

Protocol: Screening for Lung Cancer

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Section I. Purpose and Background

This report will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to inform an update of its 2003 guidelines on screening adults for lung cancer.¹ This systematic review synthesizes the benefits and harms of lung cancer screening in average and high risk asymptomatic adults and answers a number of contextual questions that consider issues including test properties and performance and participants' preferences regarding screening for lung cancer.

Definition

Lung cancer is a form of cell malignancy that begins in the lungs. Non-small cell lung cancers [(NSCLC) e.g., adenocarcinoma, squamous cell carcinoma, or large cell carcinoma] are the most common sub-types of the disease; more rarely diagnosed are the faster-growing small cell lung cancers (e.g., small cell carcinoma, mixed small cell/large cell, or combined small cell carcinoma).^{2, 3} This review deals primarily with the NSCLCs.

Prevalence and Burden of Lung Cancer

Lung cancer is estimated to be the most commonly diagnosed form of cancer in Canada (estimated 25,500 new cases in 2013) as well as the main cause of cancer related mortality among Canadians (estimated 20,200 deaths attributed to lung cancer in 2013).⁴ Almost all (97%) of the estimated new cases of lung cancer in 2013 are expected to be identified in adults aged 50 years and older.⁴ For the same year, the age-standardized incidence rate of lung cancer in men is estimated at 60.1 cases per 100,000 compared with 46.8 cases per 100,000 in women.⁴ While the incidence rate is currently higher in men than women, the rate for men became stable about 30 years ago (approximately 20 years after a reduction in smoking prevalence among men) and has been showing a significant ($P < 0.01$) annual decrease since the late 1990s; whereas the incidence rate for women has been increasing steadily ($P < 0.01$) and has not yet reached a similar plateau following a general decline in tobacco consumption in the mid-1980s.⁵ Lung cancer has a poor prognosis and the five-year relative survival ratio is among the lowest for all types of cancer in Canada (17% in 2013).⁴

Risk Factors

Cigarette smoking is the main risk factor for developing lung cancer, and is associated with over 85% of the cases of this disease in Canada.⁶ The *Canadian Tobacco Use Monitoring Survey* reported 44% of adults (4.6 million Canadians) were current or ever smokers (16% are current smokers) in 2012.⁷ Other factors that increase risk for lung cancer include second hand exposure to cigarette smoke, exposure to radon and other toxic substances (e.g., asbestos, arsenic, diesel exhaust, silica, and chromium), having a first degree relative with lung cancer, and undergoing radiation therapy to the chest.^{6, 8}

Section II. Previous CTFPHC Recommendations and Recommendations from Other Guideline Developers

Updating its 1994 guidelines on lung cancer screening, in 2003 the CTFPHC determined that there was fair evidence upon which to recommend against using CXR to screen asymptomatic individuals for lung cancer, and insufficient evidence to inform a recommendation for or against using LDCT as a screening test for asymptomatic adults.¹ Ten years ago (2004), the United States Preventive Services Task Force (USPSTF) concluded there was insufficient evidence to recommend for or against screening asymptomatic persons for lung cancer using either CXR or LDCT.⁹ Newly published mortality results from the NLST appear to have convinced guideline groups across North America to rethink their recommendations regarding lung cancer screening.¹⁰ The USPSTF's recently (2013) updated recommendation now endorses annual screening using LDCT for older adults (aged 55 to 80 years) who are current or former (quit within last 15 years) smokers with a minimum 30 pack-year smoking history (one pack=20 cigarettes; pack-year=daily consumption of one pack per day for one year; smoking two packs per day for one year would count as two pack-years).¹¹ Lung cancer screening using LDCT for similar high risk groups is also currently recommended by several other US organizations including the American Cancer Society,¹² the American College of Chest Physicians,¹³ the American Lung Association,¹⁴ the American Association for Thoracic Surgery,¹⁵ and the National Comprehensive Cancer Network.¹⁶ Likewise, in 2013 Cancer Care Ontario issued new guidelines recommending the use of LDCT to screen asymptomatic high risk adults for lung cancer.¹⁷

Section III. Scan of New Evidence since Previous Recommendation

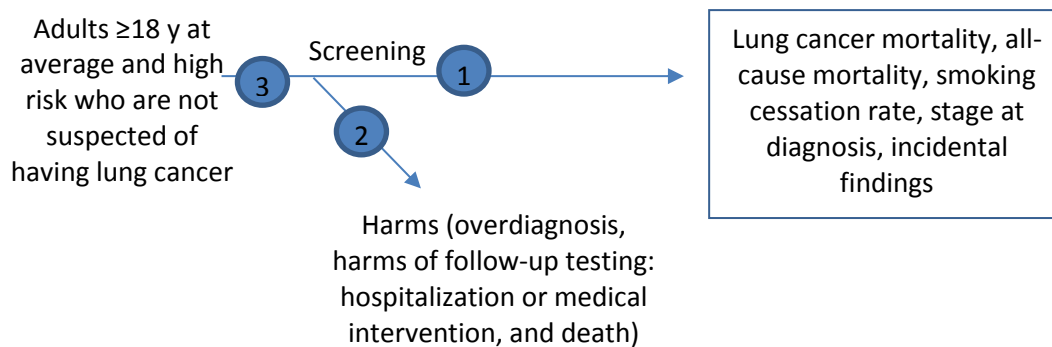
Results from the NLST trial were first published in 2011.¹⁰ This trial compared screening with LDCT to screening with CXR in a sample of high risk men and showed a 20% relative reduction in lung cancer mortality for LDCT over a median follow-up of 6.5 years.¹⁰ Several other lung cancer screening trials are underway and have published preliminary results for LDCT testing, although they have not shown the same mortality benefit as observed by the NLST.¹⁸⁻²⁴ Systematic reviews on the benefits of screening for lung cancer using LDCT have been published, including a 2013 Cochrane Review²⁵ and the systematic review that supported the most recent USPSTF recommendation.²⁶

Section IV. Review Approach

This review incorporates studies included in the 2013 Cochrane²⁵ and USPSTF²⁶ reviews on this same topic, and updates the search for benefits of lung cancer screening conducted for the 2013 Cochrane review.²⁵ A new search was conducted for harms of lung cancer screening to ensure all literature reporting harms ranked as critical would be identified. The review was

developed, conducted and prepared according to the CTFPHC methods (<http://canadiantaskforce.ca/methods/methods-manual/>). The protocol was registered with the International Prospective Registry of Systematic Reviews (PROSPERO #CRD42014009984).

Analytic Framework and Key Questions



Key Questions

1. What is the clinical benefit¹ of screening for lung cancer in adults not suspected of having lung cancer?
 - a. What is the difference in screening effectiveness in populations and subgroups with varying risk for lung cancer?
2. What are the harms of screening for lung cancer in adults not suspected of having lung cancer?
 - a. What is the difference in harms in populations and subgroups with varying risk for lung cancer?

Contextual Questions

1. What is the evidence that test characteristics for effective lung cancer screening tests (sensitivity and specificity, false positives and false negatives, and negative and positive predictive values, and test positivity rate) differ by subgroups with varying risk for lung cancer?
2. What is the difference in test performance with changes and improvements in low-dose computed tomography technology or varying protocols used by radiologists?
3. What are patient values and preferences on screening for lung cancer?
4. What is the optimal screening interval for screening for lung cancer?
5. What risk assessment tools are identified in the literature to assess the risk of lung cancer?
6. What is the evidence that subgroups have a higher burden of disease, a differential treatment response, differential performance of screening tests, or barriers to implementation? ? Subgroups include: Aboriginal populations, rural or remote populations, or other ethnic populations.
7. What is the cost-effectiveness of screening for lung cancer?

¹ Lung cancer mortality, all-cause mortality, smoking cessation rates, stage at diagnosis

Sub-group Analysis

The systematic review will include all adults 18 years of age and older from all risk categories. Although lung cancer incidence increases with age and the majority of cases are in adults 50 years of age and older,⁴ all adults will be included to ensure no literature is omitted. Subgroup analysis by age will help determine the most appropriate age for screening if applicable. The subgroup of gender will also be analyzed separately. In addition, subgroup analysis will be conducted on the varying risk profiles to aid in determining the most appropriate population for screening. Smoking history, including number of pack-years, number of years smoking, and the length of time since quitting in former smokers, will be considered. All-cause mortality and lung cancer mortality will be the outcomes assessed by the subgroups.

Literature Search

The literature search will be based on the search done for the 2013 Cochrane review on screening for lung cancer.²⁵ The Cochrane review searched CENTRAL, MEDLINE, PREMEDLINE, and EMBASE up to May 2012. An updated search from May 2012 will be done using the same databases and search terms as the Cochrane review. Studies identified in the Cochrane review will be retrieved, data extracted, and included in GRADE tables. For harms of screening, a new search will be conducted for randomized controlled trials and observational studies. CENTRAL, MEDLINE, PREMEDLINE, and EMBASE will be searched from 2000 to present for harms of screening for lung cancer. The search strategy is reported in the Cochrane review and will be identical, with the exception of harms. For the harms search, no limitations will be placed on study design.

Analysis plan

KQ1. Benefits of screening

The benefits of screening for the outcomes that were ranked as critical by the working group (lung cancer mortality, all-cause mortality) will be presented in GRADE tables for each of the tests (one line for each of the identified tests, test versus no screen comparison group). GRADE tables are not prepared for the outcomes ranked as important. Extracted data will be meta-analyzed when appropriate. To complete GRADE, all studies will be assessed for risk of bias (using the Cochrane risk of bias [RoB] tool), and for directness, precision, consistency, and publication bias. There will be no GRADE tables prepared for the important outcomes, but these data will be extracted and presented narratively with Cochrane risk of bias and meta-analysis when appropriate.

Comparisons will be made between tests where data allows, and therefore additional GRADE tables comparing the tests on any of the 2 critical outcomes will be prepared.

KQ1a. Screening benefits subgroups

The subgroups of age and gender will be analyzed separately. In addition, subgroup analysis will be conducted on the varying risk profiles to aid in determining the most appropriate population for

screening. Smoking history, including number of pack-years, number of years smoking, and the length of time since quitting in former smokers, will be considered as candidate stratification variables. All-cause mortality and lung cancer mortality will be the outcomes assessed by the subgroups. Subgroup analysis will not be presented in GRADE.

KQ2. Harms of screening or follow-up tests

We will provide GRADE tables for the harms of the screening tests that the working group ranked as critical (overdiagnosis, death from follow-up tests, or hospitalization/medical intervention from follow-up tests). GRADE tables are not prepared for the harms ranked as important. Extracted data will be meta-analyzed when appropriate. Since there is no tool to assess RoB in non-controlled observational studies, these will be assessed as very low quality.

For the outcomes ranked as important (consequences of false positives and incidental findings, anxiety, quality of life, infection from follow-up testing, and bleeding from follow-up testing), we will provide a risk of bias, extract data and meta-analyze when appropriate. There will be no GRADE tables for these outcomes.

KQ2a. Screening harms subgroups

The subgroups of age and gender will be analyzed separately. In addition, subgroup analysis will be conducted on the varying risk profiles to aid in determining the most appropriate population for screening. Smoking history, including number of pack-years, number of years smoking, and the length of time since quitting in former smokers, will be considered.

Data Analysis:

- For benefits of lung cancer screening (disease-specific mortality and all-cause mortality), the number of events, proportion, or percentage data will be used to generate the summary measures of effect in the form of risk ratio (RR) using the DerSimonian and Laird random effects models with inverse variance method for weighting the data.

For harms of lung cancer screening and follow-up tests with binary outcomes such as hospitalization or medical intervention, bleeding, death, consequences of false-positives (eg: overtreatment), negative consequences of incidental findings (eg: COPD), and infections, the number of events, proportion or percentage data will be used to generate the summary measures of effect using the DerSimonian and Laird random effects models with inverse variance methods. The binomial confidence intervals for each proportion/rate will be calculated using “Wilson score interval” method.²⁷

- For continuous outcomes of harms of lung cancer screening such as anxiety and quality of life, the results will be synthesized descriptively using median with range.

The Cochran’s Q ($\alpha=0.05$) and I^2 statistic will be employed to quantify the statistical heterogeneity between studies, where $p<0.05$ indicates a high level of statistical heterogeneity between studies.²⁸

Table 1: GRADE table for each screen (Low dose computed tomography, chest x-ray, or sputum cytology)

Outcome	Type	Summary measure of Effect
Lung cancer Mortality	Events / Binary	Risk ratio (RR)
All-Cause Mortality	Events / Binary	Risk ratio (RR)
Harms		
Harms - Overdiagnosis	Proportion/percentage	Pooled Effect size
Harms from follow-up tests		
Hospitalization or medical intervention	Proportion/rates	Pooled Effect size
Death	Proportion/rates	Pooled Effect size

Table 2: Inclusion and Exclusion Criteria (GRADE rating)

	INCLUSION	EXCLUSION
Population	Adults ≥18 years of average risk and high risk who are not suspected of having lung cancer (e.g. may have a cough); includes current, former, and second-hand smokers; as well as those with exposures to substances that may affect risk, as well as other identified factors that may increase risk	Adults ≥18 years suspected of having lung cancer or previously diagnosed with lung cancer; individuals under the age of 18 years
Intervention	Low dose computed tomography, chest x-ray, or sputum cytology	
Comparator	No screening, studies that compare two or more screening tests	Studies with no comparator except for the harms studies which might not have a comparison group
Patient-important Outcomes (GRADE RANKING)	All-cause mortality (9) Lung cancer mortality (9) Smoking cessation rate (6) Stage at diagnosis (6) Incidental findings (such as diagnosis of a thoracic aneurysm; 6)	
Harms (GRADE RANKING)	Overdiagnosis (9) Death from follow-up testing (9) Hospitalization or medical intervention (such as emergency room visits) from follow-up testing (7) False positives and consequences (e.g. overtreatment; 6)	

	Negative consequences of incidental findings (such as diagnosis of COPD;6) Anxiety (5) Quality of life (5) Infection from follow-up testing (5) Bleeding from follow-up testing (5)	
Study design	RCTs for screening benefits Any quantitative study for harms	case-controls, case series and ecological

GRADE rating: 7-9 = critical; 4-6 = important; 1-3 = not important (thus, not included in table)

Section V. Planned Schedule and Timeline

- Draft Protocol: March 2014
- Final Protocol: May 2014
- Draft Evidence Review: September 2014
- Final Evidence Review: January 2015
- Draft Recommendation Statement: January 2015
- Published Recommendation Statement: June 2015

Literature will be updated 6 weeks prior to publication to ensure that the recommendations include all relevant data. In addition authors of key studies will be contacted to determine if they are planning to release data on their trials in the immediate future.

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