population age-gender strata to estimate the number of lung cancers observed if LDCT were applied to the Canadian population who met NLST age-eligibility and risk entry criteria. Given five-year survival proportions observed in Canada (17%) and a 20% reduction in lung cancer mortality (observed in the NLST), it is estimated that roughly 1,246 (478 female, 768 male) lung cancer deaths might be prevented per year. Details of estimate calculations are presented in Appendix 1. It is important to note that these estimates are simplified and based on U.S. data that might not apply in Canada, and that the mortality reduction estimate attributable to screening comes from an ideal, optimistic setting, albeit from a randomized controlled trial.

Figure 3: Number of lung cancers per 10,000 person-years of follow-up for individuals in four age groups at start of follow-up, in PLCO control subjects who meet the NLST criteria (N = 11,775)



Principles of Screening and Biases

Screening is intended to detect disease at an earlier, more treatable stage than if the disease were to present clinically by means of symptoms. Screening is a process. It requires the use of tests to detect unrecognized health risks or diseases to permit timely intervention. For a screening program to demonstrate effectiveness at a population level, the screening tests must be applied systematically on a large scale. They are used to distinguish between those apparently unaffected from those who *may* have a disease. A screening test is not intended to be diagnostic. Screening procedures are generally easier to perform and cheaper than diagnostic procedures. The test results require confirmation through definitive diagnostic tests, followed by treatment of confirmed cases. Screening can be effective only if effective treatment is available for the abnormality or disease revealed by screening.

Screening tests can cause anxiety and the subsequent investigations and treatment can be hazardous. Thus, ensuring the safety of screening is of importance because large numbers of individuals will be screened, many of whom will not be found to have a disease.

The principles of screening articulated by the World Health Organization[27,28] include the following:

- The test should be suitable – accurate, acceptable, safe and relatively inexpensive.
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and effective treatment should be available.

Screening may be organized or opportunistic. Organized screening programs are population-based programs that target asymptomatic people in a specific age group or certain high risk groups. Usually there are specific mechanisms to encourage participation for screening, and follow-up if necessary.

Organized screening programs should be implemented only:

- where there is good evidence of reduced cancer-specific mortality; and
- to achieve a population-level benefit and a balance of benefits and harms.

Opportunistic or ad hoc screening occurs when the test is available, but no specific mechanisms are set up to target the at-risk group. Some regard this as "case-finding". Such opportunistic screening can be helpful for those who are in the defined age and high-risk group, but carries a risk of causing net harm if performed on patients who have only a low risk and therefore low probability of benefit. For example, for cancer of the cervix, opportunistic screening has been shown to be inefficient and only partly effective.[29] This is likely true for other cancer sites. In Canada, major mechanisms are under way to ensure screening programs are organized.

When screening is offered the following should be noted:

- Where the cancer incidence is low (e.g., those aged <50 years), the pick-up rate will be low and the false positive rate and costs consequently higher.
- Detection of cancer *per se* is not an appropriate screening endpoint – population-based disease-specific mortality, morbidity and quality-of-life effects are.
- Survival alone cannot be used as an endpoint because of biases associated with screening: lead time, length bias and over-diagnosis bias, which systematically lead to over-estimation of survival.

Screening Biases

Lead time is the advancement of the time of diagnosis of the disease from that which would have occurred if the disease had presented clinically. Inevitably, survival will be increased by lead time even if there is no effect of early detection on the probability of death from the cancer. Length bias occurs because fast-growing cancers are less likely than slow-growing ones to be detected by screening in a curable stage, therefore slow-growing cancers will be over-represented among those detected. Selection bias occurs because screening is a voluntary activity. People who are health conscious, and therefore likely to present early for diagnosis when a symptom of disease occurs, will be over-represented in screening programs. This has been called the healthy volunteer effect.[26]

Over-diagnosis refers to the discovery of a cancer that would never come to light, nor cause any symptoms or problems for the remainder of the person's life either because of slow growth or because some other illness brought about death before the diagnosis of the cancer. Even CXR screening has demonstrated over-diagnosis bias.[30] Given the improved sensitivity for the detection of small lung cancers using LDCT, over-diagnosis is much greater for LDCT screening than CXR screening. Over-diagnosis increases costs, and the investigation and treatment of an over-diagnosed cancer often results in complications, even death that would not otherwise occur. Thus it is desirable that the screening test results in minimal over-diagnosis.

For a screening test to be effective in a population, it has to be acceptable to the target group, it has to be valid, and it has to be known to have efficacy and effectiveness. These basic requirements are further considered below.

Acceptability

In screening, individuals who have not been diagnosed with the disease for which screening is offered are approached. In general that means they are healthy, though it is still possible to screen people already with another condition. In practice, some people approached will have symptoms of the disease, but they or their medical advisor may not have recognized that a disease is present.

To ensure acceptability, the test should not involve too much embarrassment, and privacy and cultural beliefs must be respected. Those who accept screening should be as little disadvantaged as possible by the process needed to obtain the test, by the test itself and by its consequences. It helps considerably if the administration of the test is simple. In general, LDCT is considered to be a simple test involving breath holding for about 20 seconds in a CT scanner.

Validity

The two components of validity of a screening test are sensitivity and specificity. These are two completely independent parameters, though in many circumstances, there is a reciprocal relationship between them (a test with high sensitivity tends to have low specificity, and vice versa). As presented in Table 1, sensitivity is the proportion of those who have the disease who test positive; specificity is the proportion of those free of the disease that test negative.

Table 1: Validity components – sensitivity and specificity

Test Result	Disease Present	Disease Absent
Positive	True positive (TP)	False positive (FP)
Negative	False negative (FN)	True negative (TN)

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)

Two process measures are useful in describing the yield of screening tests, but they are not measures of validity. The positive predictive value of a test is represented by TP/(TP + FP), and the negative predictive value by TN/(TN + FN). They are affected by the prevalence of disease. The positive predictive value of the test will be increased if persons at high risk for the disease are recruited into the screening program. For lung cancer, this means screening persons who have been heavy smokers for a long duration, as they will have a higher prevalence of disease. However, disease may also occur in those at low risk, and the cut point between low and high risk will have to be carefully selected to ensure the maximal cost-effectiveness of the screening program.

The process of screening requires that those with positive results undergo diagnostic tests to distinguish the true from the false positives. However, a corresponding evaluation does not occur for those negative to the test, so that the false negatives are not identified. Thus without follow-up, the sensitivity of a test is unknown. For specificity, as false negatives comprise a small proportion of total negatives, an approximation is obtained by (TN – FP)/TN.

In general, determination of sensitivity requires follow-up of those screened, and the identification of those who develop disease in the interval between screening tests. Then sensitivity is represented by the expected incidence in the group screened less the interval cancer rate as a proportion of the expected incidence, that is, the amount of disease destined to occur that did not occur because of the prior screen. This is most validly determined in a randomized screening trial, as the control (unscreened) group provides the measure of expected incidence. Determination of relative sensitivity by administering two or more tests in the same individual can result in a biased estimate if one (or both) of the tests result in over-diagnosis. For further discussion of these issues, see Hakama, Auvinen, Day and Miller.[31]

Efficacy and Effectiveness

Efficacy is determined in ideal circumstances, such as in a randomized screening trial. Effectiveness measures what screening achieves in actual use in a population. However, without efficacy, one cannot expect effectiveness, so a screening test should not be offered to a population without efficacy first being demonstrated.

The desired outcome of screening for cancer is reduction in mortality from the disease, that is, cause-specific deaths with the population as the denominator. This is not the same as reduction in case fatality (improvement in survival), which is expected for screening because of the biases discussed earlier. Using a screening test that identifies a cancer precursor will also reduce cancer incidence, such as is seen for screening for cancer of the cervix and for colorectal cancer. Definite precursors of lung cancer detected by screening have not been identified, so reduction in incidence is not anticipated as a result of lung screening.

Simple case detection is not equivalent to efficacy as:

- some cancers may not be curable, nor have their natural history modified by available treatment;

- some cancers may never have become life-threatening in the patient's lifetime; and
- only some cancers are curable.

Demonstration of Effectiveness

Demonstration that screening does achieve the desired outcome in the population is not easy, especially if other changes, such as improvement in treatment, occur at the same time, as shown by some of the recent controversies over breast screening. However, reduction in cancer mortality is the definitive requirement to confirm that the screening test is effective. Extensive monitoring will be necessary. Various intermediate indicators are useful as part of this process, including participation rates of the target group, cancer detection rates, interval cancer rates and the proportion of diagnosed cancers detected as a result of screening. If all are on target, and the test is known to have efficacy, eventually reduction in cancer mortality should be seen.

Lung Cancer Screening Tests

Imaging and non-imaging tests have been investigated to detect early lung cancer.

The use of imaging to detect lung cancer rests on the fundamental principle that lung cancer tissue, compared with normal healthy lung tissue, exhibits a different response to an imaging test. While a number of imaging modalities exists, those best adapted to imaging lung tissue rely on the relative attenuation of x-rays. X-ray attenuation is essentially a measure of tissue density. Lung cancer tissue is a solid soft tissue mass while normal lung tissue is a mixture of air, supporting soft tissue and blood vessels. These two tissue types have a large difference in density and thus have a large difference in their x-ray attenuation. Imaging detection of lung cancer therefore rests on a radiologist identifying shadows on x-ray images that indicate abnormal soft tissue residing within normal lung tissue.

The two most common x-ray–based chest imaging techniques are the plain radiograph (CXR) and Computed Tomography (CT) scanning.

Chest X-Ray

The chest radiograph provides a single view of the chest and is usually obtained in either the posterior–anterior (PA) or both the PA and the lateral view. Usually these two projections are obtained at the same setting and these two images are jointly reviewed by the radiologist. The radiologist combines information from the two views, searching for abnormal soft tissue within normal lung tissues. The complexity of the structures within the adult chest (heart, blood vessels, lungs, bones, musculature, air) make it very difficult to separate out the contribution of a small amount of additional lung cancer tissue from the normal chest tissues. Research studies have shown that for this reason, using two view chest radiography, a substantial number of small lung cancers are missed (with the average diameter of 16 mm).[32]

Low-Dose Computed Tomographic Scanning

LDCT scans (20% of a standard CT radiation dose) measure the same fundamental physical property, the attenuation of x-rays by body tissues. Again, this is effectively a measurement of the density of body tissues. However, the method of image formation is fundamentally different. While the plain radiograph provides a single view of the chest, the LDCT scan obtains 800 to 1,400 views of the chest in a 360° rotation. A computer is then used to reconstruct an image that is viewed as a slice of the chest. Compared with the two views of the chest radiograph, this view-rich technique provides much more accurate information on the separation of lung cancers from surrounding normal chest tissues. This provides more confident identification of nodules.[33] Unfortunately, the large number of views used in LDCT scanning translates into substantially increased radiation dose in comparison to the chest radiograph.[34] However, the increased detection of smaller lung cancers and efficient use of radiation make it practical to consider using LDCT for early lung cancer detection. Finally, the LDCT technique that was invented in the early 1970s has rapidly evolved. Multi-detector LDCT scanners currently in use can obtain 400 1-mm thick sections of the lung in less than 5 seconds while using the same amount of radiation that the average Canadian receives every half-year in the natural environment (Table 2). These facts combine to make it practical from both simplicity and a radiation exposure viewpoint to consider using LDCT to detect early lung cancers.

Table 2: Background Radiation[35,36]

Examination	Radiation dose (milliSieverts)
Natural background (per year)	2–4
PA digital chest radiograph (per exposure)	0.02
Lateral digital chest radiograph (per exposure)	0.04
PA and lateral chest radiograph (per exposure)	0.06
Low-dose chest CT (per exposure)	1.4[37,38]
Regular-dose chest CT (per exposure)	4–18

Non-Imaging Tests

Several non-imaging early detection tests using sputum, blood or exhaled breath have been investigated. Conventional sputum cytology has not been shown to be effective in detection of early lung cancer in several clinical trials sponsored by the U.S. National Cancer Institute. Other sputum tests that use image analysis, measurement of DNA methylation or specific oncogene mutations are under investigation.[39-42] Blood DNA markers, miRNA, auto-antibodies and proteomic biomarkers have been reported to discriminate between cancer and non-cancer subjects[43-47], but have not been validated in prospective screening trials in high-risk populations. Analysis of exhaled breath using mass spectrometry or electronic nose technology[48,49] appears attractive but *none to date have been proven to be effective in rigorous scientific studies*. The incremental value of these tests to detect early lung cancer over and above a risk prediction model based on clinical and demographic data alone[15] requires further study.

Follow-up of Screen-Detected Abnormalities and Management of Disease

Abnormalities on LDCT scans are common – up to 80% of scans in some studies. However, this is highly dependent on the definition of abnormal and the prevalence of conditions such as fungal infections in the community that can cause non-neoplastic lung nodules. Presently, most studies ignore lesions less than 4 mm. For lesions 4 mm and larger there are a variety of categorization algorithms in use based on the size and characteristics of the lesion to further evaluate the probability that the lesion is benign or malignant. However, at this time the separation of suspicious lesions into benign or malignant etiologies is an imperfect science and therefore very much in evolution.

The clinical significance of a lung nodule on a single scan and the optimum follow-up remains controversial. Traditionally, the medical community has recommended 24-month observation but this is not based on published longitudinal LDCT data, instead being based on follow-up of lesions on a CXR. LDCT practice guidelines have not been developed although regular-dose CT practice guidelines have been published by the Fleischner Society (Table 3).[50] These guidelines were developed to guide the performance of follow-up CT scans in patients with incidentally detected pulmonary nodules.

Table 3: Fleischner Society guidelines for follow-up and management of incidental small nodules (<8mm) detected on non-screening CT scans[50]

Nodule size	Low-risk patients	High-risk patients
≤ 4 mm	No follow-up needed	Follow-up at 12 months; if no change, no further imaging needed
>4–6 mm	Follow-up at 12 months; if no change, no further imaging needed	Initial follow-up LDCT at 6–12 months and then at 18–24 months if no change
>6–8 mm	Initial follow-up LDCT at 6–12 months and then at 18–24 months if no change	Initial follow-up LDCT at 3–6 months and then at 9–12 and 24 months if no change
>8 mm	Follow up LDCTs at around 3, 9 and 24 months; dynamic contrast enhanced LDCT, positron emission tomography and/or biopsy	

The guidelines that have evolved are based on both LDCT and practical considerations. The size, shape and density of the lesion (solid, semi-solid or non-solid also known as ground-glass opacity) all need to be considered. A semi-solid lesion for example is more likely to be an adenocarcinoma than a ground glass opacity, which may be inflammatory, pre-malignant (atypical adenomatous hyperplasia) or adenocarcinoma *in situ* (previously referred to as bronchioloalveolar carcinoma).[51,52]

If the lesion is less than ~8 mm, it is very difficult to biopsy percutaneously or to image by positron emission tomographic (PET) scan. Depending on its location in the lung, it may also be quite challenging to find at surgery. Most commonly, these smaller lesions are followed with a repeat LDCT scan in 3-6 months. If there is interval growth in two consecutive scans (defined as an increase in either long axis or short axis diameter of ≥ 1 mm or an increase in the volume by 25% or more), over 75% are invasive cancers and a tissue diagnosis is warranted.[53,54] In patients with lesions over 8 mm, a diagnostic work-up to evaluate for malignancy should be recommended if the patient is willing and capable of undergoing potentially curative treatment, be that surgery or radiation.

Since local expertise and resources vary considerably between institutions, screening studies have usually left the subsequent work-up of a screen-detected suspicious lesion to the physicians at the individual institutions with general guidelines on diagnostic work-up pathways rather than trying to mandate a standardized policy.

Lung Cancer Screening Trials/Studies

This section describes the key randomized controlled trials (RCTs) on lung cancer screening. A brief summary of the initial CXR studies precedes individual descriptions of the international RCTs that have the greatest number of subjects. These large trials will potentially provide definitive answers about the impact of screening on lung cancer mortality:

1. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, United States
2. National Lung Screening Trial, United States
3. Dutch-Belgian Randomized Lung Cancer Screening Trial, Netherlands and Belgium
4. Danish Randomized Lung Cancer CT Screening Trial, Denmark

These are summarized in chronological order later in this section, including a description of the International Early Lung Cancer Action Program (I-ELCAP) multicentre study. While the I-ELCAP study is not an RCT, it is a large high-profile study that has published results in recent years. This study illustrates the pitfalls in study designs that utilize only a single intervention arm, with no control arm.

Lung cancer, when diagnosed at an early stage (Stage IA), has a five-year survival rate that exceeds 70%,[55,56] raising hopes that early detection of lung cancer would reduce mortality. However, non-randomized studies of lung cancer screening in the United States and United Kingdom using CXR alone or combined with sputum cytology showed no reduction in mortality.[57-63] Subsequently, four randomized controlled trials that each included 6,300–11,000 participants, three in the United States and one in Czechoslovakia, evaluated the benefits of lung cancer screening using CXR alone or in combination with sputum cytology in male cigarette smokers over 45 years of age. Two of the U.S. studies evaluated the potential benefit of adding four monthly sputum cytology to annual CXRs.[64,65] The third U.S. study compared a screened group offered four-monthly CXR and sputum cytology with a control group who were recommended annual CXRs (the Mayo lung trial).[66] The Czechoslovakia study compared 6-monthly CXRs with no intervention in the control group.[67] Although the lung cancers detected by screening were less advanced and had better survival than those not detected by screening, none of the trials found a reduction in mortality from lung cancer in the group offered more extensive screening, while long-term follow-up of the Mayo lung trial found evidence of over-diagnosis.[30,68]

In practice, two of these trials evaluated the effect of sputum cytology but provided no data on the efficacy of CXR screening. The other two evaluated CXRs, but one of them (the Mayo trial) recommended annual CXRs to controls (as was then the policy for heavy smokers) so that there was in effect some contamination of the control group. All the trials were relatively small, so that an effect could have been missed because of low power. These considerations led to the design of the lung cancer screening component of the PLCO trial using CXR.[69]

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

The lung cancer component of the PLCO trial differed in several important respects from the earlier trials, specifically with respect to the inclusion of women and never-smokers, the absence of scheduled CXRs in the control group, and the large sample size, 77,464 randomized to the screened group and 77,470 to the control. Men and women, aged 55–74 years, who reported no prostate, lung, colorectal or ovarian cancer, or undergoing treatment for any cancer other than non-melanoma skin cancer, were included in the trial at 10 screening centres across the United States from 1993 to 2001. Four rounds of annual screening were offered to the screened group (except for non-smokers, who were not offered the fourth round) and participation in the screening was high; screening in the trial ceased in 2006. A total of 564 lung cancers were diagnosed: 431 in the screen group, of which 306 (54%) were screen-detected cancers, 183 (32%) were interval cancers and 75 (13%) in the participants who were never screened. Of the total, 87% were

NSCLCs. Among NSCLCs, 59.6% of screen-detected cancers and 33.3% of interval cancers were early stage (I–II).[70] Mortality results from this trial are pending. A subgroup of trial participants with the same eligibility criteria as NLST has been identified. It is anticipated that the findings from this subgroup will help to interpret the findings from the NLST trial.

International Early Lung Cancer Action Program

The availability of LDCT led to its evaluation as a screening test for lung cancer. Early uncontrolled studies suggested that a high proportion of lung cancers detected were early stage.[33] The investigators were so convinced that such screening would be beneficial that they initiated a collaborative multi-centre study with the intention of determining lung cancer survival without a control group – a single-arm study.[33,71,72] By doing so, they deliberately ignored the possibility that their results would be un-interpretable because of the biases associated with screening discussed elsewhere in this document. Critical was the fact that survival would be un-interpretable if the screening was associated with any degree of over-diagnosis.[70] In addition, the group of patients they selected for study were undefined (being left to the collaborating institutions to determine) so that even though they reported a high rate of survival from lung cancer, it seemed probable that much of this was due to selection bias. Therefore, a randomized trial was needed to evaluate the true benefit of LDCT screening.

National Lung Screening Trial

The methodologically flawed I-ELCAP study received a good deal of public attention. In response, the U.S. National Cancer Institute decided to move ahead quickly in the early 2000s with a well-designed study to evaluate the efficacy of LDCT for lung cancer screening, the NLST trial. The NLST is a randomized multi-centre lung cancer screening trial (33 U.S. sites) comparing LDCT with CXR among high-risk individuals. LDCT uses only 20% of a standard CT radiation dose. Each trial arm received a baseline screening followed by two annual follow-up screens. With a planned enrolment of 25,000 in each of the study arms, the study was planned to have 90% statistical power to detect a 20% reduction in lung cancer mortality.[73]

Study participants were between 55 and 74 years of age at baseline, had a cigarette smoking history of 30 or more pack-years, and former smokers had to have quit smoking within the 15 years prior to study entry. Exclusion criteria included metallic implants or devices in the chest or back, treatment for cancer in the five years before eligibility assessment (with a few exceptions), history of lung cancer, history of removal of part of the lung (excluding needle biopsy), need for home oxygen supplementation, participation in another cancer screening trial or cancer prevention study (except smoking cessation), unexplained weight loss of more than 15 pounds in the last 12 months, recent hemoptysis, pneumonia or acute respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment, and chest CT in the 18 months prior to eligibility assessment.

The primary study outcome was lung cancer mortality. The study intervention of interest was LDCT and the comparison group was chosen to be chest radiography, rather than regular care, for a number of reasons.[74] Primarily, the already ongoing PLCO Screening Trial[69,71] was comparing chest radiography versus regular care; data from that trial could be used to inform the NLST comparison. In addition, a large proportion of individuals in the high-risk age group under study routinely obtained chest radiographs as part of their medical care, which would have made contamination with CXR a problem if the control group had been usual care.

Details of the NLST study design and the characteristics of the baseline population have been reported.[73,75,76] Participant recruitment began in September 2002 and accrual was completed in April 2004. The enrolment was 53,456 individuals, with 26,733 randomized to the CXR arm and 26,723 randomized to LDCT.

The study plan had been to have a minimum of five years of follow-up for all participants and to conclude the study in the summer of 2011. The Data and Safety Monitoring Board that regularly evaluated NLST data determined that a definitive result had been reached for the primary endpoint of the trial and

recommended in October 2010 that the results be reported according to prearranged statistical guidelines. On November 4, 2010, the initial study findings were made public.[76,77] The full manuscript was released online on June 29th, 2011 in the New England Journal of Medicine.[1] LDCT screening led to a 20.0% reduction in lung cancer mortality in comparison with CXR screening (95% CI, 6.8 to 26.7; P=0.004) and a 6.7% overall (all causes) reduction in mortality (95% CI, 1.2 to 13.6, P=0.02) most of which were related to lung cancer deaths. The incidence rate ratio for LDCT versus CXR was 1.13 (95% CI 1.03 to 1.23). The rates of death from lung cancer were 247 and 309 per 100,000 person-years for LDCT and CXR respectively. These statistics suggest that LDCT lung screening can lead to reduced mortality from lung-cancer but not to a significant reduction in other non-lung-cancer deaths. However, there was an excess of lung cancers detected in the LDCT arm compared to the CXR arm that approximates to 13% of screen-detected cancers in the LDCT arm. Longer follow-up and data from the PLCO trial (under review) would help to clarify the magnitude of over-diagnosis which is known to be present in cancer screening of any organ.

The number needed to screen (NNS) to prevent one lung cancer death is 320[1]. However, the number could be higher since the cancers were found by more than one round of screening. Nevertheless, this NNS is relatively low compared with the NNS to screen for other cancers, such as breast and colorectal cancer because only for lung cancer is it possible to define a high-risk group with precision (heavy or ex- smokers of 30 or more pack-years): the NNS for breast cancer screening with mammography has ranged from 1,000 to 10,000, and the NNS for colorectal cancer with the fecal occult blood test (FOBT) is estimated to be 1,200 over 10 years.[78] However, it is important to appreciate that the NNS presented for screening trials represents a number obtained under ideal conditions of screening on a defined high-risk group in an efficacy trial, and in the real world setting it may not approach this low value (effectiveness).

The statistically significant reduction in lung cancer mortality, together with the relatively low NNS, suggests that LDCT lung screening may be beneficial. Before a policy decision is made on a population-based lung cancer screening program, an adequate cost-effectiveness analysis should be completed. Such a cost-effectiveness analysis will have to take into account the size of the target population, the potential for benefits, the potential downsides for participants, the magnitude of over-diagnosis and the feasibility of introducing services with adequate programmatic components to maximize benefits, while minimizing potential harms.

Dutch-Belgian Randomized Lung Cancer Screening Trial and Danish Randomized Lung Cancer CT Screening Trial

The NELSON trial (a Dutch acronym for a Dutch-Belgium lung cancer screening trial) is a randomized multi-centre study comparing LDCT with no screening. Participants underwent LDCT screening at baseline, 1 year later (second round), 2 years later (third round) and 2.5 years later (fourth round) or no screening. A total of 15,428 participants have been randomized. When the NELSON participants are pooled with the Danish Randomized Lung Cancer CT Screening Trial (DLCST) involving 4,104 participants, the trial is expected to have 80% power to show a lung cancer mortality reduction of ≥25%, 10 years after randomization.[79,80]

In the NELSON trial, participants were between 50 and 75 years of age at baseline, had a smoking history of >15 cigarettes/day over 25 years or >10 cigarettes/day over 30 years. Former smokers had to quit smoking no more than 10 years prior to study entry. The study excluded persons who were unable to climb two flights of stairs; had a body weight of 140 kilograms or more; had a history of renal cancer, melanoma or breast cancer; had a history of lung cancer diagnosed less than five years ago; or had received a chest LDCT scan for any reason less than one year prior to enrolment. Approximately 85% of the participants were men. In the DLCST, the inclusion criterion for smoking is 20 or more pack-years. A former smoker had to have quit after 50 years of age and no more than 10 years prior to the study. Their lung function as expressed by the forced expiratory volume in 1 second had to be at least 30% of predicted normal. About 45% of the Danish participants were women.

The NELSON trial was launched in April 2004. Recruitment was completed in October 2005. The DLCST enrolment and randomization ran from October 2004 to March 2006. Details of the design and characteristics of the baseline population in the screened arm of the NELSON trial and the DLCST have

been reported.[54,80,81] The prevalence rate of lung cancer was 0.97% in the NELSON study and 0.8% in the DLCST. After ≥2 years of follow-up, 1.8% of the screened cohort was found to have lung cancer in the NELSON trial. In the DLCST trial, after 5 years of follow-up, 3.4 % of the participants were found to have lung cancer. The total number of lung cancers from the combined NELSON-Danish trials in the LDCT arm is 203 (World Conference on Lung Cancer, Amsterdam, July 7, 2011). It is uncertain if the number of lung cancer deaths will be sufficient to draw a definitive conclusion regarding the efficacy of LDCT screening in reducing lung cancer mortality by the target date of 2016.

Summary of Trials

Table 4: Summary of trials

Features	PLCO[70]	NLST[73,75]	NELSON[54,79,81,82]	DLCST[80]
Country	United States	United States	Netherlands, Belgium, plus Denmark	Denmark, in collaboration with the NELSON trial
STUDY POPULATION				
Underlying risk factors	Not an eligibility factor	30 pack-years cigarette smoking history; former smokers only if they quit within past 15 years	Current and former smokers with up to 10 years of cessation history; smoked either >15 cigarettes /day for >25 years or >10 cigarettes a day for >30 years	At least 20 pack-years
Age, gender	55–74 years, men and women	55–74 years, men and women	50–70 years, men and women	50–70 years, men and women
Source	Healthy volunteers in general population, recruitment using multiple strategies enhanced recruitment for minority populations from 10 centres in the United States	Healthy high-risk volunteers meeting the smoking criteria were recruited from 33 medical institutions across the United States via multiple strategies plus enhanced recruitment for minority populations	Healthy high-risk volunteers meeting the smoking criteria were invited from respondents to a population-based health questionnaire, which was administered to help plan selection criteria and necessary sample size	Healthy volunteers were enrolled from those responding to newspaper advertisements
Number randomized	154,942	53,454	15,822	4,104
STUDY GROUP				
Randomization	1993–2001	2002–2004	2003–2006	2004–2006
Study arms	Two-arm 1. CXR 2. Control	Two-arm 1. LDCT 2. CXR	Two-arm 1. LDCT 2. Control	Two-arm 1. LDCT 2. Control
Screening test	CXR	LDCT	LDCT	LDCT

Features	PLCO[70]	NLST[73,75]	NELSON[54,79,81,82]	DLCST[80]
evaluated				
Intervention arm	Baseline CXR; then three annual single-view CXRs	Baseline LDCT; then two annual LDCTs (26,722 participants)	Baseline LDCT; then three annual LDCTs	Baseline LDCT; then three annual LDCTs
Control arm	Usual care	Baseline CXR; then two annual CXRs (26,732 participants)	Usual care	Usual care
Power calculation assumptions	90% power to detect a 10% reduction in lung cancer mortality in the CXR arm compared with the control arm	90% power to detect a ≥20% mortality reduction in the LDCT arm compared with the CXR arm	80% power to show a ≥25% mortality reduction from lung cancer after 10 years (NELSON + DLCST)	80% power to show at least a 25% mortality reduction from lung cancer after 10 years (NELSON + DLCST)
Planned follow-up period/ endpoint year	13 years from randomization/2014	7 years from randomization/2011	10 years from randomization/2016	10 years from randomization/2016
Compliance with screening (intervention arm)	Baseline: 86.6% Round 1: 84.1% Round 2: 82.9% Round 3: 78.9%	Baseline: 98.5% Round 1: 94% Round 2: 92.9%		Baseline: 99.95%
Definition of an abnormal screen (positive screen)	Suspicious abnormalities included mass >3 cm or nodules <3 cm or infiltrate	≥4 mm	Positive: Solid component of nodule >500 mm^3 (>9.8 mm in diameter) Indeterminate: volume of the largest solid nodule or of the solid component of a partially solid nodule 50–to 500 mm^3 (4.6–9.8 mm in diameter) or if the diameter of a nonsolid nodule was >8 mm An indeterminate nodule with a volume-doubling time of less than 400 days on the three-month follow-up scan	Cat.3: 5–15 mm and not classified benign >15 mm and all growing nodules by 2.25% in volume Indeterminate: 5–15 mm

Features	PLCO[70]	NLST[73,75]	NELSON[54,79,81,82]	DLCST[80]
% positive screens	Baseline: 8.9% Round 1: 7.1% Round 2: 6.6% Round 3: 7.0%	Baseline: 27.3% Round 1: 27.9% Round 2: 16.8%	Baseline: 2.6% Round 1: 1.8%	Baseline: 8.7% (179/2,052)
False positive rate in screening arm	In terms of numbers screened: Baseline: 8.7% (5,845/67,084) Round 1: 7.0% (4,561/65,147) Round 2: 6.4% (4,095/64,218) Round 3: 9.0% (2,836/31,537) In terms of numbers positive at screen: Baseline: 98.0% (5,845/5,965) Round 1: 98.8% (4,561/4,614) Round 2: 98.5% (4,095/4,157) Round 3: 97.6% (2,836/2,907)	Baseline: 26.3% (6,923/26,314) Round 1: 27.2% (6,734/24,718) Round 2: 15.9% (3,843/24,104)	Baseline: 1.5% (116/7,557) Round 1: 1.0% (74/7,289)	In terms of numbers screened: Baseline: 7.9% (162/2,052) In terms of numbers positive at screen: Baseline: 90.5% (162/179)
Endpoints of Trial				
Primary	Lung cancer mortality	Lung cancer mortality	Lung cancer mortality	Lung cancer mortality
Secondary	• All-cause mortality • Incidence of lung cancer • Lung cancer case survival • Cancer stage distribution	• All-cause mortality • Lung cancer prevalence, incidence and interval cancers • Lung cancer case survival • Cancer stage distribution • Screening and treatment morbidity • Medical resource utilization (for positive screen)		• Overall mortality in each arm • No. of lung cancers in each arm • Five-year survival after diagnosis • Cancer stage distribution • Surgical resection rate • Effect on smoking behaviour • Frequency of false positives and psychosocial

Features	PLCO[70]	NLST[73,75]	NELSON[54,79,81,82]	DLCST[80]
				consequences • Health economic evaluations
RESULTS				
Lung cancer mortality		247,000/100,000 person years (LDCT) 309/100,000 person years (CXR) 20.0% reduction in LDCT arm compared with CXR arm 95% CI (6.8 to 26.7; P=0.004)	Pending	Pending
All-cause mortality		6.7% lower in LDCT arm compared with CXR arm 95% CI (1.2 to 13.6; P=0.02)	Pending	Pending

Risks and Benefits

Radiation Risks and Lung Cancer Screening

Ionizing radiation is a known carcinogen with an assumed linear dose-response relationship down to low levels of exposure.[34] Our environment contains multiple sources of natural radiation exposure that cannot be avoided. The average Canadian receives approximately 3 mSv of radiation exposure in the home environment each year. It is well known that age is the largest modifier of individual sensitivity to radiation, with children being most sensitive and older adults the least sensitive.

While the cancer-causing effects of high radiation dose are clear, the effects of low-level exposure, similar to that received from our environment, remain controversial in some circles.[77,83] The basis for the controversy rests on the difficulty in determining individual risk at radiation doses less than 100 mSv. A typical diagnostic CT scan delivers approximately 7 mSv (range 4 to 18 mSv), with a calculated radiation risk of approximately one fatal cancer in 2,000 exposed individuals.[84] *This radiation risk must be compared with the baseline risk of any cancer of approximately 500 fatal cancers per 2000 individuals.* Compared with the baseline risk of fatal cancer, the small amount of the radiation from an LDCT (~1.4 mSv or less) has made it very difficult to confidently measure its effects. Technical improvements in LDCT scanner technology, specifically in reconstruction algorithms and acquisition dose modulation techniques, make it likely that further dose reductions are possible while retaining diagnostic accuracy. In the absence of accurate data, the current evidence – extrapolated from higher dose exposures – suggests that when screening/medical radiation is used appropriately in those aged 50 years or older, the potential imaging benefit for individuals outweighs the small potential radiation risk.[38] However, it is an important factor in determining the risk to the population offered screening, as the large majority of those screened will not be found to have the disease.

Risks of Downstream Investigation for LDCT-Detected Lung Nodules

Diagnostic investigations may be performed for LDCT-detected lung nodules that turn out to be benign. These investigations may be non-invasive (e.g., repeat LDCT, PET/CT), minimally invasive (e.g., bronchoscopy), or moderately invasive (e.g., CT-guided fine needle aspiration or core biopsy, video-assisted thoracoscopy).[85] In a small proportion of cases, a major surgical procedure (thoracotomy and lung resection) is performed for lung nodules that turn out to be benign. The risk of any invasive procedure is estimated to be ~7%.[85] In the NLST study, for participants with a positive LDCT screen who did not turn out to have lung cancer, the probability of having an unnecessary diagnostic procedure or surgery was: 1.7% for bronchoscopy or transthoracic needle biopsy; and 0.96% for thoracotomy, thoracoscopy or mediastinoscopy. Major complication after a diagnostic procedure was 0.1% and death within 60 days after the most invasive diagnostic procedure was 0.035% among those who did not turn out to have lung cancer. Using volumetric measurements and a higher nodule size threshold for a positive test, the rate of any invasive procedure in the NELSON trial was 1.2% in round 1 and 0.8% in round two screening. The recall rate for repeat CT for indeterminate test result was 19% in round 1 and 3.8% in round 2.[54]

Incidental Findings

Other malignancies, such as breast cancer, lymphoma, thymoma and renal cell carcinoma, can be discovered by LDCT as an incidental finding. Common non-malignant findings include coronary artery calcification and emphysema. The implication of these incidental findings on health outcome needs to be defined in future research studies. In the NLST trial, there was a 6.9% (95%CI, 1.2 to 13.6; P=0.02) reduction in overall mortality but no significant reduction in all-cause mortality less deaths due to lung cancer. *However, there is currently no evidence-based guideline regarding management of non-malignant incidental findings such as coronary artery calcification nor specific interventions to prevent deaths due to*

cardiovascular disease or respiratory illness such as chronic obstructive pulmonary disease (the major causes of non-lung cancer deaths was not part of the NLST trial protocol).

Adoption into Public Health Practices

Policy

With the publication of the results of the NLST, policy-makers will likely be faced with demands by the public and some health care providers to provide publicly funded lung cancer screening services. The initial announcement of a significant reduction in mortality from the NLST in November 2010 resulted in the promotion of lung screening by various commercial interests (private health care services) in the United States and by various stakeholders. Some recommendations have not been confined to individuals with a smoking history of 30 or more pack-years, the population studied in the NLST.

Provincial program planners and policy-makers require clear key messages that can be used to respond to demands and inquiries that address the following areas: the potential benefit of screening and for which specific populations; the magnitude of the potential harms – including the likelihood of false positives and subsequent follow-up procedures required to complete the investigation of screen-detected nodules. If screening in certain subpopulations at increased risk is considered, there will need to be development of evidence-informed algorithms to manage the different categories of nodules that will be found on LDCT scans. There could be a large increase in demand for diagnostic services, given the high "abnormal screen" rate of lung LDCT scans, and capacity in the system may be an issue. Thus, specific monitoring and evaluation of screening and follow-up services utilization would need to be implemented. In addition, program planners and policy-makers will face ethical dilemmas in making decisions about lung cancer screening. The questions about what level of risk related to screening should be publicly funded, how to allocate program resources and give access to services in accordance with distributive justice, and other ethical considerations require further debate and clarification. The outcomes of these debates and cost-effectiveness analyses will shape lung cancer screening policies and programs in each jurisdiction.

Education

The results of the NLST will need to be communicated clearly to physicians and other health care providers in order to support their role in educating patients and the public. The initial release of results by the U.S. National Cancer Institute included advice to individuals who considered themselves at risk, and initiating a discussion with their doctors. The concept of informed decision-making will be important to address, to weigh the advantages of screening against the disadvantages and harms, including the cumulative radiation exposure from LDCT scans, unnecessary surgical and medical procedures for those with false positive screen results, and potential over-diagnosis of cancers that would not cause problems in an individual's lifetime. Treatment could result in reduced lung capacity, even post-operative mortality.

It will be important that any messages to the public and medical profession communicate the pros and cons of screening and what constitutes high risk. For example, the duration of smoking is more important than the number of cigarettes smoked a day, and other factors influence lung cancer risk, such as family history of lung cancer and co-existence of chronic obstructive pulmonary disease.

An additional educational need for the public is to ensure that the recommendation to stop smoking or not start smoking is given prominence in any screening information. The potential misunderstanding that a normal screening result or a negative investigation for an abnormal screening result means that there has been no harm from previous smoking and that the behaviour can be continued must be avoided. The significant benefits from stopping smoking to reduce the morbidity and mortality of heart, lung and other diseases need to be communicated effectively to the participants.

Resources

Screening requires the development of population penetration strategies, including but not limited to specialized experts working closely together as a team, for example:

- radiologists skilled in the interpretation of lung cancer screening LDCT scans, biopsy and localization of small lung nodules;
- respirologists and thoracic surgeons experienced in management of lung nodules;
- interventional pulmonologists skilled in diagnosis of peripheral lung lesions and staging of lung cancer using endoscopic ultrasound;
- surgeons skilled in the management of small lung nodules and lung cancer in general; and
- pathologists experienced with interpretation of small biopsy specimens.

Further development of screening would also require quality assurance programs for radiologists, medical physicists, medical technologists, picture archiving and communications specialists (PACS), and external evaluators. Some form of periodic external review of these quality assurance processes would be required with appropriate anonymized public disclosure to ensure transparency.

The Cancer Risk Management Model (CRMM),[86] initiated by the Canadian Partnership Against Cancer in 2008, is a decision-support web-based micro-simulation platform. The CRMM can project the potential disease burden, economic impact and cost-effectiveness of different cancer control interventions in Canada at the provincial and/or national level. Work is currently under way to enhance the existing lung cancer model with a screening component. The launch of the lung cancer screening module is planned for Fall 2011, and can be used to answer important questions such as:

- In comparison to the status quo, how would lung cancer incidence rates and stage distribution shift if provinces implement lung cancer screening using LDCT on heavy smokers? What is the relative proportion of population diagnosed at an early stage (specifically stage I–II NSCLC)?
- What additional resources would be needed (e.g., number of scans, diagnostic tests, surgeries, radiotherapy, chemotherapies) as a result of lung cancer screening with LDCT scan in the near and long terms?
- If a lung cancer screening strategy using LDCT scans proves to be effective, what would be the optimal implementation strategy (e.g., scan frequency, phase-in period, enrolment criteria) in relation to system capacity and cost-effectiveness measured by cost per cancer diagnosed by screening, cost per life-year saved, and cost per quality-adjusted life-year?
- Based on the sensitivity and specificity of LDCT scan, what would be the number of unnecessary diagnostic tests and surgeries as a result of lung cancer screening?
- What would be the additional life-years gained by incorporating screening with primary prevention strategies?

The Pan-Canadian Early Lung Cancer Detection Study sponsored by the Canadian Partnership Against Cancer and the Terry Fox Research Institute is active in eight centres across Canada and has provided a cadre of highly skilled experts. Radiologists, respirologists, surgeons, thoracic oncologists and lung pathologists knowledgeable in the detection and management of early lung cancer will be a source of expertise going forward.

In addition to human resources, facilities for screening, diagnosis and effective treatment should be considered. A clinical pathway from screening, diagnosis, treatment and follow-up, along with recommended standards, should be mapped out with ongoing quality assurance oversight.

Follow-up Investigation and Treatment

In the Canadian health care system LDCT scanners are widely available. Most regional hospitals have the technology to perform lung cancer screening with chest LDCT scans. The expertise to guide subsequent work-up of a screen-detected abnormality is not nearly as available. Patients with screen-detected nodules would therefore need to be referred to a centre that possesses the appropriate expertise, including:

- interventional thoracic radiology;
- interventional pulmonology;
- lung cytopathology;
- PET imaging; and
- thoracic surgery.

If lung cancer screening were to be adopted on a large scale, algorithms could potentially be developed whereby small, indeterminate nodules could be followed locally with clear recommendations regarding repeat scanning intervals and cases would only be sent to the thoracic referral centre if the nodule is suspicious of malignancy, because of growth or increased density. The management of screening and treatment requires the coordinated efforts of radiologists, thoracic surgeons, respirologists, radiation and medical oncologists. This would significantly decrease the number of referrals to the thoracic centre, thus cutting cost, travel and inconvenience to the patient.

Quality Control in Lung Cancer Screening

Currently, there is no publicly funded lung cancer screening taking place in Canada, aside from a small number of specific initiatives that have largely been research studies. If it is determined by health authorities in the provinces and territories that lung screening with LDCT scans in high-risk populations is appropriate, then guidelines, standards and quality monitoring will be necessary to ensure that the right individuals are being screened, at the right intervals, with high-quality and safe imaging techniques. In addition, quality screening depends on the provision of appropriate investigation and monitoring of nodules found during screening and this will also need quality monitoring processes.

LDCT Scans

The complex image acquisition, image transfer, qualitative and quantitative analysis, and final interpretation that make up the elements of lung cancer screening using LDCT requires a robust quality assurance mechanism. This mechanism would need to be developed and monitored by a team consisting of radiologists, medical physicists, technologists, computer network support personnel and PACS. Start-up and ongoing monitoring would need to focus on radiation dose (medical physics, technologists), acquisition image quality, lossless data transmission, image-viewing fidelity and diagnostic accuracy issues. This team would provide feedback during set-up and initial training, validation of diagnostic skills, and longitudinal evaluation of quality standards.

Accreditation programs similar to that for mammography, the Mammography Accreditation Program of the Canadian Association of Radiologists, would need to be considered to provide provincial and national monitoring of quality.

Reaching High-Risk Populations

The Canadian Partnership Against Cancer recently conducted a survey on colorectal cancer screening awareness in Canada and identified that a high percentage of the population (60%) are not aware that screening applies to the situation where no symptoms are present.[87] Furthermore, a large proportion of the population does not have an appropriate understanding of what a screening program is intended to accomplish. It is likely that screening messages can be more effectively communicated to well-educated individuals through use of the print and electronic media than to those with lesser education. In addition, it may be difficult to reach those whose primary language is not English or French, those who are mistrustful of the Canadian health care system, those who come from very different health care systems, and those who are socially disadvantaged. This is particularly true of new immigrant populations who tend to congregate with fellow immigrants and, through satellite connections, retain their connection to their homeland and its local media. These issues apply to all population-based screening programs but may present an even greater challenge with the potential introduction of lung cancer screening as described below.

The problem of introducing lung cancer screening is made more difficult by the fact that smoking and smoking-related diseases are increasingly a disease of those of lower socioeconomic status. Statistics clearly show that a greater proportion of college and university educated individuals in Canadian society have quit smoking leaving a predominance of lesser-educated individuals as today's smokers who may become future lung cancer patients.[88]

The wide variety of languages in use in Canada poses challenges to communicating the message of the benefit of any screening program. Educational materials for lung cancer screening will need to be created in multiple languages, using many different media that speak to the various cultures within Canada.

Reaching rural and remote populations is particularly challenging in Canada because of its size, especially in vast areas where the population is dispersed such as Canada's North. It is a challenge not only to reach these dispersed populations but also to facilitate access for these individuals to the screening tests.

Consideration should be given to using mobile LDCT scanners and telemedicine linkage to major screening centres for quality CT interpretation and recommendation for follow-up. Since interpretation of LDCT scans is a specialized segment of chest radiology, consideration of either teleradiology centralized reading of these studies or minimum yearly volume requirements for accreditation must be considered.

The Canadian Partnership Against Cancer's survey on colorectal cancer screening also identified that the patient's family physician needs to communicate the importance of the screening test if the individual is to comply. Therefore it will be important for family physicians to have an accurate summary of current evidence in order to appropriately advise their patients. If lung cancer screening is introduced on a population basis, it will be important to overcome the attitude of many physicians towards lung cancer, which is not infrequently that it is a disease brought on by the smokers' own behaviour. The stigma associated with smokers fails to recognize that approximately half of all lung cancers being seen in Canada today occur in those who have quit smoking.

For some populations, it has been observed that patients often do not attend the diagnostic tests required after a screen-detected abnormality for a variety of reasons, which include personal cost in time, travel and out-of-pocket expenses, lost income, and failure to understand the importance of the diagnostic procedures.[89] Therefore, an important aspect of introducing a new screening maneuver is to ensure that there is access to the diagnostic tests/procedures that are required if screening detects an abnormality.

Implications for Family Practice

If systematic screening is established, physicians will need to learn how to work with it, to encourage the right target groups to participate and be followed up properly, and to discuss the policy and its justification with those who are not eligible, whether by age, lower smoking level or co-morbidity.

Until now the general opinion has been that screening is not warranted, and may be harmful. There is a need, therefore, to inform family physicians in detail of what the findings mean so that they can explain the potential benefits and harm of lung cancer screening and treatment to their patients. People who are long-term smokers often have a series of health problems caused by smoking – heart disease, peripheral vascular disease and chronic obstructive pulmonary disease – and they are also at risk of dying from cancers in other organs. Combined, the risk of these health problems is greater than the risk for lung cancer alone. There is little point in detecting early lung cancer in a person who is unlikely to withstand the treatment. Thus it is crucial that family physicians have access to accurate ways of assessing risk[15,90] to help decide whether lung screening is worthwhile balancing against any co-morbidity in their patients.

Physicians require appropriate tools and educational materials to help their patients understand the complexities of the benefits and harms of lung cancer screening. They need to have prepared arguments ready to help their patients understand the relatively small value of this screening in reducing smoking-related disease, and the harms from not only the screening but also the follow-up procedures.

Knowledge Gaps, Research Needs and Future Considerations

Further research is required in a number of areas in lung cancer screening including: features that best define the optimal screening population, discrimination of benign versus malignant lung nodules, most efficient follow-up diagnostic and treatment pathways, and the optimal frequency and duration of screening. Evidence-based guidelines for treatment of small lung cancers using sub-anatomic resection or stereotactic body radiation versus conventional anatomic resection need to be established. More accurate tools to identify individuals at risk of lung cancer beyond age and smoking history are being developed.[15,90] These tools are being validated using data in randomized trials. The incremental value of biomarkers to risk assessment over and above what can be achieved with age and smoking data alone and for discriminating benign versus malignant lung nodules needs to be evaluated. Data from the British Columbia Lung Health Study and the Pan-Canadian Early Detection of Lung Cancer Study suggests lung function (spirometry) adds significantly to lung cancer risk prediction.[90,91] The refined lung cancer risk prediction model needs to be evaluated prospectively.

Cost-effective, widespread lung cancer screening might be best introduced in stages to ensure that adequate infrastructure is available and that quality assurance and performance can be evaluated, at least at a local level, allowing efficient troubleshooting of problems before screening is widely implemented. The data collected could then be used to model the effect of potential strategies, to facilitate the development of guidelines. Through its CRMM initiative, the Canadian Partnership Against Cancer will undertake refined mathematical modelling that will help provide additional information on risk versus benefit in Canada within the next year. Well-designed screening can also provide the opportunity for research, for example, on tobacco addiction and smoking cessation modifiers, as well as on lung cancer risk reduction through the use of chemoprevention or immunotherapy.

Appendix 1: NLST Estimation of Canadian Lung Cancer Deaths Preventable by LDCT Screening

Crude estimation of the potential number of lung cancer deaths preventable by LDCT screening in the Canadian population in one year by gender under ideal and simplified conditions*

Women					
A	B	C	D	E	F
Age strata (years)	**Canadian 2010 population†**	**Proportion meeting NLST criteria‡**	**Number meeting NLST screening criteria (columns B x C)**	**Lung cancer risk per 1 person-years‡**	**Number of lung cancers in 1 year (columns D x E)**
55–59	1,160,100	0.1188	137,820	0.0047493	655
60–64	1,003,700	0.1300	130,481	0.0056405	736
65–69	756,400	0.1150	86,986	0.0084786	738
70–74	585,000	0.0943	55,166	0.0136000	750
			Total lung cancers in women:		2,878
			5-year mortality if at 83%:		2,389
			Mortality reduction in women if at 20%:		**478**

Men					
A	B	C	D	E	F
Age strata (years)	**Canadian 2010 population†**	**Proportion meeting NLST criteria‡**	**Number meeting NLST screening criteria (columns B x C)**	**Lung cancer risk per 1 person-year‡**	**Number of lung cancers in 1 year (columns D x E)**
55–59	1,128,200	0.2184	246,399	0.0034836	858
60–64	965,000	0.2310	222,915	0.0065964	1,470
65–69	712,600	0.2127	151,570	0.0088858	1,347
70–74	519,500	0.1645	85,458	0.0111079	949
			Total lung cancers in men:		4,625
			5-year mortality if at 83%:		3,839
			Mortality reduction in men if at 20%:		**768**
			Total lung cancer deaths prevented in 1 year in men and women:		**1,246**

Abbreviations: LDCT, low-dose computed tomography; NLST, National Lung Screening Trial; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

* The age- and gender-specific proportion of individuals meeting the NLST criteria in the PLCO trial were applied to the age- and gender-specific Canadian population numbers to identify the number at risk. The age- and gender-specific lung cancer incidence rates observed in the PLCO trial for individuals at such risk were applied to estimate the number of lung cancers expected in each age-gender stratum. The Canadian five-year lung cancer survival proportions were estimated at 17% and the 20% lung cancer mortality reduction observed in the NLST was applied to obtain the number of lung cancer deaths potentially eliminated.

It is important to note that these are crude estimates that represent the highest numbers achievable and that the statistics used in the calculations come from two U.S. studies, the PLCO and NLST. The data in these studies may not apply in Canada. Also, the 20% reduction in lung cancer mortality observed in the NLST was achieved in an ideal clinical trial setting. Such high numbers are seldom achieved in a real world setting.

† Statistics Canada. Website: www.statscan.gc.ca. Last accessed May 14, 2011.

‡ Estimates are based on PLCO data.

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