Lung Cancer Screening with Sputum Cytologic Examination, Chest Radiography, and Computed Tomography: An Update for the U.S. Preventive Services Task Force

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Screening for lung cancer is not currently recommended by any major medical professional organization. The U.S. Preventive Services Task Force (USPSTF) gave lung cancer screening a "D" recommendation in both 1985 and 1996, meaning that there were fair-quality data to recommend against screening for lung cancer[1] based largely on 3 negative trials conducted in the United States in the 1970s. Since the last Task Force review, several new studies of lung cancer screening have been reported, and greater attention has been directed toward the limitations of existing literature. This review was conducted to aid the current USPSTF in updating its lung cancer screening recommendation.

Lung cancer is the leading cause of cancer-related death among men and women in the United States; in 2003, approximately 171,900 new cases and 157,200 lung cancer-associated deaths were predicted in the United States.[2] Worldwide, lung cancer and lung cancer-related deaths have been increasing in epidemic proportions,[3,4] with an estimated 1 million deaths in the year 2000.[5]

Although there are other important risk factors for lung cancer,[3,6–10] cigarette smoking is the major risk factor; approximately 87% of all lung, bronchial, and tracheal cancer are attributed to smoking.[3] Consequently, the most important public health intervention that could reduce lung cancer incidence and deaths is changing smoking habits. Unfortunately, although overall prevalence rates of smoking in the United States have decreased over the past 2 decades, the prevalence of current adult smokers remains high at 24%.[10,11] In the clinical setting, smoking cessation programs, even in conjunction with drug therapy, have long-term smoking cessation rates of only approximately 20% to 35% at 1 year among motivated volunteers in good-quality studies.[12–14] In addition, in 1999, approximately 45.7 million adults (23.1%) were former smokers; currently a high percentage of lung

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This study was conducted by the Oregon Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality Contract #290-97-0018, Task Order Number 2, Rockville, MD.

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This first appeared in *Ann Intern Med.* 2004;140:740–753.

cancer cases occur in former smokers, since the risk for lung cancer does not decrease for many years following smoking cessation.[15–17] Household exposure to secondhand smoke is substantial and also associated with lung cancer.[18] These smoking exposure rates, in addition to large numbers of persons with past or passive exposure to smoking, indicate that lung cancer will continue to be a major public health problem in the United States and worldwide.

Lung cancer is the cause of death in more than 90% of affected persons.[19] Survival is directly related to the stage of lung cancer at the time of diagnosis, ranging from 70% for stage I disease to less than 5% for stage IV disease.[20,21] Seventy-five percent of patients with lung cancer present with symptoms due to advanced local or metastatic disease that is incurable.[19] Since lung cancer mortality is closely associated with disease stage at the time of diagnosis, it is believed (based primarily on indirect evidence)[22–28] that early surgical resection is associated with better outcomes. Therefore, the current standard of practice is to resect most non-small-cell lung cancer without evidence of metastic spread. For many of these reasons, screening for and treating early lung cancer is intuitively appealing.

Methods

This review discusses studies of chest x-ray, sputum cytology, and low-dose computerized tomography (CT) for lung cancer screening and focuses on the outcomes of screening in populations. We reviewed the MEDLINE® and Cochrane databases from their inception through January 2003 using the search terms *lung neoplasms, lung cancer,* and *any screening*. The search strategy is detailed in Appendix Table 1. To ensure complete ascertainment, we reviewed the bibliographies of reviews, editorials, book chapters, and letters discussing lung cancer screening, as well as a recent Cochrane review and analysis.[29] We sought studies evaluating screening in the general population, as well as in high-risk populations, and included observational studies and clinical trials. Observational studies with control groups and controlled trials evaluating disease-specific mortality were evaluated for quality according to criteria created by the USPSTF[30] (Appendix Table 2). For the purposes of this review, high-risk populations include those who currently or have ever smoked and low-risk populations include those who have never smoked. To rate each of these studies, we reviewed all original articles discussing the study's methods or findings. We also used studies of the various screening methods to estimate the screening test characteristics of chest x-ray and low-dose CT. Finally, we used data from screening studies, when available, as well as clinical series, to evaluate the harms associated with screening and treatment. For completeness, all studies are described in the tables; however, only studies rated of fair or better quality are described in the text.

Methodological issues relevant to understanding screening studies include lead-time bias (when the time of diagnosis is advanced by screening but the time of death is unchanged), length bias (bias toward detecting less aggressive tumors in a population being periodically screened),[31] and volunteer bias (a type of selection bias in which volunteers are compared with non-volunteers).[32] Over-diagnosis occurs when cancer that would never have been important during an individual's lifetime is diagnosed and treated. These biases can be eliminated in randomized controlled trials (RCTs) with mortality as an outcome. Therefore, most emphasis in public health guideline and in this review is placed on information from RCTs.

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ). AHRQ staff and USPSTF members reviewed interim analyses and the final report. Prior to preparation of this manuscript, the full report was reviewed by 17 content experts in the area of lung cancer screening and revised accordingly.

Data Synthesis

In our searches, we identified 809 citations and abstracts; 149 full-text papers were reviewed. Of these, 1 randomized trial of chest x-ray, in conjunction with a multiphasic screening program,[33,34]

and 5 RCTs[35–40] of chest x-ray and/or sputum cytology screening for lung cancer were reviewed. In addition, 6 case-control studies,[41–46] 1 non-RCT[47] and 4 older cohort studies (Appendix Table 3)[48–52] were reviewed. Finally, we reviewed 6 recent cohort studies of lung cancer screening with CT.[53–62]

Lung Cancer Screening with Chest X-Ray with or without Sputum Cytology

Controlled Trials

Tables 1 and 2 summarize the methods and quality of the 6 RCTs and 1 non-RCT of lung cancer screening.[33–40,47,63–85] Figure 1 shows the relative risks and confidence intervals (CIs) of these randomized trials. In the 1960s, a cluster randomized trial of chest x-ray screening involving approximately 55,000 men older than age 40 was conducted by the Northwest London Mass Radiography Service.[35,36] In this trial, 29,723 male factory workers from 75 randomly identified firms were offered chest x-ray every 6 months and were compared with 25,300 controls from other factories who were offered screening at baseline and at 3 years. After 3 years, the annual mortality rate from lung cancer in the intervention group was 0.7/1,000; the rate was 0.8/1,000 in the control population, not different statistically.

Three National Cancer Institute (NCI)-sponsored RCTs of lung cancer screening in male smokers were conducted in the United States in the 1970s.[37–39,63,64,68,73–75,80] The Memorial Sloan-Kettering (MSK)[37,63–67] and the Johns Hopkins (JH) studies[38,68–72] were identical in design and were conducted to evaluate the incremental benefit of adding sputum cytology to annual chest x-ray. Of the 20,427 male smokers (≥ 20 pack-years of smoking) aged 45 and older who volunteered for these 2 studies, 10,234 were randomized into a dual-screening group that was offered screening with annual chest x-ray and sputum cytology every 4 months for 5 years; 10,233 were assigned to a chest x-ray group that was offered annual chest x-ray screening for 5 years. Each group was followed for 5 to 8 years.

In the MSK study, the baseline screen identified 30 (6.0/1,000) lung malignancies in the dual-screening group and 23 (4.6/1,000) in the chest x-ray group.[63] Following the prevalence screen, 114 subsequent (incident) lung cancer cases were identified in the dual-screening group and 121 in the annual x-ray group during the screening period, with 33 and 32 cases, respectively, diagnosed in the 2 years following screening. Combining the incidence and prevalence tumors, 144 cases of lung cancer were detected in each group during the study[37,64,67]; 40% of all lung cancer detected was stage I. The mortality rate was 2.7/1,000 person-years in both the chest x-ray and dual-screening groups.

In the JH study, the prevalence screen identified 39 malignancies in the dual-screening group and 40 in the chest x-ray group.[38,71] After 8 years of follow-up, 194 incident cases of cancer were identified in the dual-screening group and 202 in the chest x-ray group. The mortality rates were 3.4/1,000 person-years in the dual-screening group and 3.8/1,000 person-years in the control group (not statistically significant differences) and were similar to community lung cancer mortality rates at the time.[71,72]

The first trial to evaluate the value of intense screening with chest x-ray was the Mayo Lung Project (MLP) involving 10,933 male smokers aged 45 or older.[39,73–83] All participants underwent a prevalence screen with sputum cytology and chest x-ray, and 91 cases of cancer were identified (prevalence 0.83%).[39,73,75] After the prevalence screen, 4,618 men were randomized to a study group screened with chest x-ray and pooled 3-day sputum cytology every 4 months for 6 years, and 4,593 to a control group were advised to have annual chest x-ray and sputum cytology. During the study period, 206 incident cases of lung cancer were identified in the dual-screening group and 160 in the control group. After 20 years of follow-up, lung cancer death rates were 4.4 (95% CI, 3.9–4.9) and 3.9 (95% CI, 3.5–4.4) per 1,000 person-years in the dual-screening and control groups, respectively.[80]

The MLP was the first individual RCT to specifically evaluate the role of chest x-ray in lung cancer screening, and was the most influential in determining current public health policy. Although it is rated as fair quality by USPSTF criteria, there

Table 1. Controlled Trials of Lung Cancer Screening with Chest X-ray with or without Sputum Cytology

Study, Year (Study Began)	Population	Intervention	Prevalence (%)
Northwest London Mass Radiography Service, 1960[35,36]	Males > 40 yrs; 19% former smokers; 67% current smokers	29,723 offered CXR every 6 mos over 3 yrs; 25,300 offered CXR at baseline and at 3 yrs	Intervention: 31 (0.10) Control: 20 (0.08)
Kaiser Permanente, 1964[33,34]	10,713 members aged 35–54; 17% smokers	Intervention: 5,156 encouraged to have annual multiphasic health checkup including CXR Control: 5,557 usual care	NR
Memorial Sloan-Kettering,1974[37,63–67]	10,040 male smokers aged ≥ 45	All participants: baseline CXR; 4,968 annual CXR and sputum cytology every 4 mos for 5–8 yrs; 5,072 annual CXR and screened over 5–8 yrs	Dual screen: 30 (0.6) CXR: 23 (0.46)
Johns Hopkins, 1973[38,68–72]	10,387 male smokers aged ≥ 45	All participants: baseline CXR; 5,266 CXR and sputum cytology at baseline and every 4 mos; 5,161 annual CXR for 5–8 yrs	Dual screen: 39 (0.75) CXR: 40 (0.78)
Mayo Lung Project, 1971[39,74–76,80]	10,933 male smokers aged ≥ 45	All participants: baseline CXR, 3-day pooled sputum cytology; 4,618 to CXR and 3-day pooled sputum cytology every 4 mos for 6 yrs; 4,593 received usual care with advice for annual CXR and sputum cytology	91 (0.83)
Czech, 1975[40,84,85]	6,345 male smokers aged 40–64	After baseline CXR: 3,171 received CXR every 6 mos over 3 yrs and 3,174 received usual care; at end of study (yrs 4–6), CXR performed annually in each group	19 (0.30)
Wilde, 1972–1977[47]†	All men in 14 districts aged 40–65 (n = 143,880)	Intervention: 41,532 in 4 districts offered chest fluorography every 6 mos Control: 102,348 in 10 districts offered chest fluorography every 12–24 mos	Intervention: 54 Control: 68

* Between-group differences were not statistically significant for all studies.

† Non-randomized study.

CXR, chest x-ray; NR, not reported.

Table 1. Controlled Trials of Lung Cancer Screening with Chest X-ray with or without Sputum Cytology (cont)

Incident Lung Cancer (No)	Advanced Tumors Stage III, IV (%)	Non-resectable Tumors (%)	Mortality Rate/1,000 Person-Years*
Intervention: 101 Control: 76	Intervention: NR Control: NR	Intervention: 56 Control: 71	3 yr follow-up Intervention: 0.7 Control: 0.8
NR	NR	NR	16 yr follow-up Intervention: 8.6 Usual care: 7.6
Dual screen: 146 CXR: 155	Dual screen: 64 (1.2) (incidence) CXR: 63 (1.2) (incidence)	Dual screen: 49 CXR: 47	5-8 yr follow-up Dual screen: 2.7 CXR: 2.7
Dual screen: 194 CXR: 202	NR	Dual screen: 53 CXR: 56	5-8 yr follow-up Dual screen: 3.4 CXR: 3.8
Dual screen: 206 Usual care: 160	Dual screen: 107 (2.3) Usual care: 109 (2.4)	Dual screen: 32 Usual care: 19	20 yr follow-up Intervention: 4.4 Usual care: 3.9
Dual screen: 108 Control: 82	Dual screen: 53 (1.7) Control: 46 (1.4)	Dual screen: 77 CXR: 77	15 yr follow-up: Dual screen: 7.8 Control: 6.8
Intervention: 320 Control: 599	NR	Intervention: 72 Control: 81	10 yr follow-up: Intervention: 0.8 Control: 0.6

Table 2. Methods and Quality of Controlled Trials of Lung Cancer Screening

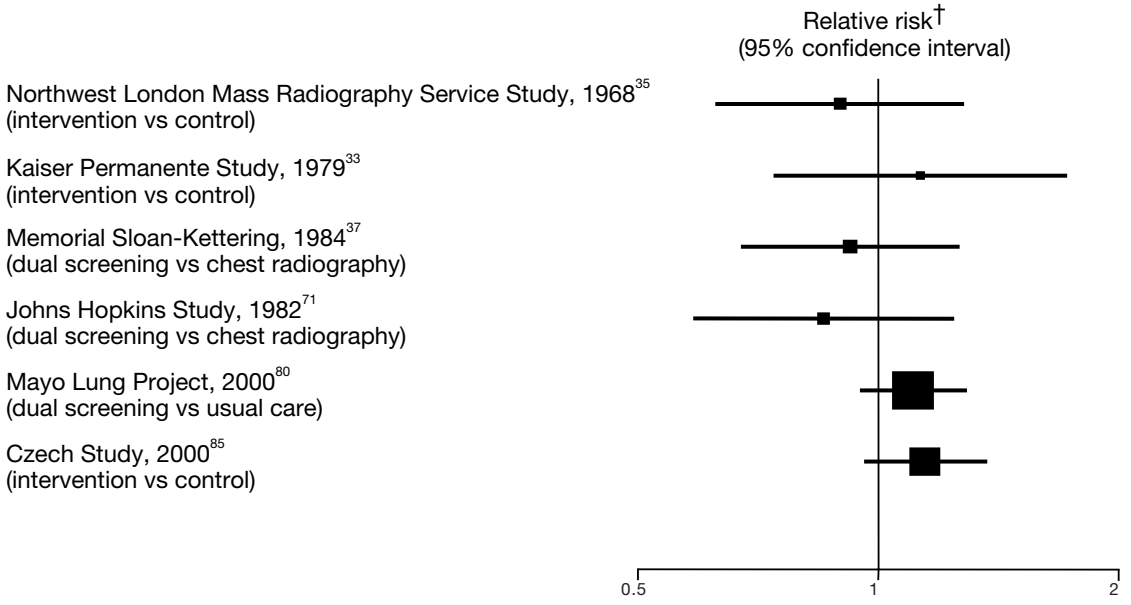
Study	Assembly of Comparable Groups: Randomization/ Allocation Concealment	Maintenance of Comparable Groups	Outcomes Assessment: Validity of Method, Masking
Northwest London Mass Radiography Service[35,36]	Cluster randomized by random number; examiners not clearly blind; comparable in age structure and smoking habits; no apparent occupational exposures	99% follow-up	Cause of death determined from hospital records and General Register's office; blinding not described
Kaiser Permanente[33,34]	Randomized by patient record numbers with concealed code; more chronic lung disease in intervention group (8.9% vs 7.5%)	Poor follow-up	Blind review of death
Memorial Sloan-Kettering[37,63–67]	Computer-generated randomization (not described); all cause mortality similar	Formal protocol/ algorithm for follow-up; 55 lost to follow-up	All deaths reviewed by statisticians, clinicians, and pathologists blind to study group
Johns Hopkins[38,68–72]	Computer generated randomization (not described); allocation concealment unclear; fairly comparable when evaluated by age, smoking history, non-tobacco carcinogen exposure	Formal algorithm for follow-up; 1.3% lost to follow-up	All deaths reviewed by statisticians, clinicians, and pathologists blind to study group
Mayo Lung Project[39,74–76,80]	Randomization method not described; allocation concealment unclear; similar distribution age, smoking exposure to non-tobacco carcinogens, and pulmonary disease	Adequate; good follow-up of all participants in both groups	All deaths reviewed by statisticians, clinicians, and pathologists blind to study group; National Death Index used for latest follow-up
Czech[40,84,85]	Randomization stratified by age, smoking history, socioeconomic status, residence, occupational exposure; allocation concealment unclear; no differences observed in these characteristics; all cause mortality, smoking-related deaths higher in intervention group	Not well reported	Cause of death ascertained from death certificates; autopsy in 1/3 of patients; blind review not described
Wilde[47]	Nonrandomized; similar community distribution of smoking habits and economic structure; similar all-cause mortality rates; population age not described	Adequate description; greater number dropouts in control group	Blinding not described; nonsystematic ascertainment of cause of death

CXR, chest x-ray; MHC, multiphasic health checkups; NR, not reported.

Table 2. Methods and Quality of Controlled Trials of Lung Cancer Screening (cont)

Attendance, Compliance, Contamination, Crossovers	Analysis, Exclusions, and External Validity	Study Quality
Intervention: 63% Control: 63% Cross-over: NR	Intention-to-treat analysis; no reported exclusions; age and smoking habits similar	Fair
Intervention: 60% underwent MHC (mean, 6.8 exams) Cross-over: 64% of controls had MHC (mean, 2.8 exams)	Very low-risk population	Poor
Dual screen: 63.2% CXR: 65.2%	Intention-to-treat analysis; only exclusion was prior lung cancer	Fair
Uncertain; 19% withdrew from active screening	Intention-to-treat analysis; formal protocol for evaluation; only exclusion was prior lung cancer	Fair
Intervention: 75% Cross-over: 73% of controls had CXR within last 2 yrs of study	Intention-to-treat analysis; formal protocol for evaluation; Mayo Clinic population with life expectancy estimates of 5 yrs	Fair
Intervention: 92.5% Cross-over: rare	Significantly higher all-cause mortality in screened group, suggesting bias in randomization	Poor
NR	Intention-to-treat analysis; no reported exclusions; mortality rates not adjusted for age	Poor

Figure 1. Mortality in Randomized Controlled Trials* of Lung Cancer Screening with Chest Radiography with or without Sputum Cytology



* Follow-up ranged from 3 to 20 years among the 6 studies.
† Solid black square size represents Mantel-Haenszel weight.

are several limitations of the study. First, a prevalence screen detected 91 cases of lung cancer (0.83%). Thus, there was no completely unscreened control group. Also, these cases were followed separately and were not evaluated in the randomized comparison. Thus, any effect of these cases on mortality could not be determined. Second, nearly half of the controls obtained annual chest x-rays during the course of the study, with one-third of the malignancies in the control group discovered by screening chest x-ray; 73% of the controls received chest x-rays during the study's last 2 years. Third, compliance of the intervention group was 75%, reducing the study's power.[73]

The incidence of lung cancer in the MLP intervention group was approximately 22% higher than in the control group.[73] The possibility of nonrandom distribution of lung cancer risk factors was evaluated by Marcus and Prorok[81]; the distribution was not found to vary significantly between the intervention and control groups. Although little detailed information is provided, there is evidence on review of the MLP publications that not all patients were asymptomatic,[39,73] which could alter the findings of the screening study if patients with symptoms were disproportionately enrolled in the intervention group. However, there is no evidence to support this. The radiation exposure associated with chest x-ray in the MLP is generally thought insufficient to increase lung cancer incidence.[86] Finally, another possibility is that the higher incidence of lung cancer in the screened population may represent the diagnosis of insignificant disease, eg, over-diagnosis.

Case-Control Studies

Five fair-quality case-control studies were conducted in Japan between 1992 and 2001 (Table 3).[42–46] As a generalization, the cases were comprised of fatal lung cancer and included high-risk men and low- or unknown-risk women. All cases were matched to controls by age, gender, and health insurance status. Some studies included adjustment for geographic region, number of prior

Table 3. Case Control Studies of Lung Cancer Screening with Chest X-ray and Lung Cancer Mortality

Study, Setting, Year	Cases: Patients with Fatal Lung Cancer	Controls	Matching/ Adjustment Factors	Odds Ratio for Lung Cancer Mortality Associated with Screening (95% Confidence Interval)	Study Quality
Ebeling and Nischan, Berlin, 1987[41]	130 men aged < 70	204 patients from community center	Age; opportunity for screening; location	0.88 (0.53–1.45)	Poor †‡
		194 patients from hospital outpatient department	Age; opportunity for screening	1.09 (0.67–1.78)	
Okamoto et al, Japan, 1999[42]	158 men and 35 women aged 40–74	579*	National Health Insurance; smoking status; opportunity for screening; location	0.54 (0.34–0.85) ≤ 12 mos 0.54 (0.30–0.96) ≤ 24 mos 0.50 (0.30–1.15) 24–36 mos	Fair
Sobue, Japan, 2000[43]	208 high-risk men, 65 low-risk women	1,269*	National Health Insurance; smoking status; opportunity for screening; health checkups	0.72 (0.5–1.03) ≤ 12 mos§ 0.83 (0.56–1.23) ≤ 12–24 mos§	Fair
Sagawa et al, Japan, 2001[44]	258 smoking and nonsmoking men and 70 nonsmoking women aged > 39	1,886*	Smoking status; opportunity for screening (all screened negative in 1989); location	0.54 (0.41–0.73) ≤ 12 mos§ 1.24 (0.59–2.59) 12–24 mos§ II 0.62 (0.42–0.92) ≤ 24 mos§ 0.64 (0.36–1.14) ≤ 36 mos§ 2.41 (0.54–10.7) ≤ 48 mos§	Fair
Tsukada et al, Japan, 2001[45]	149 high-risk men and 25 non-high-risk (nonsmoking) women aged > 40	801*	National Health Insurance; smoking status; opportunity for screening	0.40 (0.27–0.59) ≤ 12 mos§ 1.42 (0.63–3.17) ≤ 12–24 mos§	Fair
Nishii et al, Japan, 2001[46]	412 men and women aged 40–79	3,490*	National Health Insurance; smoking status; opportunity for screening; location	0.59 (0.46–0.74) ≤ 12 mos§	Fair

* All matched by age, sex, and location.

† Received a poor score because selection of controls was potentially biased.

‡ Received a poor score for not controlling for smoking.

§ High-risk individuals were also screened with sputum cytology.

II Excluding screening < 12 months.

CXR, chest x-ray.

health examinations, or both, and all accounted for smoking either by matching or statistical adjustment. For screening with chest x-ray, with or without sputum cytology occurring within 1 year of diagnosis, the odds ratios ranged from 0.40 to 0.72, 4 with statistically significant findings.

Lung Cancer Screening with Low-Dose CT

Several recent cohort studies, all without control groups, have evaluated screening for lung cancer with CT. The details of these studies are shown in Table 4. The Early Lung Cancer Action Project (ELCAP)[54] involved 1,000 asymptomatic volunteers (46% female) aged 60 or older, with a median of 45 pack-years of smoking, and no prior malignancy, who were evaluated as medically fit for surgery and who each underwent chest x-ray and CT. Baseline chest x-ray identified 68 persons with concerning nodules, of which 33 were confirmed by CT; 7 patients were malignant, and all were resectable. Baseline CT identified 233 persons with nodules. After follow-up of 30 recommended biopsies, 27 malignancies were identified, of which 26 were resectable and 23 were stage I.[54] Four other cases of lung cancer were also diagnosed based on non-nodule CT abnormalities. Approximately 1,184 subsequent annual examinations resulted in 40 persons (4%) requiring further evaluation, usually high-resolution CT, 9 biopsies, and 9 lung cancer diagnoses (7.2/1,000) (6 stage IA).[55] There are no mortality data available yet on this cohort.

Three CT studies conducted in Japan involved large numbers of both high- and low-risk men and women aged 40 and older.[56,58,59] Each study used a different protocol but also included chest x-ray and sputum cytology; at least 2 were conducted in areas where lung cancer screening with chest x-ray and sputum cytology had been conducted for many years. Among 15,050 baseline screens, 993 (6.6%) had abnormalities requiring high-resolution CT, at least 21 underwent biopsy; 71 lung tumors were identified (prevalence 0.47%), 63 of them stage I (89%). Researchers performed 21,762 incidence screens that resulted in at least 1,166 subsequent high-resolution CTs and identified 60 lung cancer cases (2.76/1,000), of which 45 were stage I (Table 4).

A study conducted at the Mayo Clinic involved 1,520 men and women aged 50 and older with 20 or more pack-years of smoking.[60–62] A baseline screen identified 782 (51.4%) persons with 1 or more nodules requiring further evaluation; 26 (1.7%) were diagnosed with primary lung cancer based on CT alone. Among this cohort, 2,916 annual incidence screens identified 336 persons (12%) with new nodules; 10 new diagnoses of lung cancer (6.7/1,000) were made with CT alone. There were 2 cases of interval cancer and 2 diagnosed with sputum cytology only. Of the 40 persons with malignancies, 36 were non-small-cell lung cancer, of which 31 (86%) were resected for cure; 8 patients underwent surgery for benign disease.

Finally, a German study[53] involving 817 asymptomatic volunteers aged 40 and older, with at least 20 pack-years of smoking, was conducted between November 1995 and July 1999. Baseline CT identified 350 persons with nodules, 269 of these persons underwent high-resolution CT, ultimately identifying nodules in 29 persons. Thirteen of the 29 persons with nodules underwent biopsy; malignancy was diagnosed in 10 of the persons, as well as 1 interval cancer. After an average of 2.7 years of follow-up, 6 patients are alive without evidence of recurrence.

Lung Cancer Screening among Women

Lung cancer is the leading cause of cancer-related death among women in the United States, and most cases are attributed to smoking.[2] In addition, women have substantial exposure to passive smoking, and a significant proportion of lung cancer in nonsmoking women is attributed to passive smoking.[18] Furthermore, although controversial, some studies suggest that for any level of smoking, women are at higher risk for developing lung cancer than men.[4,87,88] For unknown reasons, women also tend to develop adenocarcinoma of the lung disproportionately to men,[17,88,89] and adenocarcinoma is also found more commonly among nonsmokers.[17] This cell type

tends to occur peripherally[89,90] and may be more apt to be detected with chest x-ray, CT, or both than other cell types. Consequently, radiological imaging and screening for lung cancer may perform differently among women. Unfortunately, no randomized trials of lung cancer screening have included women. The only data evaluating screening among women and including control populations come from 4 Japanese case-control studies evaluating screening among primarily nonsmoking women (passive smoking not assessed).[43–46] These studies are summarized in Table 5 and show lung cancer mortality odds ratios for screening conducted within 12 months of lung cancer diagnosis ranging from 0.39 to 0.61; 2 studies found statistically significant differences; however, interpretation is limited by the screening biases discussed in this review. Five studies of CT have included women; mortality data are not yet available. In addition, randomized trials of lung cancer screening with chest x-ray and/or low-dose CT involving women are currently underway.

Discussion

The personal and public health importance of lung cancer in the United States and worldwide is enormous, and even a small benefit associated with screening could save many lives. However, the outcomes of screening, as shown in this report, are mixed, with some lower grades of evidence evaluating chest x-ray with or without sputum cytology (case-control studies) showing benefit, and higher-grade evidence (RCTs) not showing benefit. The CT screening studies show that lung cancer can be diagnosed at an earlier stage than in usual clinical practice, but little is known about patient outcomes. Unfortunately, none of the existing randomized trials answer the question faced by clinicians: Should patients be screened for lung cancer at all?

The case-control studies from Japan give some support to chest x-ray screening for lung cancer. Although case-control studies are not considered the gold standard in evaluating screening efficacy and effectiveness, several authors believe they can be a useful and efficient way to evaluate a screening method.[31,91,92] However, it is very difficult to overcome the possibility of volunteer/healthy screenee bias in case-control studies, even well-conducted ones; this might bias the study toward benefit, since persons choosing screening may differ from those not being screened in factors which of themselves influence lung cancer mortality.[93]

The CT cohort studies indicate that earlier-stage lung cancer can be detected. However, drawing conclusions from the uncontrolled CT studies is difficult because of the methodological biases discussed earlier. It is possible, based on the stage distribution of the detected tumors, that mortality may be reduced. However, because of lead-time and length bias, survival may be prolonged but mortality unchanged. Randomized trials of CT with mortality as an outcome are needed to definitively evaluate this issue. The higher rate of abnormal CT findings and lung cancer in U.S. and German studies compared with Japanese studies most likely result from (1) higher-risk populations being screened in the U.S. and Germany; (2) prior population lung cancer screening has been conducted in Japan; (3) different CT methods among studies; and (4) possible higher rates of histoplasmosis in the U.S.

The hope of benefit from lung cancer screening is high; however, the implications of screening, especially in the absence of proven benefit, are also great. Evaluating harm or potential harm associated with screening for lung cancer is difficult. One approach to this issue is to evaluate the 4 possible outcomes of screening: false-positive, false-negative, true-positive, and true-negative findings. The best data about outcomes from chest x-ray screening come from the recent CT studies, since data from the chest x-ray trials accumulated prior to the use of CT for evaluation of x-ray abnormalities, and many patients previously underwent thoracotomy or biopsy than would have in current clinical practice. Table 4 shows positive chest x-ray rates and the diagnostic outcomes associated with chest x-ray from the CT studies; most chest x-ray abnormalities are resolved or found to be false-positive results when evaluated by CT.[54,59] For x-rays identified as suspicious for cancer in the NCI studies, the positive predictive value for cancer ranged from 41% to 60%.[29]

Table 4. Low-Dose Computerized Tomography Lung Cancer Screening Outcomes*

Study, Year	Screening Type	Screening Interval (Months)	Number of Screens	Positive Test Results (%)
Diederich et al, 2002[53]	Baseline LDCT		817	350 (43)
Henschke et al, 1999, 2001[54,55]	Baseline LDCT	6–18	1,000	237 (24)
	*Incidence LDCT		1,184	40
	Baseline CXR		1,000	68 (6.8)
				(33) (3.3)‡
Nawa et al, 2002[56]	Baseline LDCT	12	7,956	2,099 (26.4)
	*Incidence LDCT		5,568	NR
Sone et al, 2001[58]	Baseline LDCT	12	5,483	279 (5.1)
	*Incidence LDCT		8,303†	309
Sobue et al, 2002[59]	Baseline LDCT	6	1,611	186 (11.5)
	*Incidence LDCT		7,891	721
	Baseline CXR		1,611	55 (3.4)
			7,891	202
Swensen et al, 2002, 2003[61,62]	Baseline LDCT	12	1,520	782 (51.4)
	Combined data			
	*Incidence LDCT		2,916	336

* All data presented by individual except incidence, which indicates screening tests performed.

† Percentage of lung cancer for incidence = cases of lung cancer identified with incidence screening/cases of lung cancer in cohort minus cases of prevalence cancer.

‡ After LDCT.

§ One case of malignant disease.

CXR, chest x-ray; HRCT, high-resolution computerized tomography; LDCT, low-dose computerized tomography; NR, not reported.

Table 4. Low-Dose Computerized Tomography Lung Cancer Screening Outcomes* (cont)

Recommendation for Follow-up Based on LDCT (Number)			Surgery for Diagnosis (Benign) (Number)	Lung Cancer† (%)	Stage 1 Disease (%)
HRCT	Referral	Biopsy			
269	29	13	1 (1)	11 (1.3) (1 interval)	58
233	104	27	0	31 (3.1)	85
40	NR	9	NR	9 (0.9)	67
33	NR	NR	0	7 (0.7)	
541	64	NR	NR	36 (0.5)	86
148	7	NR	NR	4 (0.1)	100
266	NR	NR	NR (7)	22 (0.4)	100
297	NR	NR	NR (9)	37 (0.6)	86
186	25	21	0	13 (0.8)	77
721	57	35	1 (0)	19 (0.2)	79
22	9	8	0	5 (0.3)	60
89	7	4	0	3 (0.2)	0
NR	NR	NR	NR (8)	27 (1.8)§	66
NR	NR	NR		11 (0.7) (+ 2 interval)§	

Table 5. Lung Cancer Screening Studies Including Women

Study, Year	Study Type	Setting	Description of Sample	Intervention	Odds Ratio or Relative Risk or Number of Malignancies Identified
Sobue, 2000[43]	Case-control	Japan	65 low-risk patients	CXR with or without sputum cytology	0.42 (0.20–0.87) for screening < 12 mos
Sagawa et al, 2001[44]	Case-control	Japan	70 low-risk patients aged > 39	CXR with or without sputum cytology	0.57 (0.30–1.11) for screening < 12 mos
Tsukada et al, 2001[45]	Case-control	Japan	25 low-risk patients aged > 40	CXR with or without sputum cytology	0.61 (0.23–1.68) for screening < 12 mos
Nishii et al, 2001[46]	Case-control	Japan	412 mixed-risk patients aged 40–79	CXR	0.39 (0.24–0.64) for screening < 12 mos
Henschke et al, 1999, 2001[54,55]	Cohort	U.S.	460 high-risk participants	Baseline LDCT and repeated LDCT	NR by sex
Sone et al, 2001[58]	Cohort	Japan	2,512 participants 1,816 participants	Baseline LDCT Repeated LDCT	11 malignancies identified 4 malignancies identified
Diederich et al, 2002[53]	Cohort	Germany	229 high-risk participants	Baseline LDCT	NR by sex
Nawa et al, 2002[56]	Cohort	Japan	1,367 participants (4.3% current or former smokers)	Baseline LDCT Annual repeated LDCT	12 malignancies identified, all in nonsmokers 0
Swensen et al, 2002, 2003[61,62]	Cohort	U.S.	735 participants	Baseline and repeated LDCT	NR by sex

CXR, chest x-ray; LDCT, low-dose computerized tomography; NR, not reported.

In the CT studies, the false-positive rate was the number of patients with CTs requiring further evaluation who did not have cancer. Using this criterion, the false-positive rates in the CT studies ranged from 5% to 50% in prevalence screens and 3% to 12% in incidence screens; most abnormalities were resolved with high-resolution CT. Among the CT studies reporting referral rates, 4.8% to 14.5% of patients undergoing high-resolution CT were referred for biopsy, from which most (63% to 90%) were diagnosed with cancer. These data are shown in Table 4. For comparison, in U.S. and European clinical practices, approximately half of patients undergoing surgical biopsy of indeterminate nodules subsequently receive a benign diagnosis.[61,94] In the current practice setting, positron emission tomography scans are commonly used as a noninvasive means of discriminating between malignant and nonmalignant lesions[95] and may reduce the rate of invasive procedures performed to evaluate indeterminate nodules.

Persons with false-positive results can experience a period of time potentially associated with high anxiety and concern, and for those pursuing further evaluation, the cost and risk associated with it. Although the false-positive rate is high in the lung cancer screening studies, the meaning of a false-positive lung cancer screening study (either chest x-ray or CT) to a patient may be different than for other types of cancer screening tests, since patients who currently smoke potentially have some control over their subsequent risk and may be able to more effectively modify their high-risk behavior. Data from the ELCAP study suggest that CT scan results, in combination with smoking cessation counseling, improved smoking cessation rates among all participants[54] and that an abnormal CT finding was associated with nearly 2-fold greater odds of decreased smoking or cessation among current smokers.[96] It is reasonable to assume that an abnormal screening chest x-ray might also influence smoking behavior.

An important and controversial issue in lung cancer screening is the question of over-diagnosis (and consequent over-treatment). The relatively high prevalence of unrecognized lung cancer in several studies suggests that there is a significant preclinical pool of lung cancer in high-risk populations.[38,54,97] Whether all of these tumors would eventually present clinically is uncertain. Supporting over-diagnosis are data from the MLP showing increased rates of early tumors in the screened group compared with the control group without a change in the number of advanced tumors or subsequent mortality rates, suggesting diagnosis of a pool of indolent tumors.[98] Although the higher lung cancer mortality rate among the intervention group in the MLP was not statistically significant, a major concern is that the increase in mortality might not be due to chance and may be a consequence of screening (eg, more persons undergo evaluation and treatment in the screened group and with treatments-associated risk, result in a true increase in mortality). Alternatively, an increase in lung cancer mortality rates among screened persons may be a consequence of misclassification of cause of death or "sticky-diagnosis bias,"[98] meaning that in the absence of autopsy data, there is a propensity to label any diagnosed malignancy as the cause of death, regardless of the tumor's clinical course, which results in bias against screening when evaluating disease-specific mortality.[99] Black et al[100] noted that the excess lung cancer mortality observed among the screened group in the MLP, particularly death from metastatic adenocarcinoma, was probably at least partially a consequence of this type of differential misclassification.

Arguments against an important role for over-diagnosis in lung cancer are based on autopsy studies showing low rates (0.8%) of unrecognized lung cancer.[101] Whether autopsy data are generalizable to living populations is questionable, particularly given selection biases for autopsy. Further data against over-diagnosis come from 2 natural history studies of both screen- and symptom-detected unresected stage I non-small-cell lung cancer that have shown that almost all patients die of lung cancer over 5 to 10 years.[25,26] Whether a strong case for over-diagnosis should be made on the basis of current data is uncertain. However, it is possible that with an increasingly sensitive detection tool, such as CT, over-diagnosis may occur. The issue of over-diagnosis is particularly relevant to the harm associated with lung resection for cancer, where there is significant

mortality and morbidity associated with treatment. More data are needed to definitively evaluate this issue.

Another potential harm of screening is false-negative findings with possible false reassurance. In current practice, the best estimate of the rate of false-negative results on chest x-rays comes from the CT studies, where false-negative rates as high as 75% were shown.[54,59] Clinical series of chest x-ray suggest retrospective identification of lung cancer ranges from 12% to 90%.[102,103] While CT is considered the gold standard for evaluating nodules, it has also been shown to have false-negative results[62]; and the potential for false reassurance with CT certainly exists, particularly if those screened believe that they are undergoing a definitive examination.

The rate of complications associated with biopsy was not described in the CT studies. The morbidity and/or mortality associated with thoracotomy for positive test results (true or false) is also difficult to evaluate. Studies of symptomatic patients suggest that the more lung tissue removed the greater the morbidity and mortality. Overall, mortality rates range from 1.3% to 11.6% and morbidity rates from 8.8% to 44% among several series reviewed, with lower rates among patients undergoing smaller resections, less comorbidity, and centers with greater surgical volume.[28,47,104–110] Complication rates from studies among symptomatic patients are likely to be greater than complication rates among asymptomatic persons in screening programs directed at those judged healthy enough to undergo surgery.

Currently, most patients in the United States are not screened for lung cancer.[111] However, because conclusions about lung cancer screening have been based on limited data and no trials have compared screening with no screening or screening among women, the issue is being reevaluated. Routine annual chest x-ray is being compared with usual care in the Prostate, Lung, Ovarian, and Colorectal Cancer trial (PLCO), which involves over 100,000 men and women aged 55 to 74.[112,113] Data from this study should be available in 2010. The National Lung Screening Trial (NLST) will compare routine screening CT with chest x-ray in high-risk men and women aged 55 to 74.[114]

New technologies may also contribute to the early detection of lung cancer and potentially screening for lung cancer. Some currently being investigated include: immunocytochemical analysis of sputum with monoclonal antibodies[115]; identification of genetic mutations[116]; abnormal DNA methylation[117,118]; abnormal patterns of immunostaining, and other molecular changes.[119–122] There are several other potential targets in sputum, bronchial fluid, and expired air that may have a role in early lung cancer detection and are currently being investigated.[123,124]

In summary, studies evaluating chest x-ray screening for lung cancer have had mixed findings, with stronger types of evidence from 30-year-old trials suggesting no benefit among male smokers and possible over-diagnosis, and weaker study designs suggesting benefit to men and women. There are important methodological limitations to all of these studies. The studies of CT have demonstrated that lung cancer can be diagnosed at a significantly earlier stage than what currently occurs in clinical practice. However, whether this will translate to a mortality benefit is unclear. In addition, even if CT is shown to be effective, the issue of cost-effectiveness remains.[125] Critical information will come from the current RCTs of screening CT. Given the uncertainty associated with chest x-ray screening, it is unfortunate that the NLST does not include non-screened control groups. However, data will be available on chest x-ray screening from the PLCO trial in the next 5 to 8 years. In the meantime, other approaches for evaluation of screening should be considered, such as rigorously conducted case-control studies of chest x-ray and/or screening CT. We hope that new methods of screening for lung cancer will be developed and refined. Even a small decrease in lung cancer mortality attributed to screening would save thousands of lives each year.

Acknowledgments

The authors would like to thank Kathryn Krages, AMLS, MA; Susan Wingenfeld; and Kim Peterson, MS, for their help in preparation of the full evidence report and the manuscript. They also thank Mark Helfand, MD, MPH; William Holden, MD; John McAnulty, MD; and James Reuler, MD, for their helpful reviews of the manuscript.

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Appendix

Appendix Table 1. Search Strategy for Screening for Lung Cancer

1. Exp lung neoplasms or lung cancer.mp (mp = text words from title and abstracts)
   - bronchogenic carcinoma
   - pulmonary coin lesions
   - Pancoast's syndrome
   - pulmonary blastoma
2. Exp mass screening or screen.mp
   - genetic screening
   - mass chest x-ray
   - multiphasic screening
   - mandatory testing
3. 1 **and** 2
4. Exp clinical trials or clinical trials.mp
   - clinical trials, phase 1 through 4
   - controlled clinical trials
   - multicenter studies
5. Cohort studies.mp
6. Exp epidemiologic studies or epidemiologic studies.mp
   - case-control studies
   - cohort studies
   - longitudinal studies
   - follow-up studies
   - prospective studies
   - cross-sectional studies
   - seroepidemiologic studies
7. Review$.mp
8. 4 **or** 5 **or** 6 **or** 7
9. 3 **and** 8
10. *Limit* 9 to human
11. *Limit* 10 to English (foreign-language articles that had English abstracts were included)

Appendix Table 2. U.S. Preventive Services Task Force Quality Rating Criteria

Randomized Controlled Trials (RCTs)

Criteria:

- Initial assembly of comparable groups: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination).
- Levels of follow-up: differential loss between groups; overall loss to follow-up.
- Measurements: equal, reliable, and valid, and including masking of outcome assessment.
- Clear definition of interventions.
- Important outcomes considered.
- Analysis: intention-to-treat analysis.

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study; follow-up at least 80%; reliable and valid measurement instruments applied equally to the groups; interventions clearly defined; important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention-to-treat analysis is used.

Fair: Generally comparable groups assembled initially, but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTs.

Poor: Groups assembled initially are not close to being comparable or maintained throughout the study; measurement instruments are unreliable or invalid or not applied at all equally among groups; outcome assessment not masked; and key confounders are given little or no attention. For RCTs, no intention-to-treat analysis.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases.
- Nonbiased selection of cases and controls with exclusion criteria applied equally to both.
- Response rate.
- Diagnostic testing procedures applied equally to each group.
- Measurement of exposure accurate and applied equally to each group.
- Appropriate attention to potential confounding variables.

Definition of ratings based on above criteria:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80%; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Appropriate ascertainment of cases and controls and exclusion criteria applied equally to cases and controls, and without major apparent selection or diagnostic work-up bias; response rate less than 80%; or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases; response rates less than 50%; or inattention to confounding variables.

Appendix Table 3. Cohort Studies of Lung Cancer Screening with Chest X-ray (CXR)

Study, Year	Study Population	Intervention	Number Malignancies (%)	Percent Resectable	Survival
Philadelphia Neoplasm Research Project, 1951[48,49]	6,136 men, age 45+	Photofluorograms and questionnaires every 6 mos for 10 yrs	Prevalence: 84 (1.37) Incidence: 121	35	8% (5 yrs)
Tokyo Metro-politan Government Study, 1953[51]	1,871,374 men and women, all ages	Intermittent CXR over 26 yrs (sputum cytology in some)	193 (0.01)	56	44% (5 yrs for resectable tumors) (usual 5-yr survival at that time, 20%)
Veterans Administra-tion Trial, 1958[50]	141,607 men, median age 62.8	CXR and sputum cytology	73 (0.052)	36	17% (32 mos)
South London Cancer Study, 1959[52]	67,400 men, age 45+	CXR every 6 mos	234 (0.35)	56	18% (4 yrs) (usual survival at that time, 9%)

AHRQ Pub. No. 04-0537-B
May 2004