

Screening for Lung Cancer: Updated Recommendations from the Canadian Task Force on Preventive Health Care

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ABSTRACT

Objectives: This review updates the 1994 recommendations of the Canadian Task Force on Preventive Health Care for lung cancer screening.

Options: Effectiveness was reviewed for chest radiographic examination and spiral computed tomography (CT) scanning.

Outcomes: Mortality from lung cancer was the main outcome considered.

Evidence: MEDLINE and Cochrane databases were searched for articles indexed under the MeSH terms “lung neoplasms”, “mass screening”, “case-control studies”, “tomograph, x-ray computed”, “diagnosis” and/or the text words “helical CT”, “low-dose CT”, “spiral CT”. The search was limited to controlled trials or diagnostic studies involving adult human subjects and published in the English language between the years 1990 and July 2002.

Benefits, harms and costs: Lung cancer is the most common cause of cancer deaths among both men and women. It is largely, but not solely, attributable to smoking. Approximately 70% of lung cancer cases have mediastinal or distant metastases at presentation. Potential benefits of screening include increased rates of detection and decreased mortality from cancer. Potential harms of screening include false-positive and false-negative test results.

Values: The strength of evidence was evaluated using the evidence-based methods of the Canadian Task Force on Preventive Health Care.

Recommendations:

- The CTFPHC concludes that there is **fair** evidence to recommend against screening asymptomatic people for lung cancer using chest radiographic examination. (**D recommendation**).
- The CTFPHC concludes that there is **insufficient** evidence (in quantity and/or quality) to make a recommendation as to whether spiral CT scanning should be used for screening asymptomatic people for lung cancer. However, other factors may influence decision-making. (**I recommendation**).

Because few cancers have such an identifiable and preventable risk factor, it is advised that patients should stop smoking.

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Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

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BACKGROUND

Burden of Illness

In response to a call for reconsideration of existing lung cancer screening recommendations,¹ the Canadian Task Force on Preventive Health Care (CTFPHC) agreed at its June 2000 meeting to evaluate new evidence that might have an impact on the 1993 grade D recommendation against routine screening for lung cancer.²

Lung cancer kills more people in North America annually than breast, prostate and colon cancer combined.³ It is largely, but not solely, attributable to smoking. It is the most common cause of cancer deaths among both men and women. Approximately 70% of lung cancer cases have mediastinal or distant metastases at presentation.⁴ The prognosis of these late stage cancers is abysmal. Most cases of early stage, resectable lung cancer are detected incidentally on a chest radiographic examination (CXR), which is usually done for reasons other than screening (eg. preoperative risk stratification). Currently it is only resectability that offers a chance of cure and long-term survival. The large burden of illness, earlier detection of lesions by testing, and better prognosis associated with resectability are compelling reasons to consider screening in lung cancer.

Rationale for Reconsidering Screening

In the last few years, new literature has been published on spiral computed tomography (CT), cited as a more sensitive tool for detection of early lung cancer. Additionally, the results from new case-control studies of screening projects in Japan have been described. Updates of earlier RCTs have provided long-term survival data, and new randomized trials of screening are planned or underway, but results will not be available until the next decade.⁵

The purpose of this document was to systematically review publications on lung cancer screening in smokers since 1990, and reconsider earlier CTFPHC recommendations.²

METHODS

The MEDLINE and Cochrane databases were searched for articles indexed under the Medical Subject Headings ‘lung neoplasms’, ‘mass screening’, ‘case-control studies’, ‘tomography, x-ray computed’, and / or ‘diagnosis’. The text words ‘helical CT’, ‘low-dose CT’, or ‘spiral CT’ were also used as to identify relevant publications. The search was limited to controlled trials or diagnostic studies involving adult human subjects and published in the English language between the years 1990 and July 2002.

The two principal authors independently reviewed all articles. Publications that were not relevant to lung cancer screening or diagnosis were excluded from further consideration. Also excluded were review articles, case-cohort studies, retrospective autopsy-based studies, and cost-effective analyses. Radiologic studies that were done for purposes other than screening for or diagnosing lung cancer were excluded. Finally, studies that investigated the technical aspects of computed tomography as they relate to lung cancer screening were excluded.

The evidence was critically appraised and recommendations deliberated and finalized using the evidence-based methods of the CTFPHC (see Appendix 1).

RESULTS

The Cochrane database search generated one relevant article for review.⁷ The MEDLINE search identified 2 updates of RCTs not captured by the Cochrane review.^{8,9} as well as 5 case-control studies of lung cancer screening, all from Japan.¹⁰⁻¹⁴ Lastly, 3 studies of CT scanning as a screening test were identified. Some of these were serial publications of the same subjects.¹⁵⁻¹⁹ All studies retrieved are summarized in Table 1.

Updated RCTs

The Mayo Lung Project, Czechoslovakian study, Kaiser Permanente Multiphasic Evaluation study, Johns Hopkins Lung Project and the Memorial Sloan Kettering Study represent the most recent RCTs examining lung cancer screening. These trials were included in the Cochrane review of screening for lung cancer that identified 7 controlled trials, six of which were randomized.⁷ The review used pre-specified criteria to rate the quality of design issues

such as concealment, randomization, blinding of outcome assessment and description of withdrawals and dropouts. For studies that compared more intense CXR screening with less intense screening, pooled analysis revealed a non-significant increase in lung cancer mortality (RR 1.11; 95% CI, 0.95-1.31). Within the Cochrane review, a pooled analysis of the Memorial Sloan Kettering and Johns Hopkins studies, which compared annual CXRs plus quarterly sputum cytology to annual CXR, showed a non-significant trend towards mortality reduction (RR 0.88; 95% CI, 0.74-1.03).

Recently reported data from the prolonged follow-up of the Mayo Lung Project⁹ and Czech studies⁸ revealed significantly greater mortality from lung cancer in the more frequent CXR screening group (RR 1.11; 95% CI, 1.00-1.23, p=0.05).

Case-Control Studies

The case-control studies considered in this review were all conducted in Japan in areas where population-based or, in the case of the Kanagawa study, clinic-based lung cancer screening programs had been offered for years. Together, these studies examined 1380 cases of lung cancer deaths compared to 8025 age-, sex- and district-matched controls.¹⁰⁻¹⁴ Additionally, 3 studies matched controls for smoking history.¹²⁻¹⁴ The quality ratings and study characteristics are described in Appendix 2. All the studies were rated as “fair” quality due to ambiguity regarding case ascertainment, with high rates of uncertain pathology within studies (8%-27%), and lack of correction for common screening biases. Additionally, these studies may have suffered from publication bias, with negative Japanese studies being at risk of not finding their way into the English language literature.

The results of these studies are provided in Table 2. Four of the five studies demonstrated a reduction in the smoking-adjusted odds ratio of dying from lung cancer (screened versus unscreened) for those screened 0-12 months before diagnosis (ORs 0.40-0.54).^{10-12,14} One study¹³ did not find a significant benefit associated with screening, although the point estimate OR was reduced (0.72; 95% CI, 0.50-1.03), and a benefit was found from screening in women within 12 months (OR 0.42; 0.20-0.87). The study of Okamoto et al. found that screening was more effective in adenocarcinoma and peripheral lung cancers.¹¹ They detected a higher fatal adenocarcinoma rate (40%) than most western countries (11%). One postulated reason for

improved screening effectiveness in this type of cancer is the apparent slower growth rate than squamous cancers (reported in this study with a prevalence of 34% in Japan, 48% in Germany).

Diagnostic Studies

We identified three separate studies of spiral CT scanning for lung cancer screening.¹⁵⁻¹⁹ In 1999, the Early Lung Cancer Action Project (ELCAP) published initial results from screening for lung cancer with spiral CT.¹⁵ The population consisted of 1,000 community-based volunteers ≥ 60 y of age with a ≥ 10 pack-year smoking history, but no history of cancer. Forty-six percent were female. All participants received both spiral CT and CXR. The presence of non-calcified nodules constituted a “positive” scan, and these patients followed a diagnostic protocol ranging from watchful waiting to high-resolution CT and eventual biopsy, depending on how many nodules were present, whether they were pre-existent and how large they were. The findings of this study are detailed in Table 3. This study used a standardized scoring system and calculated the kappa for radiologic interpretation of screen scans to be excellent (0.91; 95% CI, 0.88-0.94). More non-calcified lung nodules were detected by CT scan than CXR (23% versus 7%), and more cancers were detected overall by CT (2.7% versus 0.7%). Of the cancers detected by CT, 81% were stage 1A or 1B, suggesting a stage shift as compared to CXR (57%). Repeat screening at an interval of 6-18 months showed 30 positive screens (2.3%).¹⁶ Of these, 12 “nodules” resolved, and 2 individuals died of unrelated causes. Of the remaining 16, 8 nodules grew, prompting biopsy. Seven biopsies showed cancer, leading to a follow-up screen detection rate of 0.6%. Five of these were early-stage cancer. However, a shift to detection of early-stage cancers does not necessarily translate into a survival benefit, as demonstrated in the Mayo Lung Project.⁹ Prevalence screens are especially prone to detecting slower growing lesions, which may not be the ones that account for most of the mortality of the disease (over diagnosis bias). This uncontrolled trial did not compare screened to unscreened individuals and did not measure mortality or morbidity, precluding any conclusions about the benefit of spiral CT in screening for lung cancer.

Sone et al. reported results of serial low dose spiral CT scanning on 5,483 volunteers aged 40–74 years from the general population of Nagano prefecture in Japan.^{17,18} Radiologists interpreted the scans using a non-specified grading protocol, and classified scans into 7

categories. “Positive” scans included the categories “probable cancer”, “possible cancer” and “small nodule, <3mm”. Individuals with positive scans underwent a diagnostic work up that included CXR and high resolution CT, and biopsy as needed. Indeterminate lesions were re-scanned every few months and biopsied as necessary.

Approximately 46% of the scans were done on women and 54% of those scanned were life-time non-smokers. The scans were done for 3 consecutive years, with fewer of the original cohort scanned every year. Of the 5483 scanned initially, 279 (5.1%) had positive nodules, with follow up screens detecting 3.9% and 3.5% respectively. Twenty-nine patients underwent surgery for suspicious lesions, and 22 of these had cancer, resulting in an overall cancer detection rate of 0.40% (95% CI, 0.23%-0.57%). The authors partially report how many patients with negative scans subsequently went on to develop cancer, suggesting a sensitivity of 55% in 1996, and 83% in 1997. Considering only 71% of patients had all 3 scans, true interpretation of sensitivity remains impossible. CT was able to pick up many more small lung nodules (21/60 were < 10mm). Interestingly, non-smokers had a similar cancer incidence to smokers. It should be noted that the rate of adenocarcinoma was very high in this population (85%), probably due to the high proportion of women and non-smokers in the study. These populations had a much lower cancer detection rate on subsequent CT scans, suggesting that these cancers have slower growth than the prevalent North American histology of squamous cell cancer.³

Diederich et al. reported only rates of detection of cancer among “more than 700 smokers”.¹⁹ Employing low dose spiral CT of the chest, <3% of scans were “positive”; that is, met the criterion of a >10mm soft tissue density. Eight of 700 scans were confirmed to be cancer (1%). In the absence of any report about the population, the significance of the detection rates are unclear.

Adverse Effects of Screening

In the ELCAP study, 50% of positive CXR were not suspicious for cancer on spiral CT and, from RCTs, even suspicious CXRs are often false positives after diagnostic workup (positive predictive values ranging from 41%-60%).⁷ Nevertheless, spiral CT picks up many more lesions, and 90-92% of “positive” CT scans turn out not to be cancerous.^{15,17} These patients are exposed not only to radiation, but also to the anxiety and risks involved in having a

suspicious finding confirmed by invasive diagnostic procedures. The biopsy rate for spiral CT ranges from 11-12%,^{15,18} 24-26% of which prove to be non-cancerous.^{15,18} Sone et al. report that 18 CT scans were either falsely read as negative (16) or did not pick up a cancer detected by sputum cytology (1), leading to a false negative rate of 45% of spiral CT.¹⁸ Henschke et al. did not report follow-up data for patients with negative CT scans, making it impossible to determine the false negative results and to make accurate sensitivity calculations.¹⁵ False negatives carry with them a false reassurance and a risk that the patient will be less motivated to quit smoking.

Recent publications

Since the Task Force reached consensus on the final recommendations in October 2002, several new spiral CT studies have been published.²⁰⁻²⁴ The strength of the evidence in these publications is similar to that reviewed above: uncontrolled diagnostic studies showing that CT scanning carries improved sensitivity over chest x-ray as a screening modality for lung cancer. There have been no new prospective, controlled studies that investigate the effect of screening for lung cancer on survival. Since the findings of the recently published studies are not of a sufficiently strong level of evidence to change the conclusions of this review, the recently published evidence was not presented to the CTF for reconsideration of recommendations, and is not reviewed in detail here.

INTERPRETATION

Summary of Key Evidence

In order for screening to be considered effective, there must be evidence not only of earlier diagnosis, but also of delayed outcomes (such as illness and death). A randomized trial demonstrating effectiveness should show more asymptomatic, early resectable cancers detected in a screened population as compared to a control population. Later in the trial, the “unscreened” cancers should develop and become clinically apparent in the control group. This would result in a greater number of later stage cancers in the control group.

The negative results of the randomized trials have been debated at length in the literature. Hopeful reassessments of long-term results have still failed to reveal a mortality benefit. It

should be stressed that no RCT examined screening versus no screening; all looked at more intensive versus less intensive screening strategies. These “inappropriate” controls may have diluted a potential benefit of screening.

Spiral CT scanning provides the hope of a more sensitive screening test than CXR, and prospective studies have demonstrated an improved detection of smaller lesions. However, it is unclear whether improved detection will lead to improved mortality. RCTs of lung cancer screening have demonstrated that, while screening detected more early stage cancers and resulted in improved 5-year survival, it did not improve mortality. The control group did not develop more late stage cancers as predicted. The screened and control groups had essentially the same number of late stage cancers detected and the same number of lung cancer deaths.⁷

This apparent paradox has been attributed to methodological flaws of the studies. Contamination was a problem: 75% of the control group in the Mayo Lung Project received interim chest x-rays.⁹ Three forms of bias are also considered to have played a role in the results: “lead-time bias” could explain improved 5-year survival through earlier detection of preclinical disease; similarly, “length bias” could result from earlier detection of slow growing tumours; finally, the detection of approximately 15% more early stage cancers could represent “overdiagnosis” of clinically insignificant disease.

Canadian Task Force Recommendations (Table 4)

The CTFPHC deliberated the recent evidence and came to the conclusion that no new compelling evidence has emerged to change the previous recommendation of “there is fair evidence to recommend that the annual chest radiographic examination be eliminated from the periodic health examination of asymptomatic people (D Recommendation).” Additionally, the group felt that spiral CT scanning held promise as a more sensitive screening tool than chest radiography, but there was insufficient evidence as to whether this modality should be used for screening (I recommendation) (see Table 4).

In the meanwhile, patients should stop smoking. Few cancers have such an identifiable and preventable risk factor.

Recommendations of Others

In 1996, the US Preventive Services Task Force (USPSTF) recommended against routine screening for lung cancer with chest radiography or sputum cytology in asymptomatic people, and further recommended that all patients should be counselled against tobacco use.²⁵ The USPSTF is currently updating its recommendations. The American College of Chest Physicians, based on a commissioned evidence review,²⁶ also recommended against single or serial low-dose helical CT, chest x-ray and sputum cytology for early detection of lung cancer.²⁷ The American Cancer Society does not recommend routine testing for early lung cancer detection in asymptomatic people, but advocates that those at increased risk should discuss possible testing with their physician, and decisions about screening be made on an individual basis.²⁸

Research Agenda

The universally positive case-control screening studies published in the last decade from Japan do not have sufficient evidence to overturn these earlier findings, but they can lead to improvements in designing future RCTs of lung cancer screening. For example, the case-control studies have suggested that women and patients with the more slowly growing, peripheral adenocarcinomas may benefit more from screening.¹³ Based on these findings, future RCTs may include different patient populations than previously studied.

Low dose CT may pick up more cancers, but this may just propagate the problem of lead-time and over-diagnosis biases. False positives carry the real risk of harm, and in the absence of evidence of benefit, we need to await randomized trials.

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Table 1: Characteristics of studies reviewed

Type of study	N Studies (publications)	Publication year	No. of subjects
Cochrane systematic review	7 (1) ⁷	2002	245,610
Follow-up of randomized trials not included in Cochrane review	2 (2) ^{8,9}	2000,2001	15,556 (included in Cochrane)
Case-control studies	5 (5) ¹⁰⁻¹⁴	1999-2001	1,380 cases 8,025 controls
Diagnostic studies	3 (5) ¹⁵⁻¹⁹	1998-2001	7,180

Table 2: Summary of results of case-control studies of lung cancer screening

Study	Quality rating	Cases (all lung cancer deaths)	Controls	Screening procedure	Smoking-adjusted odds ratio of dying from lung cancer [screened vs unscreened] (95% CI)
Nishii et al. 2001 ¹⁰	FAIR	412	3490 age/sex matched	Annual miniature CXR for all participants and additional 3-day pooled sputum cytology for those with = 30 pack years of smoking	0-12 mo before diagnosis: 0.59 (0.46-0.76) Including smoking survey non-respondents, arbitrarily assigning them avg. smoking rate: 0.64 (95% CI: 0.51-0.81) Only including controls matched for smoking history: 0.55 (95% CI: 0.43-0.70)
Okamoto et al. 1999 ¹¹	FAIR	193	579	Annual full-sized CXR for all participants and additional 3-day pooled sputum cytology for participants with = 30 pack year history of smoking	0-12 mo before diagnosis: 0.54 (0.34-0.85) 12-24 mo before diagnosis: 0.54 (0.30-0.96) 24-36 mo before diagnosis: 0.59 (0.30-1.15)
Sagawa et al. 2001 ¹²	FAIR	328	1886	Annual miniature CXR for all participants and additional sputum cytology for high risk participants	0-12 mo before diagnosis: 0.54 (0.41-0.73) 12-24 mo before diagnosis: 1.24 (0.59-2.59) Adjustment for DPCP-initial screen excluded, steady state reached: 0.43 (0.27-0.70)
Sobue 2000 ¹³	FAIR	273	1269	In 37 of the study areas (annual?) CXR for all participants and sputum cytology for high-risk groups Screening in 13 areas was limited to CXR only	0-12 mo before diagnosis: 0.72 (0.50-1.03) After adjustment for “other tests” (diagnostic vs. screen) 0.66 (0.43-1.03) Women, within 12 months, 0.42 (0.20-0.87)
Tsukada et al. 2001 ¹⁴	FAIR	174	801	Annual miniature CXR for all participants as well as 3-day sputum cytology for those with = 20 pack years	0-12 mo before diagnosis: 0.40 (0.27-0.59) 12-24 mo before diagnosis: 1.42 (0.63-3.17) After adjustment for “other tests” (diagnostic vs. screen) 0.86 (0.55-1.33)

*In clinic-based screening programs, screening is offered at any time during the screening period and at any of the designated locations; this was a different strategy than population-based screening methods that offer screening only on specified day

Table 3: Summary of trials comparing CT with CXR as a means of lung cancer screening

Study	Individuals (scans)	Suspicious nodules N, %, [95% CI]	Cancers detected N, %, [95% CI]	Cancers = 10 mm, N, (%)	Stage Ia/b cancers among all cancers, N, %	Biopsy rate (%) True positive biopsies (%)
Early Lung Cancer Action Project Henschke 1999 ¹⁵ Henschke 2001 ¹⁶ Sone et al. 2001 ¹⁸	<u>Prevalence</u> 1000 (1000)	<u>Prevalence screen</u> CT – 233, 23%, [21-26] CXR – 68, 7%, [5-9]	<u>Prevalence screen</u> CT – 27, 2.5%, [1.8-3.8] CXR – 7, 0.7%, [0.3-1.3]	<u>Prevalence screen</u> CT – 15/27, 55% CXR – 2/27, 7%	<u>Prevalence screen</u> CT – 23/27, 81% CXR – 4/7, 57%	<u>Prevalence screen</u> CT 28/233 12% 27/28 96%
	<u>Follow-up</u> 841 (1184)	<u>Follow-up screens</u> CT – 30, 2.5%	<u>Follow-up screens</u> CT – 7, 0.6%	<u>Follow-up screens</u> CT – 4/7, 57%	<u>Follow-up screens</u> CT – 5/7, 71%	<u>Follow-up screens</u> CT 8/30 27% 7/8 88%
	<u>Prevalence</u> 5483 (5483)	<u>Prevalence</u> 279, 5.1%	<u>Prevalence</u> 23, 0.4%, [0.2-0.6]	<u>Prevalence</u> 6/23, 26%	<u>Prevalence</u> 23/23, 100%	<u>Prevalence*</u> 29/279 10% 22/29 76%
	<u>Follow-up</u> <u>1997</u> 4425 (4425)	<u>Follow-up</u> <u>1997</u> 173, 3.9%	<u>Follow-up</u> <u>1997</u> 27, 0.6%	<u>Follow-up</u> <u>1997</u> 10/27, 37%	<u>Follow-up</u> <u>1997</u> 24/27, 89%	<u>Follow-up</u> <u>1997</u> 30/173 17% 25/30 83%
	<u>1998</u> 3878 (3878)	<u>1998</u> 136, 3.5%	<u>1998</u> 10, 0.3%	<u>1998</u> 5/10, 50%	<u>1998</u> 8/10, 80%	<u>1998</u> 13/136 18% 9/13 69%
	Diederich et al. 2000 ¹⁹	“more than 700 smokers”	<3%	8/700 (1%)	Not specified	Not specified

* Some cancers detected by sputum cytology, not included in biopsy rate results

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Table 4: Summary of CTFPHC Recommendations

Maneuver	Effectiveness	Level of Evidence <Refs>	Recommendations
Annual chest radiographic examination (CXR) of asymptomatic people	Pooled analysis and updates from earlier randomized trials fail to demonstrate long-term mortality reduction in screened groups.	Cochrane systematic review of RCTs (I) ⁷ and randomized trial updates (I) ^{8,9}	The recent evidence is not sufficiently strong to overturn previous negative results from randomized trials. The CTFPHC concludes that there still is fair evidence to recommend against screening asymptomatic people for lung cancer using chest radiographic examination. (D Recommendation)
	Four of five case-control studies showed reduction in odds ratio (0.40-0.54) of dying from lung cancer for those screened. ^{10-12,14} One case- control study did not find a significant benefit associated with screening (OR=0.72, 95% CI: 0.50-1.03). ¹³	Case-control studies (II-2) ¹⁰⁻¹⁴	
Spiral CT scanning (CT scan versus CXR) of asymptomatic people	Radiologic interpretation of screen scans is excellent (kappa 0.91, 95% CI: 0.88-0.94). ¹⁵ More non-calcified lung nodules were detected by CT scan than CXR. ¹⁶ More cancers were detected overall by CT. ¹⁶ Overall cancer detection rate of 0.40% (95% CI: 0.23%-0.57%). ¹⁸ In the absence of any report about the population, significance of the detection rates are unclear. ¹⁹ False-positives & false-negatives. ^{15,17-18}	Diagnostic studies (II-2, III) ¹⁵⁻¹⁹	The CTF concludes that there is insufficient evidence (in quantity and/or quality) to make a recommendation as to whether spiral CT scanning should be used for screening asymptomatic people for lung cancer; however other factors may influence decision-making. (I Recommendation)

Despite the insufficient evidence to date regarding lung cancer screening, smoking cessation should be emphasized to the patient as the preferred modality for reducing lung cancer mortality.

Appendix 1: Methodology of the Canadian Task Force on Preventive Health Care	
<p>Critical appraisal</p> <p>The Task Force reviewed 1) the initial analytic framework and key questions for the proposed review; 2) the subsequent draft(s) of the complete manuscript providing critical appraisal of the evidence prepared by the lead author(s), including identification and critical appraisal of key studies, and ratings of the quality of this evidence using the task force's established methodological hierarchy (sidebar); and 3) a summary of the evidence and proposed recommendations.</p> <p>Consensus development</p> <p>Evidence for this topic was presented by the lead author(s) and deliberated upon during a task force meeting in October 2002. Expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead author were discussed, as were issues related to clarification of the recommendations for clinical application and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The group and lead author(s) arrived at final decisions on recommendations unanimously.</p> <p>Subsequent to the meetings, the lead author revised the manuscript accordingly. After final revision, the manuscript was sent by the Task Force to 2 experts in the field (identified by Task Force members at the meeting). Feedback from these experts was incorporated into a subsequent draft of the manuscript.</p> <p><i>Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the task force methodology were maintained at all stages during review development, the consensus process and beyond to ensure uniformity and impartiality throughout.</i></p>	<p>Levels of evidence</p> <p><i>A. Research design rating:</i></p> <p>I Evidence from randomized controlled trial(s)</p> <p>II-1 Evidence from controlled trial(s) without randomization</p> <p>II-2 Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group</p> <p>II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here</p> <p>III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees</p>
	<p><i>B. Quality (internal validity) rating (see Harris et al., 2001)²⁵:</i></p> <p>Good A study that meets all design- specific criteria* well.</p> <p>Fair A study that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known “fatal flaw”.</p> <p>Poor A study that has at least one design-specific* “fatal flaw”, or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.</p>
	<p>*General design specific criteria are outlined in Harris et al., 2001.⁶ Inclusion/exclusion criteria are detailed in the Methods section.</p>
	<p>Recommendations Grades for Specific Clinical Preventive Actions</p> <p>A The CTF concludes that there is good evidence to recommend the clinical preventive action.</p> <p>B The CTF concludes that there is fair evidence to recommend the clinical preventive action.</p> <p>C The CTF concludes that the existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.</p> <p>D The CTF concludes that there is fair evidence to recommend against the clinical preventive action.</p> <p>E The CTF concludes that there is good evidence to recommend against the clinical preventive action.</p> <p>I The CTF concludes that there is insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.</p>
	<p><i>The CTF recognizes that in many cases patient specific factors need to be considered and discussed, such as the value the patient places on the clinical preventive action; its possible positive and negative outcomes; and the context and/or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.</i></p>

Appendix 2: Summary of Quality Criteria for Case-Control studies of Lung cancer screening

Study	Quality Rating	Case Ascertainment	Controls	Diagnostic tests	Potential Confounding Variables	Comments
Nishii et al. 2001 ¹⁰	FAIR	<p>FAIR - histology unknown in 27% (pathology not reviewed)</p> <p>Diagnosis by medical record: 412 fatal lung cancer cases from 34 municipalities in Okayama Prefecture</p> <p>Inclusion criteria: age 40-79 at time of death; resident in the municipality during the entire study period; history of being screened and diagnosed with lung cancer during study period within the region of screening</p> <p>Exclusion criterion: death from cause other than primary lung cancer</p>	<p>FAIR - not matched for smoking history</p> <p>3490 living controls matched by gender, age, district</p> <p>Inclusion criteria: living in same area as corresponding case from beginning of study period until diagnosis of case</p> <p>Exclusion criteria: immigration of control into region after diagnosis of corresponding case; emigration outside region before diagnosis of corresponding case</p>	<p>FAIR - did not establish whether test for screen or diagnostic purpose</p> <p>Screening program in Okayama involved annual miniature CXR for all participants (cited sens 70%) and additional 3-day pooled sputum cytology for those with = 30 pack years of smoking</p> <p>Screening history established through review of medical records</p>	<p>FAIR - controls not matched for smoking exposure, but smoking adjusted for in analysis</p> <p>Different techniques used to obtain smoking histories of cases and controls</p>	<p>Length bias: Cases whose diagnosis preceded beginning of study period were excluded (<12 mo - more aggressive, late stage) biasing toward stage shift in screened group, resulting in possible overestimation of screening efficacy</p> <p>Established screen history for 36 months, but analysed only for preceding 12 months-adequate Diagnostic Pre-Clinical Phase (DPCP)?</p>
Okamoto et al. 1999 ¹¹	FAIR	<p>FAIR - histology unknown in 11% (pathology not reviewed)</p> <p>Diagnosis was by medical record, 193 lung cancer deaths from initial year of screening program onward in 2 cities in Kanagawa, Japan</p> <p>Inclusion criteria: age 40-74 at time of death, National Health Insurance holders, invited to screening program</p> <p>Smoking history obtained through medical records. If no mention of smoking, assumed non-smoker</p>	<p>FAIR - not matched for smoking history</p> <p>579 living controls matched for age (+1 year), gender, and area of residence</p>	<p>FAIR - not clear whether test for screen or diagnostic purpose</p> <p>Clinic-based, not population based, screening program included annual full-sized CXR for all participants and additional 3-day pooled sputum cytology for participants with = 30 pack year history of smoking</p> <p>Cytological data not included in study</p>	<p>FAIR - controls not matched for smoking exposure, but smoking adjusted for in analysis</p> <p>Different methods used to obtain smoking histories of cases and controls</p>	<p>Length bias: Does not exclude first-screen detected cases</p> <p>Lower smoking rate in cases than controls</p> <p>Screening more effective in adeno CA and peripheral CA</p> <p>Higher adenoCA rate (40%) than most western countries (11%). May grow more slowly than squamous CA (34% in Japan, 48% in Germany)</p>

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Study	Quality Rating	Case Ascertainment	Controls	Diagnostic tests	Potential Confounding Variables	Comments
						Only clinic-based study
Sagawa et al. 2001 ¹²	FAIR	<p>FAIR - histology unknown in 19% (pathology not reviewed)</p> <p>328 fatal lung cancer cases from 53 municipalities in Miyagi Prefecture, Japan</p> <p>Inclusion criteria: death in the study area between 1992-1994 at the age of 40-79 years; lived in the study area from 1989 through date of diagnosis; negative screen result in 1989; diagnosed on / after date of mass screening in 1990</p> <p>Exclusion criteria: cause of death other than primary lung carcinoma</p>	<p>GOOD</p> <p>1886 controls matched for gender, age (± 2 years), municipality, smoking history (ever/never)</p> <p>Exclusion criteria: controls who had died, emigrated out of area, or suffered from lung carcinoma before the matched case was diagnosed</p>	<p>FAIR - not clear whether test for screen or diagnostic purpose</p> <p>Screening program in Miyagi Prefecture consisted of annual miniature CXR for all participants and additional sputum cytology for high risk participants</p> <p>2 yrs DPCP</p>	<p>FAIR - doesn't adjust for "healthy screenee" bias or lead time bias</p> <p>Matched for smoking and also adjusts for smoking.</p> <p>Corrects for length bias –eliminates first screen-detected cancers (1989)</p>	
Sobue 2000 ¹³	FAIR	<p>FAIR - histology unknown in "substantially high" proportion</p> <p>273 fatal lung cancer cases from 50 municipalities in Japan where population-based lung cancer screening programs had been in place for yrs</p> <p>Inclusion criteria: age 40-74y at time of death, death between 1981-1988; diagnosis of lung cancer made after initiation of screening program; high-risk group males and nonhigh-risk group females; no emigration out of area of screening program</p>	<p>GOOD</p> <p>1269 living control patients (5 per case) matched by age (± 2 y), gender, smoking status, and health insurance type</p> <p>Inclusion criteria: residence in same municipality as case since initiation of screening program, alive at time of diagnosis of case, belonged to high-risk group for males or to non-high risk group for females –matched for smoking</p>	<p>GOOD</p> <p>Screening program in 37 of the study areas comprised chest x-ray for all participants and sputum cytology for high-risk groups</p> <p>Screening in 13 areas was limited to chest x-rays only</p> <p>Screen via medical records, checked over longer periods (DPCP), adjusted for diagnostic versus screening test</p>	<p>FAIR - no adjustment for length or healthy-screenee bias</p> <p>Adjustment as well as match for smoking</p> <p>Corrects for lead time bias: 5yr survival of screen detected was 36%, 5 yr survival of diagnosis detected as 10%</p>	Women had more benefit from screening

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Study	Quality Rating	Case Ascertainment	Controls	Diagnostic tests	Potential Confounding Variables	Comments
		Exclusion criteria: private health insurance policies	Exclusion criteria: private health insurance policies			
Tsukada et al. 2001 ¹⁴	FAIR	<p>GOOD</p> <p>174 fatal lung cancer cases in Niigata Prefecture, Japan</p> <p>Inclusion criteria: age 40-79y at time of death; death between 1990-1997; National Health Insurance holders in the study area; high-risk group males and nonhigh-risk group females; residence within area of screening</p> <p>Exclusion criteria: lung cancer diagnosis prior to study period; deaths due to causes other than lung cancer; non-high-risk males or high-risk females</p>	<p>GOOD</p> <p>801 controls matched by sex, age (± 2 y), area of residence and smoking status</p> <p>Inclusion criteria: NHI holders and alive at the time when corresponding case diagnosed; residence within same municipality as case since initiation of screening program; high-risk males and non-high risk females</p>	<p>GOOD</p> <p>Screening comprised annual miniature CXR for all participants as well as 3-day sputum cytology for those with ≥ 20 pack years</p>	<p>FAIR - no correction for lead time, length or healthy screenee bias</p> <p>Adjustment for “use of other tests” test is for diagnostic purpose, not screening.</p> <p>Matching and adjustment for smoking history</p>	