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Evidence-Based Series #15-10

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-Risk Populations for Lung Cancer

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

Report Date: April 18, 2013

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Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development and External Review Process**

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Evidence-Based Series #15-10: Section 1

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Screening High-Risk Populations for Lung Cancer: Guideline Recommendations

H. Roberts, C. Walker-Dilks, K. Sivjee, Y. Ung, K. Yasufuku, A. Hey, N. Lewis, and the Lung Cancer Screening Guideline Development Group

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BACKGROUND

Lung Cancer and Screening

Lung cancer is the most common cause of cancer death in Ontario. Contributing to the high mortality rate is a lack of an effective evidence-based screening method. Utilizing the two tests commonly used to screen for lung cancer, chest radiography (CXR) and sputum cytology, has not demonstrated a reduction in mortality. Screening for lung cancer using low-dose computed tomography (LDCT) has been the subject of research studies since the 1990s (1-3). In the intervening years, much has been learned about the detection of lung nodules using LDCT, the characterization of early lung cancers, and, more recently, the effect of LDCT on disease-specific mortality. The National Lung Screening Trial (NLST) compared LDCT with CXR in high-risk populations and found a 20% reduction in lung cancer mortality at 6 years with LDCT after an initial scan and two annual rounds of screening (4). The NLST is the first randomized controlled trial (RCT) to show a mortality benefit with lung cancer screening.

Some knowledge gaps still exist regarding the use of LDCT for lung cancer screening including the balance of benefit and harm, the optimal group of at-risk individuals to screen, the frequency and duration of screening, and the cost-effectiveness across various health environments. Thus, LDCT screening is not yet part of the standard of care, and no formal process currently exists in Ontario for lung cancer screening. However, physicians and patients are aware of the technique, and it has begun to be used without official guidelines. Injudicious use of LDCT can potentially cause more harm than benefit, including exposure of healthy persons to ionizing radiation and subsequent invasive procedures for ultimately benign lesions. When used correctly, however, LDCT screening has the potential to save lives.

Population-based Screening Programs

CCO uses the following criteria in deciding whether or not to recommend to the government that a publicly funded, organized population-based screening program be implemented:

- Burden of disease
- Clinical effectiveness and safety of screening
    - Short-term benefits (effectiveness and safety) of screening should outweigh harms

    - Long-term benefits (effectiveness and safety) of screening should outweigh harms
- Screening tests are acceptable to individuals
- Cost effectiveness
- Resource availability (e.g., system capacity required to implement screening; system capacity required to support diagnostic testing for individuals with an abnormal screening test result; resources required to implement quality assurance for every component of the screening pathway)

Purpose of this Guideline

Guidelines on the appropriate use of LDCT for lung cancer screening are urgently needed for physicians and patients to avoid the ad hoc adoption of LDCT screening for lung cancer by hospitals and diagnostic centres and to minimize the risks associated with LDCT scanning (e.g., false positives leading to unnecessary invasive follow-up, overdiagnosis, and increased radiation exposure). This guideline focuses on clinical effectiveness and safety considerations. Specifically, this guideline provides advice on the use of LDCT screening for lung cancer, including the definition of a population at risk, the definition and follow-up of a positive scan result, and the duration and interval of screening. Beyond the scope of this guideline are several key issues, including: acceptability of LDCT to individuals, feasibility of implementing LDCT, cost-effectiveness of LDCT screening, an analysis of resource availability, high prevalence of lung nodules in the target population (high false-positive rate), and definition of a "positive" screening result. These and other issues will need to be addressed by CCO.

In the guideline development process, evidence from existing trials and guidelines from relevant organizations have been reviewed. Wherever possible, information collected has been applied to the Ontario environment. Where there are discrepancies in the literature (e.g., the definition of high risk), the panel arrived at a consensus. Where there is insufficient evidence in the literature (e.g., overall duration of screening), recommendations have been based on the Working Group's best judgement at the current time, and adjustments may be made when new evidence is available.

The supporting evidence for this guideline is primarily contained in a systematic review from a collaboration of the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network (5). Data from the original publications of the primary studies were extracted when details not reported in the systematic review were required to address specific questions in the current guideline.

GUIDELINE OBJECTIVES

To determine the appropriate use, if any, of LDCT in the screening of high-risk populations for lung cancer, including:

Patient considerations

- Patient characteristics that define a high-risk population

Test considerations

- The necessary elements involved in defining a positive result on LDCT and follow-up of a positive result
- The appropriate screening interval
- The appropriate screening duration

Structural considerations that affect effectiveness and safety

- Organized versus opportunistic screening

Recommendations

TARGET POPULATION

Men and women considered at high risk for lung cancer based on their age and smoking history.

INTENDED USERS

This guideline is intended for provincial policy makers, primary care physicians, nurse practitioners, radiologists, respirologists, thoracic surgeons, thoracic oncologists, and any health professionals involved with patients who may be at risk for developing lung cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Screening High-risk Populations for Lung Cancer:

The Working Group is in favour of screening high-risk individuals for lung cancer with LDCT. The primary evidence base for this proposal is the NLST, a large (>50,000 participants) RCT that compared LDCT screening with CXR and showed a 20% decrease in death from lung cancer in high-risk persons (4).

The primary benefit associated with LDCT screening is a statistically significant reduction in mortality, both lung cancer specific and all cause. LDCT can identify smaller nodules than can CXR and thus can detect lung cancer at an earlier stage when a cure is more possible. Under current circumstances, most lung cancer patients are diagnosed at an advanced stage, and lung cancer accounts for more than a quarter of all cancer deaths (6).

LDCT screening is not without risk. CT scanning, with its acquisition of multiple images, exposes an individual to a greater radiation dose than does CXR and may place patients at increased risk of lung and breast cancer. Based on models from official bodies and commissioned studies of estimates of harm from radiation, Bach et al estimate using the NLST data that one cancer death may be caused by radiation from imaging per 2500 persons screened (5). The serial CT scans required as part of a screening program necessitate judicious and efficient use of the technology with strict rules pertaining to quality control and training. The information obtained from a CT scan of the chest provides more precise visualization of lung nodules leading to a higher rate of detection of lung nodules. Although the majority of these nodules (>90%) will be benign, the detection of these nodules may lead to further imaging and follow-up that can involve invasive diagnostic procedures and possibly to harmful and unnecessary treatment. Completely addressing the clinical and cost implications of this high false-positive rate [e.g., in the NLST, 27% of scans were positive, and 96% of those were false positive (4)] is critical and remains a challenge. In the interim, the Working Group endorses a strict application of screening to only a high-risk targeted population.

In general, the recommendations below reflect the parameters of the NLST (4). Where there are deviations from those parameters, we provide justification. While there are still ongoing trials comparing LDCT with usual care, none are as large (and therefore as statistically powerful) as the NLST, and it is unlikely that another trial the size of the NLST will be undertaken. Some aspects of the ongoing trials may affect the recommendations once their results are known, and we have qualified our recommendations to acknowledge these uncertainties.

RECOMMENDATIONS AND SPECIFIC EVIDENCE

Main Recommendation

Recommendation 1: Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years* who currently smoke or have quit within the past 15 years and are disease free at the time of screening.

*Pack-years = number of cigarette packs smoked per day x the number of years smoked.

Key Evidence

- Among the studies in the collaborative review, the age for initiation of screening ranged from 47 to 60 years in the RCTs and from 40 to 60 years in the single-arm studies (5).
- The upper age for screening ranged from 69 to 80 years in the RCTs and 73 to 85 years in the single-arm studies (5). The NLST initiated screening in persons ≥55 years of age and stopped at age 75 years (4).
- The minimum smoking history in the RCTs ranged from ≥15 to ≥30 pack-years, and in the single-arm studies from ≥10 to ≥20 pack-years (5). The NLST enrolled persons with a smoking history of ≥30 pack-years and former smokers who had quit within the previous 15 years (4).
- Seven RCTs reported previous cancer history in the eligibility criteria, stipulating a minimum numbers of years disease free since a previous cancer diagnosis. These ranged from 5 years to an indefinite period with variations for different types of cancers. Among 11 single-arm studies, this criterion was described as a minimum of 5 years since a previous cancer diagnosis, any previous lung cancer, any known pulmonary metastases, and any previous cancer diagnosis (5). In the NLST, exclusion criteria were a previous diagnosis of lung cancer, a previous diagnosis of other cancer within the previous 5 years, chest CT scan within 18 months before enrollment, haemoptysis, or unexplained weight loss >6.8 kg in the preceding year (4).

Justification

- There is no evidence to support a specific age to initiate screening, a specific age to cease screening, or a specific screening-frequency interval. The highest quality and most compelling evidence is from the NLST. As such, the parameters used in this trial were endorsed by the Working Group as clinically reasonable. Patient acceptability, cost-effectiveness, feasibility, and system capacity may influence whether or not these parameters are reasonable and implementable.
- Smoking history is a subjective risk factor, and we acknowledge that it cannot be precisely measured. If smoking is begun in early adulthood (i.e., early 20s) as it commonly is, by age 50 to 55, most people will have exceeded 20 pack-years. Although the NLST enrolled participants with a minimum smoking history of 30 pack-years, several other studies used a threshold of 20 pack-years or less. These studies had lung cancer detection rates similar to those of the NLST. It is anticipated that an increased detection rate would lead to a mortality reduction. The Working Group agreed on a 30 pack-year smoking history threshold to recommend lung cancer screening, aligning with that study entry criterion in the NLST. The panel will update this recommendation when the results of the NELSON trial (which had a 15 pack-year requirement) are published.
- It is reasonable to define the screening population by age and smoking history, but there is currently insufficient evidence to include participants based on other risk

factors such as family history, passive smoking, occupational exposure, radon exposure, previous cancer, and other diseases.

Qualifying Statements

Screening may be a reasonable option in persons with a smoking history of <30 pack-years. However, as this risk group was not included in the NLST, an explicit recommendation in favour of screening such persons cannot be made at this time. A current trial (NELSON) includes patients with a minimum smoking history of 15 pack-years and may provide additional data to determine the minimum smoking history appropriate for screening.

Defining a Positive Result on LDCT and Follow-up of a Positive Result

Recommendation 2: Positive Result and Follow-up

- **Screening modality: Screening for lung cancer should be done using an LDCT multi-detector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv).**
- **Collimation should be ≤2.5 mm.**
- **Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy.**
- **Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). The Lung Cancer Diagnosis Pathway should be consulted for guidance on clinical work-up.**

Key Evidence

- Most of the studies published since 2008 used multi-detector CT scanners. The voltage ranged from 100 to 140 kVp, with all but one study using 120 to 140 kVp. The current ranged from 20 to 100 mAs, with all but one study not exceeding 60 mAs. The average effective dose was reported in 5 studies and ranged from 0.6 to 1.5 mSv (5). The NLST used multi-detector scanners with a minimum of 4 channels, 120 to 140 kVp, 20 to 30 mAs, and an average effective dose of 1.5 mSv (4).
- Among the studies, collimation ranged from 0.75 to 10 mm (5). Collimation in the NLST was ≤2.5 mm (4).
- Nodule size found on LDCT warranting further investigation ranged from a minimum size of any diameter to a maximum of >15 mm (5). In the NLST, nodules measuring ≥4 mm received further work-up (4).
- Nine studies defined tumour growth. Growth can be determined with calliper measurements of diameter (6 studies) or 3-dimensional volume measurements (4 studies). One RCT and one single-arm study described significant growth as an increase in tumour diameter of ≥1 mm. Three single-arm studies described significant growth as an increase in diameter in at least 1 dimension. Two RCTs described growth as a change in tumour volume of ≥25%. One single-arm study defined growing lesions as those with volume-doubling time between 30 and 400 days, and another used tumour volume and time between high-resolution CT scans to calculate doubling time (5). A definition of growth was not reported in the NLST.

Recommendations

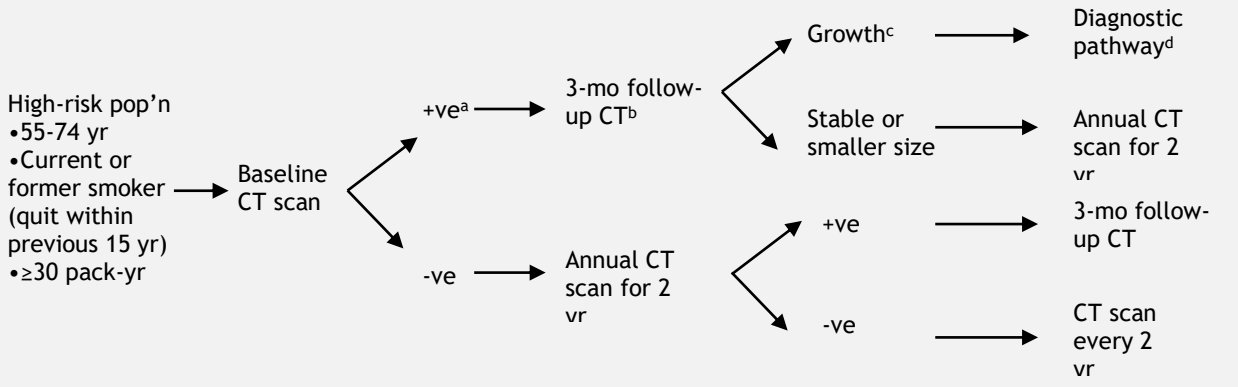
- Guidance on the presentation and clinical work-up of a lung cancer diagnosis is detailed in the CCO Lung Cancer Diagnosis Pathway (7).

Justification

- For screening modality, the parameters listed in the recommendations are derived from the NLST and ongoing studies.
- With respect to collimation, newer scanners are able to provide 1-mm collimation with a short breath-hold time, but a large amount of images are produced making scrolling and reading cumbersome. At the current time, the collimation used in the NLST is recommended.
- With respect to nodule size warranting further investigation, the recommendation deviates from the parameters of the NLST. In general, the smaller the nodule that defines a positive scan, the larger the number of positive scans, and the larger the number of false-positive results and unnecessary investigations for benign nodules. Based on a 4-mm threshold, 7191 of 26,309 (27.3%) scans in the NLST were positive; 6921 (96%) of the positive results were false positive. A 5-mm threshold will lower the rate of false-positive results, and if nodules between 4 and 5 mm are assessed on an annual scan, it is unlikely a significant finding will be missed. A prospective study of 1035 high-risk individuals found that nodules <5 mm identified by LDCT could be safely monitored at 1-year intervals (8). A retrospective study of two cohorts of patients (n=1000 and n=1897) determined that had no immediate attention been given to nodules between 3 and 5 mm until the first annual repeat screening, immediate further work-up would have been recommended in only 13% of patients rather than the 28% that received diagnostic interventions (9). Raising the threshold for a positive scan from a diameter of 4 mm to a diameter of 5 mm will help lower the false-positive rate without sacrificing the early detection of curable lung cancers. A recent study has suggested that increasing the threshold for a positive scan to 7 or 8 mm may decrease further work-up without delaying diagnosis (10). This will be revisited in future versions of this guideline when more information becomes available.
- The recommended follow-up is based on common standard of care actions in the presence of positive findings. Short-term follow-up CT scans are recommended in the event of a positive-screening CT scan to assess the growth of a parenchymal nodule. These CT scans do not need to cover the entire chest; it is sufficient to limit the scan to the location of a nodule (i.e., a slab of a few centimetres covering the location of the nodule). This can substantially decrease the radiation exposure to the patient.

LDCT Screening Interval

Recommendation 3: Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative (-ve) scan.



[a]A positive (+ve) test is defined as a solid nodule ≥5 mm or a non-solid nodule (part solid or ground glass) ≥8 mm.
[b]If the nodule appearance dictates a different approach (e.g., bronchoscopy or PET), this can be chosen at the discretion of the reading physician.
[c]Doubling time of between 30 and 400 days.
[d]Lung Cancer Diagnosis Pathway (7).

Key Evidence

- LDCT was done on an annual basis in 18 studies; on years 1, 2, and 4 in one study; every 6 months in one study; and after 2 years in one study (5). The NLST conducted LDCT screens annually for 3 years (4).
- The MILD trial did not demonstrate a shift to higher stage disease with biennial screening compared with annual screening. Of 49 lung cancers, 20 were detected in the biennial group and 29 in the annual group (11).

Justification

- The current evidence stems from research studies on lung cancer screening, which by definition have a beginning and an end (e.g., in the case of the NLST, three rounds of screening). This guideline, however, extends this evidence to a screening program, which does not have a defined end. The annual to biennial approach is based on best evidence balancing expected benefit from regular scanning with accumulated harms from costs, radiation, and burden on the health care system.
- The current evidence is not sufficient to confirm the benefit of a specific screening interval. The recommendation of annual screening for 3 years is subject to change when longer term trial evidence or further stratification methods become available from the NELSON trial.

Organized Versus Opportunistic Screening

The decision to implement an organized, population-based screening program involves many factors, not just the existence of supportive RCT clinical evidence. However, because the benefit of screening to date has only been demonstrated in the context of an organized screening effort (i.e., a randomized clinical trial that compared two types of screening

technology), it is the opinion of the Working Group that screening should be conducted in a manner similar to the NLST trial: that is, in an organized fashion. The ASCO guideline [(5) supplementary online content] also supports screening of high-risk individuals, but only in the settings that can deliver comprehensive care such as that provided to NLST participants. The NLST authors themselves advise restraint in contemplating lung cancer screening recommendations on the basis of the NLST findings claiming the need for rigorous analysis of the cost-effectiveness of LDCT, and the weighing of the reduction in mortality against the harms of positive screening results, overdiagnosis, and cost (4). However, we are aware that these issues would be examined by provincial policy makers before screening policy decisions were made and approved.

Because of the potential harms that may arise with LDCT screening done contrary to the recommendations above, a program is required that explicitly describes the target population that will benefit the most, the referral process, the frequency and duration of screening, the locations where screening may take place, the personnel involved in performing and interpreting the scans, and the precise criteria that define a positive scan. The inclusion of smoking-cessation counseling within the screening program is crucial. If elements of data collection and monitoring, quality assurance, and evaluation are built into the screening program from the start, it can be modified while in operation.

Opportunistic screening takes the form of CT scans applied to individuals who are asymptomatic, may not qualify for the test, or are referred on an ad hoc basis outside of a programmatic structure. These scans often include contrast, are not done with the low-dose technique, and lack appropriate follow-up of detected lung nodules. This type of screening results in unnecessarily high radiation to the individual, potential side effects from contrast, and invasive procedures for potentially benign lesions. The Working Group believes strongly that screening outside a centre with experience and expertise in identifying the high-risk population, interpreting results and counselling patients, and performing the appropriate diagnostic techniques is ill advised. Such ad hoc screening will lead to an increase in the false-positive rate and in peri-procedure morbidity and mortality, and will threaten to mitigate some or all of the benefits of the screening process.

Next Steps

The Lung Cancer Screening Working Group believes that the benefits of screening high-risk populations for lung cancer with LDCT outweigh the harms. The benefits stem from the documented improvement in mortality observed in the NLST showing that LDCT can not only detect small, early-stage lung cancers, but it can also facilitate curing an individual of lung cancer. The harms stem from the investigation itself (radiation exposure) and the sequelae from the false-positive results (detection of lung nodules that ultimately turn out to be benign), and the risk associated with diagnostic evaluation [in the NLST, the frequency of death within 60 days of a diagnostic evaluation was 8 per 10,000 individuals screened by LDCT and 5 per 10,000 screened by CXR (4)].

We address the concern over radiation exposure by recommending a low-dose regimen and by increasing the screening interval to every 2 years after three negative annual scans. We also suggest that the follow-up CT of a suspicious nodule be done as a limited scan to further reduce the radiation exposure.

We address the impact of false-positive results by the definition of a positive CT scan: we intentionally deviated from the parameters of the NLST in this instance. In the NLST, the threshold for a positive result was a nodule ≥4 mm in diameter. At baseline, >27% of the screening tests were positive and 96% of those were false-positive results. By increasing the threshold of a positive test to 5 mm, the rate of positive baseline scans can be reduced to

<20% while still detecting early-stage, curable lung cancers. We also recommend a follow-up algorithm of CT-detected nodules that is simple and straightforward based on size and growth, and results in an extremely low rate of invasive procedures for benign lesions (12).

Lung cancer screening with LDCT is recommended and can be most effectively and safely offered through an organized screening program and administered by specialized centres with multidisciplinary care teams.

To determine whether or not a population-based screening program is appropriate for Ontario will require the CCO Prevention and Cancer Control division to investigate the other criteria relevant to the decision-making process. Priorities include:

- Safety and effectiveness (long-term)
- Cost effectiveness
- Resources available

JOURNAL REFERENCE

A practice guideline has been published in the peer-reviewed journal, *Journal of Thoracic Oncology* (http://journals.lww.com/jto/pages/default.aspx):

- Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, et al. Screening high-risk populations for lung cancer: guideline recommendations. J Thorac Oncol. 2013 Oct;8(10):1232-7.

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