

# 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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**Background:** Lung cancer is the leading cause of cancer-related death in the United States and worldwide. No major professional organizations, including the U.S. Preventive Services Task Force (USPSTF), currently recommend screening for lung cancer.

**Purpose:** To examine the evidence evaluating screening for lung cancer with chest radiography, sputum cytologic examination, and low-dose computed tomography (CT) to aid the USPSTF in updating its recommendation on lung cancer screening.

**Data Sources:** MEDLINE, the Cochrane Library, reviews, editorials, and experts.

**Study Selection:** Studies that evaluated mass screening programs for lung cancer involving the tests of interest were selected. All studies were reviewed, but only studies with control groups were rated in quality since these would most directly influence the USPSTF screening recommendation.

**Data Extraction:** Data were abstracted to data collection forms. Studies were graded according to criteria developed by the USPSTF.

**Data Synthesis:** None of the 6 randomized trials of screening

for lung cancer with chest radiography alone or in combination with sputum cytologic examination showed benefit among those screened. All studies were limited because some level of screening occurred in the control population. Five case-control studies from Japan suggested benefit to both high- and low-risk men and women. All studies were limited by potential healthy screenee bias. Six cohort studies showed that when CT was used to screen for lung cancer, lung cancer was diagnosed at an earlier stage than in usual clinical care. However, these studies did not have control groups, making mortality evaluation difficult. In addition, the studies demonstrated a high rate of false-positive findings.

**Conclusions:** Current data do not support screening for lung cancer with any method. These data, however, are also insufficient to conclude that screening does not work, particularly in women. Two randomized trials of screening with chest radiography or low-dose CT are currently under way and will better inform lung cancer screening decisions.

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No major medical professional organization currently recommends screening for lung cancer. The U.S. Preventive Services Task Force (USPSTF) gave lung cancer screening a grade 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 (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 is attributed to smoking (3). Consequently, the most important public health intervention that could reduce lung cancer incidence and deaths is changing smok-

ing 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 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 cancer cases occur in former smokers, since the risk for lung cancer does not decrease for many years after smoking cessation (15–17). Household exposure to secondhand smoke is substantial and is also associated with lung cancer (18). These smoking exposure rates, combined with large numbers of individuals 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 fatal 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 related to incurable advanced local or metastatic disease (19). Since lung cancer mortality is closely associated with disease stage at the time of diagnosis, it is

believed (primarily on the basis of 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 metastatic spread. For many of these reasons, screening for and treating early lung cancer is intuitively appealing.

## METHODS

This review discusses studies of chest radiography, sputum cytologic examination, and low-dose computed 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** (available at [www.annals.org](http://www.annals.org)). 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, available at [www.annals.org](http://www.annals.org)). For the purposes of this review, high-risk persons are those who currently smoke or have ever smoked and low-risk persons are those who have never smoked. To rate each of the 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 radiography 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 as fair or better quality are described in the text.

Methodologic 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 periodically screened sample) (31), and volunteer bias (a type of selection bias in which volunteers are compared with nonvolunteers) (32). Overdiagnosis occurs when cancer that would never have been important during an individual's lifetime is diagnosed and treated. These biases can be eliminated only in randomized, controlled trials that include death as an outcome. Therefore, public health guidelines and this review place the most emphasis on information from randomized, controlled trials.

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Before preparation of this manuscript, the full report was reviewed by 17 content experts in lung cancer screening and was 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 radiography in conjunction with a multiphasic screening program (33, 34) and 5 randomized, controlled trials of chest radiography, sputum cytologic examination, or both as screening for lung cancer (35–40) were reviewed. In addition, 6 case–control studies (41–46), 1 nonrandomized controlled trial (47), and 4 older cohort studies (48–52) were reviewed (**Appendix Table 2**, available at [www.annals.org](http://www.annals.org)). We also reviewed 6 recent cohort studies of lung cancer screening with CT (53–62).

### Lung Cancer Screening with Chest Radiography with or without Sputum Cytologic Examination

#### Controlled Trials

The methods and quality of the 6 randomized, controlled trials and the single nonrandomized controlled trial of lung cancer screening (33–40, 47, 63–85) are shown in **Tables 1** and **2**. The **Figure** shows the relative risks and 95% CIs of these randomized trials. In the 1960s, the Northwest London Mass Radiography Service conducted a cluster randomized trial of chest radiography screening in approximately 55 000 men older than 40 years of age (35, 36). In this trial, 29 723 male factory workers from 75 randomly identified firms were offered chest radiography 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 was 0.7 per 1000 person-years in the intervention group and 0.8 per 1000 person-years in the control group, not a statistically significant difference.

The National Cancer Institute sponsored 3 randomized, controlled trials of lung cancer screening in male smokers in the United States in the 1970s (37–39, 63, 64, 68, 73–75, 80). The Memorial Sloan-Kettering Study (37, 63–67) and the Johns Hopkins Study (38, 68–72) were identical in design and were conducted to evaluate the incremental benefit of adding sputum cytologic examination to annual chest radiography. Of the 20 427 male smokers ( $\geq 20$  pack-years of smoking) age 45 years or older who volunteered for these 2 studies, 10 234 were randomly assigned to a dual-screening group that was offered screening with chest radiography annually and sputum cytologic examination every 4 months for 5 years; 10 233 were assigned to a chest radiography group that was offered annual screening for 5 years. Each group was followed for 5 to 8 years.

In the Memorial Sloan-Kettering Study, baseline screening identified 30 (6.0 per 1000) malignant tumors in the dual-screening group and 23 (4.6 per 1000) in the chest radiography group (63). After prevalence screening,

**Table 1. Controlled Trials of Lung Cancer Screening with Chest Radiography with or without Sputum Cytologic Examination\***

Study (Reference)	Year Study Began	Sample	Intervention
Northwest London Mass Radiography Service Study (35, 36)	1960	Men age >40 y; 19% former smokers; 67% current smokers	29 723 offered CXR every 6 mo over 3 y; 25 300 offered CXR at baseline and at 3 y
Kaiser Permanente Study (33, 34)	1964	10 713 members age 35–54 y; 17% smokers	Intervention group: 5156 encouraged to have annual multiphasic health checkup, including CXR Control group: 5557 received usual care
Memorial Sloan-Kettering Study (37, 63–67)	1974	10 040 male smokers age ≥45 y	Baseline CXR for all participants; 4968 received annual CXR and sputum cytologic examination every 4 mo for 5–8 y; 5072 received annual CXR and were screened over 5–8 y
Johns Hopkins Study (38, 68–72)	1973	10 387 male smokers age ≥45 y	Baseline CXR for all participants; 5266 received CXR annually and sputum cytologic examination at baseline and every 4 mo; 5161 received annual CXR for 5–8 y
Mayo Lung Project (39, 74–76, 80)	1971	10 933 male smokers age ≥45 y	Baseline CXR, 3-day pooled sputum cytologic examination in all participants; 4618 received CXR and 3-day pooled sputum cytologic examination every 4 mo for 6 y; 4593 received usual care with advice for annual CXR and sputum cytologic examination
Czech Study (40, 84, 85)	1975	6345 male smokers age 40–64 y	After baseline CXR, 3171 received CXR every 6 mo over 3 y and 3174 received usual care. At end of study (years 4–6), CXR performed annually in each group
Wilde (47)‡	1972–1977	All men in 14 districts age 40–65 y (n = 143 880)	Intervention group: 41 532 in 4 districts offered chest fluorography every 6 mo Control group: 102 348 in 10 districts offered chest fluorography every 12–24 mo

\* CXR = chest radiography; NR = not reported.

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

‡ Nonrandomized study.

114 subsequent (incident) cases of lung cancer were identified in the dual-screening group and 121 were identified in the annual radiography group during the screening period. Thirty-three and 32 cases, respectively, were diagnosed in the 2 years following screening. When the incidence and prevalence tumors are combined, 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 per 1000 person-years in both the chest radiography and dual-screening groups.

In the Johns Hopkins Study, prevalence screening identified 39 malignant tumors in the dual-screening group and 40 in the chest radiography group (38, 71). After 8 years of follow-up, 194 incident cases of cancer were identified in the dual-screening group and 202 were identified in the chest radiography group. The mortality rates were 3.4 per 1000 person-years in the dual-screening group and 3.8 per 1000 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 radiography was the Mayo Lung Project, which

involved 10 933 male smokers age 45 years or older (39, 73–83). All participants underwent prevalence screening with sputum cytologic examinations and chest radiography, and 91 cases of cancer were identified (prevalence, 0.83%) (39, 73, 75). After prevalence screening, 4618 men were randomly assigned to a study group screened with chest radiography and pooled 3-day sputum cytologic examination every 4 months for 6 years; 4593 were assigned to a control group advised to have annual chest radiography and sputum cytologic examination. During the study period, 206 incident cases of lung cancer were identified in the dual-screening group and 160 were identified in the control group. After 20 years of follow-up, lung cancer death rates were 4.4 (95% CI, 3.9 to 4.9) and 3.9 (CI, 3.5 to 4.4) per 1000 person-years in the dual-screening and control groups, respectively (80).

The Mayo Lung Project was the first individually randomized, controlled trial to specifically evaluate the role of chest radiography in lung cancer screening. It was also the most influential in determining current public health policy. Although it is rated as fair quality by USPSTF criteria, the study has several limitations. First, prevalence screening

Table 1—Continued

Prevalence	Patients with Incident Lung Cancer	Advanced Tumors (Stages III and IV)	Nonresectable Tumors	Mortality Rate per 1000 Person-Years†
<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	%	
Intervention group: 31 (0.10)	Intervention group: 101	Intervention group: NR	Intervention group: 56	3-y follow-up Intervention group: 0.7 Control group: 0.8
Control group: 20 (0.08)	Control group: 76	Control group: NR	Control group: 71	16-y follow-up Intervention group: 8.6 Usual care group: 7.6
NR	NR	NR	NR	
Dual-screening group: 30 (0.6)	Dual-screening group: 146	Dual-screening group: 64 (1.2) (incidence)	Dual-screening group: 49	5- to 8-y follow-up Dual-screening group: 2.7
CXR group: 23 (0.46)	CXR group: 155	CXR group: 63 (1.2) (incidence)	CXR group: 47	CXR group: 2.7
Dual-screening group: 39 (0.75)	Dual-screening group: 194	NR	Dual-screening group: 53	5- to 8-y followup Dual-screening group: 3.4
CXR group: 40 (0.78)	CXR group: 202		CXR group: 56	CXR group: 3.8
91 (0.83)	Dual-screening group: 206	Dual-screening group: 107 (2.3)	Dual-screening group: 32	20-y follow-up Intervention group: 4.4 Usual care group: 3.9
	Usual care group: 160	Usual care group: 109 (2.4)	Usual care group: 19	
19 (0.30)	Dual-screening group: 108	Dual-screening group: 53 (1.7)	Dual-screening group: 77	15-y follow-up Dual screening group: 7.8
	Control group: 82	Control group: 46 (1.4)	CXR group: 77	Control group: 6.8
Intervention group: 54	Intervention group: 320	NR	Intervention group: 72	10-y follow-up Intervention group: 0.8 Control group: 0.6
Control group: 68	Control group: 599		Control group: 81	

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 they had on mortality could not be determined. Second, nearly half of the controls obtained annual chest radiography during the study, and one third of the malignant tumors in the control group were discovered by screening chest radiography; 73% of controls received chest radiography during the study's last 2 years. Third, adherence was 75% in the intervention group, reducing the study's power (73).

The incidence of lung cancer in the Mayo Lung Project was approximately 22% higher in the intervention group than in the control group (73). Marcus and Prorok (81) evaluated the possibility of nonrandom distribution of lung cancer risk factors and found that distribution did not vary significantly between the intervention and control groups. Although little detailed information is provided, review of the Mayo Lung Project publications reveals evidence showing that not all patients were asymptomatic (39, 73). This 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 radiography in the Mayo Lung Project is generally considered insufficient to increase lung cancer incidence (86). Finally, another possibility is that the higher incidence of lung cancer in the screened sample may represent the diagnosis of insignificant disease, that is, overdiagnosis.

#### Case-Control Studies

Five fair-quality case-control studies were conducted in Japan between 1992 and 2001 (42–46) (Table 3). Lung cancer was fatal in all participants (high-risk men and low- or unknown-risk women). All case-patients were matched to controls by age, sex, and health insurance status. Some studies included adjustment for geographic region, number of previous health examinations, or both, and all accounted for smoking by matching or statistical adjustment. For screening with chest radiography, with or without sputum cytologic examination within 1 year of diagnosis, the odds

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

Study (Reference)	Assembly of Comparable Groups: Randomization/Allocation Concealment	Maintenance of Comparable Groups	Outcomes Assessment: Validity of Method, Masking
Northwest London Mass Radiography Service Study (35, 36)	Cluster randomization 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 Study (33, 34)	Randomization 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 Study (37, 63–67)	Computer-generated randomization (not described); similar all-cause mortality	Formal protocol/algorithm for follow-up; 55 lost to follow-up	All deaths reviewed by statisticians, clinicians, and pathologists who were blind to study group
Johns Hopkins Study (38, 68–72)	Computer-generated randomization (not described); allocation concealment unclear; fairly comparable when evaluated by age, smoking history, nontobacco carcinogen exposure	Formal algorithm for follow-up; 1.3% lost to follow-up	All deaths reviewed by statisticians, clinicians, and pathologists who were blind to study group
Mayo Lung Project (39, 74–76, 80)	Randomization method not described; allocation concealment unclear; similar distribution for age, smoking, exposure to nontobacco carcinogens, and pulmonary disease	Adequate; good follow-up of all participants in both groups	All deaths reviewed by statisticians, clinicians, and pathologists who were blind to study group; National Death Index used for latest follow-up
Czech Study (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 rates, smoking-related deaths higher in intervention group	Not well reported	Cause of death ascertained from death certificates; autopsy performed in one third of patients; blind review not described
Wilde (47)	Nonrandomized; similar community distribution of smoking habits and economic structure; similar all-cause mortality rates; sample age not described	Adequate description; more dropouts in control group	Blinding not described; nonsystematic ascertainment of cause of death

\* CXR = chest radiography; MHC = multiphasic health checkups; NR = not reported.

ratios ranged from 0.40 to 0.72. Four studies had statistically significant findings.

**Lung Cancer Screening with Low-Dose CT**

Several recent cohort studies, all without control groups, have evaluated CT screening for lung cancer. The details of these studies are shown in Table 4. The Early Lung Cancer Action Project (54) involved 1000 asymptomatic volunteers (46% women) age 60 years or older who had a median of 45 pack-years of smoking and no previous malignant disease. Participants were evaluated as medically fit for surgery and underwent chest radiography and CT. Baseline chest radiography identified 68 individuals with suspicious nodules, and diagnosis was confirmed by CT in 33. Seven patients had malignant nodules, all of which were resectable. Baseline CT identified 233 persons with nodules. After follow-up of 30 recommended biopsies, 27 malignant tumors were identified, of which 26 were resectable and 23 were stage I (54). Four other cases of lung cancer were also diagnosed on the basis of non-nodule CT abnormalities. Approximately 1184 subsequent annual examinations resulted in further evaluation (usually high-resolution CT) in 40 persons (4%); biopsies in 9 persons; and lung cancer diagnoses in 9 persons (7.2 per

1000), 6 of which were stage IA (55). No mortality data are yet available on this cohort.

Three CT studies conducted in Japan involved large numbers of both high- and low-risk men and women age 40 years or older (56, 58, 59). Each study used a different protocol but also included chest radiography and sputum cytologic examination; at least 2 were conducted in areas where lung cancer screening with chest radiography and sputum cytologic examination had been performed for many years. Among 15 050 baseline screening tests, 993 (6.6%) showed abnormalities requiring high-resolution CT, and at least 21 underwent biopsy. Seventy-one lung tumors were identified (prevalence, 0.47%), 63 of which were stage I (89%). Researchers performed 21 762 incidence screening tests that led to subsequent high-resolution CT in 1166 persons and identified 60 cases of lung cancer (2.76 per 1000), of which 45 were stage I (Table 4).

A study conducted at the Mayo Clinic involved 1520 men and women age 50 years or older with 20 or more pack-years of smoking (60–62). Baseline screening identified 782 individuals (51.4%) with 1 or more nodules requiring further evaluation; 26 (1.7%) received a diagnosis of primary lung cancer on the basis of CT alone.

Table 2—Continued

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

Among this cohort, 2916 annual incidence screening tests identified 336 individuals (12%) with new nodules, and 10 new diagnoses of lung cancer (6.7 per 1000) were made with CT alone. There were 2 cases of interval cancer and 2 cases of cancer diagnosed with sputum cytologic examination only. Of the 40 persons with malignant tumors, 36 were non-small-cell lung cancer; 31 (86%) were resected for cure. Eight patients had surgery for benign disease.

Finally, a German study (53) involving 817 asymptomatic volunteers age 40 years or older with at least 20 pack-years of smoking was conducted between November 1995 and July 1999. Baseline CT identified 350 persons with nodules. Of these, 269 underwent high-resolution CT, and nodules were ultimately identified in 29 persons. Thirteen of these 29 had biopsies; malignant disease was diagnosed in 10, and 1 case of interval cancer was also diagnosed. 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, which is thought to cause a significant proportion of lung cancer in non-smoking women (18). Although controversial, some studies suggest that for any level of smoking, women are at higher risk for 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 radiography, CT, or both than other cell types. Consequently, radiologic 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 controls come from 4 Japanese case-control studies involving primarily nonsmoking women (passive smoking was not assessed) (43–46). These studies, which are summarized in Table 5, showed that lung cancer mortality odds ratios or relative risks for screening conducted within 12 months of lung cancer diagnosis ranged from 0.39 to 0.61; 2 studies found statistically significant differences. However, interpretation of these studies is limited

**Table 3. Case–Control Studies of Lung Cancer Screening with Chest Radiography and Lung Cancer Mortality Rates**

Study, Year (Reference)	Setting	Case-Patients with Fatal Lung Cancer	Controls
Ebeling and Nischan, 1987 (41)	Berlin	130 men age <70 y	204 patients from community center 194 patients from hospital outpatient department
Okamoto et al., 1999 (42)	Japan	158 men and 35 women age 40–74 y	579*
Sobue, 2000 (43)	Japan	208 high-risk men, 65 low-risk women	1269*
Sagawa et al., 2001 (44)	Japan	258 smoking and nonsmoking men and 70 nonsmoking women age >39 y	1886*
Tsukada et al., 2001 (45)	Japan	149 high-risk men and 25 non–high-risk (nonsmoking) women age >40 y	801*
Nishii et al., 2001 (46)	Japan	412 men and women age 40–79 y	3490*

\* 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 cytologic examination.  
 || Excluding screening at <12 mo.

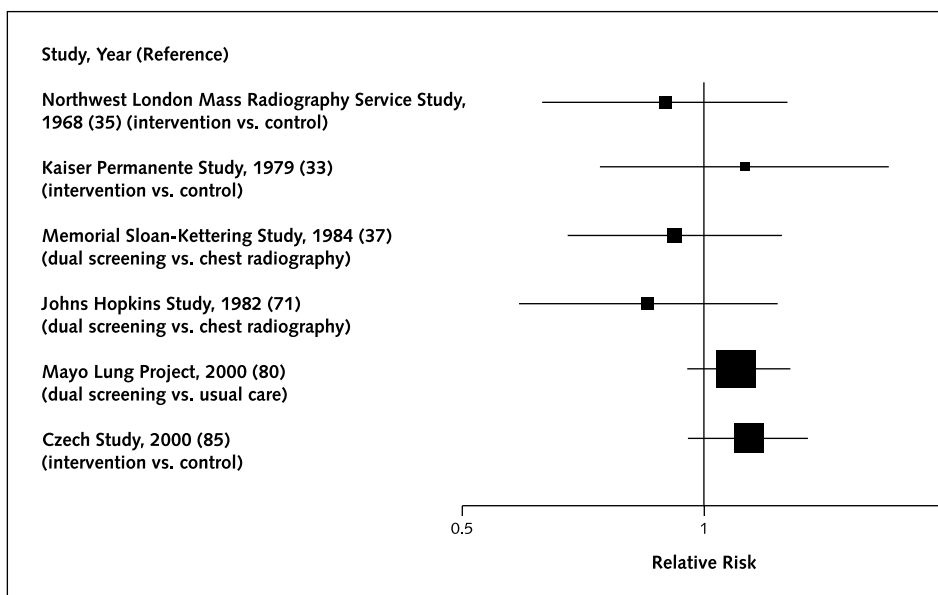
by the screening biases discussed in this review. Five studies of CT have included women, but mortality data are not yet available. Randomized trials of lung cancer screening with chest radiography, low-dose CT, or both involving women are under way.

**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. Some lower-quality evidence evaluating chest radiography with or without sputum cytologic examination (case–control studies) has shown benefit, and higher-quality evidence (randomized, controlled trials) has not. Studies show that lung cancer can be diagnosed at an earlier stage with CT screening than in usual clinical practice, but little is known about patient

**Figure. Mortality in randomized, controlled trials of lung cancer screening with chest radiography with or without sputum cytologic examination.**



Follow-up ranged from 3 to 20 years among the 6 studies. The solid black squares represent Mantel–Haenszel weight.

Table 3—Continued

Matching/Adjustment Factors	Odds Ratio for Lung Cancer Death Associated with Screening (95% CI)	Study Quality
Age; opportunity for screening; location	0.88 (0.53–1.45)	Poor†‡
Age; opportunity for screening	1.09 (0.67–1.78)	
National Health Insurance; smoking status; opportunity for screening; location	0.54 (0.34–0.85) ≤12 mo 0.54 (0.30–0.96) ≤24 0.59 (0.30–1.15) 24–36 mo	Fair
National Health Insurance; smoking status; opportunity for screening; health checkups	0.72 (0.5–1.03) ≤12 mo§ 0.83 (0.56–1.23) ≤12–24 mo§	Fair
Smoking status; opportunity for screening (all had negative screening results in 1989); location	0.54 (0.41–0.73) ≤12 mo§ 1.24 (0.59–2.59) 12–24 mo§   0.62 (0.42–0.92) ≤24 mo§ 0.64 (0.36–1.14) ≤36 mo§ 2.41 (0.54–10.7) ≤48 mo§	Fair
National Health Insurance; smoking status; opportunity for screening	0.40 (0.27–0.59) ≤12 mo§ 1.42 (0.63–3.17) ≤12–24 mo§	Fair
National Health Insurance; smoking status; opportunity for screening; location	0.59 (0.46–0.74) ≤12 mo§	Fair

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 screening for lung cancer with chest radiography. 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 or healthy screenee bias in case-control studies, even well-conducted ones. This might bias such studies toward ben-

Table 4. Outcomes of Lung Cancer Screening with Low-Dose Computed Tomography\*

Study, Year (Reference)	Screening Interval	Screening Type	Screening Tests Performed	Positive Test Results	Recommendation for Follow-up Based on LDCT			Surgery for Diagnosis (Benign Nodules)	Lung Cancer†	Stage 1 Disease
					HRCT	Referral	Biopsy			
					←	n	→			
Diederich et al., 2002 (53)		Baseline	817	350 (43)	269	29	13	1 (1)	11 (1.3) (1 interval)	58
Henschke et al., 1999, 2001 (54, 55)	6–18	Baseline	1000	237 (24)	233	104	27	0	31 (3.1)	85
		LDCT	1184	40	40	NR	9	NR	9 (0.9)	67
		Incidence LDCT	1000	68 (6.8)	33	NR	NR	0	7 (0.7)	
Nawa et al., 2002 (56)	12	Baseline	7956	2099 (26.4)	541	64	NR	NR	36 (0.5)	86
		LDCT	5568	NR	148	7	NR	NR	4 (0.1)	100
Sone et al., 2001 (58)	12	Baseline	5483	279 (5.1)	266	NR	NR	NR (7)	22 (0.4)	100
		LDCT	8303†	309	297	NR	NR	NR (9)	37 (0.6)	86
Sobue et al., 2002 (59)	6	Baseline	1611	186 (11.5)	186	25	21	0	13 (0.8)	77
		LDCT	7891	721	721	57	35	1 (0)	19 (0.2)	79
		Incidence LDCT	1611	55 (3.4)	22	9	8	0	5 (0.3)	60
Swensen et al., 2002, 2003 (61, 62)	12	Baseline	1520	782 (51.4)	NR	NR	NR	NR (8)	27 (1.8)‡	
		LDCT	2916	336	NR	NR	NR		11 (0.7) (+2 interval)‡	66

\* All data are presented by individual except incidence, which refers to screening tests performed. CXR = chest radiography; HRCT = high-resolution computed tomography; LDCT = low-dose computed tomography; NR = not reported.

† 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.

‡ 1 case of malignant disease diagnosed with sputum cytologic examination only.

Table 5. Lung Cancer Screening Studies Including Women\*

Study, Year (Reference)	Study Type	Setting	Description of Sample	Intervention	Odds Ratio or Relative Risk of Lung Cancer Death (95% CI) or Number of Malignant Tumors Identified
Sobue, 2000 (43)	Case-control	Japan	65 low-risk patients	CXR with or without sputum cytologic examination	0.42 (0.20–0.87) for screening <12 mo
Sagawa et al., 2001 (44)	Case-control	Japan	70 low-risk patients age >39 y	CXR with or without sputum cytologic examination	0.57 (0.30–1.11) for screening <12 mo
Tsukada et al., 2001 (45)	Case-control	Japan	25 low-risk patients age >40 y	CXR with or without sputum cytologic examination	0.61 (0.23–1.68) for screening <12 mo
Nishii et al., 2001 (46)	Case-control	Japan	412 mixed-risk patients age 40–79 y	CXR	0.39 (0.24–0.64) for screening <12 mo
Henschke et al., 1999, 2001 (54, 55)	Cohort	United States	460 high-risk participants	Baseline LDCT and repeated LDCT	NR by sex
Sone et al., 2001 (58)	Cohort	Japan	2512 participants	Baseline LDCT	11 malignant tumors identified
Diederich et al., 2002 (53)	Cohort	Germany	1816 participants	Repeated LDCT	4 malignant tumors identified
			229 high-risk participants	Baseline LDCT	NR by sex
Nawa et al., 2002 (56)	Cohort	Japan	1367 participants (4.3% current or former smokers)	Baseline LDCT	12 cases of malignant disease identified, all in nonsmokers
				Annual repeated LDCT	0
Swensen et al., 2002, 2003 (61, 62)	Cohort	United States	735 participants	Baseline and repeated LDCT	NR by sex

\* CXR = chest radiography; LDCT = low-dose computed tomography; NR = not reported.

efit, since persons choosing screening may differ from those not being screened in factors that 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 methodologic 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 that include death as an outcome are needed to definitively evaluate this issue. Abnormal CT findings and lung cancer are probably more common in U.S. and German studies than in Japanese studies because 1) higher-risk samples were screened in the United States and Germany; 2) previous population lung cancer screening has been conducted in Japan; 3) CT methods differed among studies; and 4) rates of histoplasmosis may be higher in the United States.

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 radiography screening come from the recent CT studies, since data from the chest radiography trials precede the use of CT for evaluation of radiography abnormalities, and more patients had previous thoracotomy or biopsy than would have in current clinical practice. Table 4 shows positive chest radiography rates and the diagnostic outcomes associated with chest radiography from the CT studies. Most abnormalities on chest radiography are resolved or screening results are found to

be false-positive when evaluated by CT (54, 59). For radiographs identified as suspicious for cancer in the National Cancer Institute studies, the positive predictive value ranged from 41% to 60% (29).

In the CT studies, the false-positive rate was the number of patients who required further evaluation after CT but did not have cancer. When this criterion was used, the false-positive rates in the CT studies ranged from 5% to 50% in prevalence screening and 3% to 12% in incidence screening; 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, and most (63% to 90%) then received a diagnosis of cancer (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 is 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 high anxiety and concern, and those pursuing further evaluation experience associated cost and risk. Although the false-positive rate is high in the lung cancer screening studies, false-positive results on a lung cancer screening study (either chest radiography or CT) may have a different effect on patients than false-positive results on other types of cancer screening tests. Patients who smoke potentially have some control over their subsequent risk and may be able to more effectively modify their high-risk behavior. Data from the Early Lung Cancer Action Project 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 radiograph might also influence smoking behavior.

An important and controversial issue in lung cancer screening is the question of overdiagnosis and consequent overtreatment. 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 overdiagnosis are data from the Mayo Lung Project 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. These findings suggest diagnosis of a pool of indolent tumors (98). Although the higher lung cancer mortality rate among the intervention group in the Mayo Lung Project 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 (that is, more persons in the screened group were evaluated and treated, which, with treatment-associated risk, resulted in a true increase in mortality rates). Alternatively, an increase in lung cancer mortality rates among screened individuals 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 malignant condition as the cause of death regardless of its clinical course. This results in bias against screening in evaluations of disease-specific mortality (99). Black and colleagues (100) noted that the excess lung cancer mortality, particularly death from metastatic adenocarcinoma, observed among the screened group in the Mayo Lung Project was probably at least partially a consequence of this type of differential misclassification.

Arguments against an important role for overdiagnosis 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 persons is questionable, particularly given selection biases for autopsy. Further data against overdiagnosis come from 2 natural history studies of screening- and symptom-detected unresected stage I non-small-cell lung cancer, which showed that almost all patients with lung cancer die of the disease over 5 to 10 years (25, 26). Whether a strong case for overdiagnosis 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, overdiagnosis may occur. The issue of overdiagnosis is particularly relevant to the harm associated with lung resection for cancer, which involves significant associated mortality and morbidity. More data are needed to definitively evaluate this issue.

Another potential harm of screening is false-negative findings and possible false reassurance. In current practice,

the best estimate of the rate of false-negative results on chest radiography comes from the CT studies, where false-negative rates as high as 75% were shown (54, 59). Clinical series of chest radiography suggest that 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 yield false-negative results (62). The potential for false reassurance with CT certainly exists, particularly if those screened believe that they are undergoing a definitive examination.

The rate of biopsy-associated complications was not described in the CT studies. The morbidity and mortality associated with thoracotomy for positive test results (true or false) are also difficult to evaluate. Studies of symptomatic patients suggest that morbidity and mortality are directly related to the amount of lung tissue removed. Overall, mortality rates ranged from 1.3% to 11.6% and morbidity rates ranged from 8.8% to 44% among several series reviewed. Rates are lower among patients undergoing smaller resections, those with fewer comorbid conditions, and those treated at centers with greater surgical volume (28, 47, 104–110). Complication rates from studies of symptomatic patients are likely to be greater than complication rates among asymptomatic individuals in screening programs directed at those judged healthy enough for 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 radiography is being compared with usual care in the Prostate, Lung, Ovarian, and Colorectal Cancer Trial, which involves more than 100 000 men and women age 55 to 74 years (112, 113). Data from this study should be available in 2010. The National Lung Screening Trial will compare routine screening CT with chest radiography in high-risk men and women age 55 to 74 years (114).

New technologies may also contribute to the early detection of and possibly 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). Several other potential targets in sputum, bronchial fluid, and expired air may have a role in early lung cancer detection and are currently being investigated (123, 124).

In summary, studies evaluating chest radiography screening for lung cancer have had mixed findings. Stronger evidence from 30-year-old trials suggest no benefit among male smokers and possible overdiagnosis, and weaker study designs suggest benefit to men and women. There are important methodologic limitations to all of these studies. The studies of CT have demonstrated that

lung cancer can be diagnosed at a significantly earlier stage with CT screening than in current 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 randomized, controlled trials of screening CT. Given the uncertainty associated with chest radiography screening, it is unfortunate that the National Lung Screening Trial does not include non-screened control groups. However, data on chest radiography screening will be available from the Prostate, Lung, Ovarian, and Colorectal Cancer 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 radiography, screening CT, or both. We hope that new methods of screening for lung cancer will be developed and refined. Even a small decrease in lung cancer mortality from screening would save thousands of lives each year.

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## References

1. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services. 2nd ed. Alexandria, VA: International Medical Publishing; 1996.
2. American Cancer Society. Cancer Facts and Figures 2003. Accessed at [www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf](http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf) on 11 March 2004.
3. Strauss GM. Bronchiogenic carcinoma. In: Textbook of Pulmonary Diseases. 6th ed. Philadelphia: Lippincott-Raven; 1998.
4. Zang EA, Wynder EL. Differences in lung cancer risk between men and

women: examination of the evidence. *J Natl Cancer Inst.* 1996;88:183-92. [PMID: 8632492]

5. Strauss GM. Screening for lung cancer: an evidence-based synthesis. *Surg Oncol Clin N Am.* 1999;8:747-74, viii. [PMID: 10452939]

6. Osann KE. Lung cancer in women: the importance of smoking, family history of cancer, and medical history of respiratory disease. *Cancer Res.* 1991;51:4893-7. [PMID: 1654203]

7. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. *Ann Intern Med.* 1987;106:512-8. [PMID: 3826952]

8. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ.* 1996;313:711-5; discussion 715-6. [PMID: 8819439]

9. Trichopoulos D, Mollo F, Tomatis L, Agapitos E, Delsedime L, Zavitsanos X, et al. Active and passive smoking and pathological indicators of lung cancer risk in an autopsy study. *JAMA.* 1992;268:1697-701. [PMID: 1527879]

10. Davila DG, Williams DE. The etiology of lung cancer. *Mayo Clin Proc.* 1993;68:170-82. [PMID: 8423698]

11. Cigarette smoking among adults—United States, 1999. *MMWR Morb Mortal Wkly Rep.* 2001;50:869-73. [PMID: 11666113]

12. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med.* 1991;325:311-5. [PMID: 2057036]

13. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195-202. [PMID: 9337378]

14. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999;340:685-91. [PMID: 10053177]

15. Burns DM. Primary prevention, smoking, and smoking cessation: implications for future trends in lung cancer prevention. *Cancer.* 2000;89:2506-9. [PMID: 11147637]

16. Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. *J Natl Cancer Inst.* 1993;85:457-64. [PMID: 8445673]

17. Tong L, Spitz MR, Fueger JJ, Amos CA. Lung carcinoma in former smokers. *Cancer.* 1996;78:1004-10. [PMID: 8780538]

18. Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA.* 1994;271:1752-9. [PMID: 8196118]

19. Jett JR. Current treatment of unresectable lung cancer. *Mayo Clin Proc.* 1993;68:603-11. [PMID: 8388526]

20. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7. [PMID: 9187198]

21. American Cancer Society. Cancer Facts and Figures 2000. Accessed at [www.cancer.org/downloads/STT/F&F00.pdf](http://www.cancer.org/downloads/STT/F&F00.pdf) on 11 March 2004.

22. Keller SM, Adak S, Wagner H, Johnson DH. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. *Ann Thorac Surg.* 2000;70:358-65; discussion 365-6. [PMID: 10969645]

23. Greenwald HP, Polissar NL, Borgatta EF, McCorkle R, Goodman G. Social factors, treatment, and survival in early-stage non-small cell lung cancer. *Am J Public Health.* 1998;88:1681-4. [PMID: 9807536]

24. Yoshino I, Baba H, Fukuyama S, Kameyama T, Shikada Y, Tomiyasu M, et al. A time trend of profile and surgical results in 1123 patients with non-small cell lung cancer. *Surgery.* 2002;131:S242-8. [PMID: 11821819]

25. Flehinger BJ, Kimmel M, Melamed MR. The effect of surgical treatment on survival from early lung cancer. Implications for screening. *Chest.* 1992;101:1013-8. [PMID: 1313349]

26. Sobue T, Suzuki T, Matsuda M, Kuroishi T, Ikeda S, Naruke T. Survival for clinical stage I lung cancer not surgically treated. Comparison between screen-detected and symptom-detected cases. The Japanese Lung Cancer Screening Research Group. *Cancer.* 1992;69:685-92. [PMID: 1730119]

27. Snijder RJ, Brutel de la Riviere A, Elbers HJ, van den Bosch JM. Survival in resected stage I lung cancer with residual tumor at the bronchial resection margin.

- Ann Thorac Surg. 1998;65:212-6. [PMID: 9456120]
28. Fang D, Zhang D, Huang G, Zhang R, Wang L, Zhang D. Results of surgical resection of patients with primary lung cancer: a retrospective analysis of 1,905 cases. *Ann Thorac Surg*. 2001;72:1155-9. [PMID: 11603429]
  29. Manser RL, Irving LB, Stone C, Byrnes G, Abramson M, Campbell D. Screening for lung cancer. *Cochrane Database Syst Rev*. 2001;CD001991. [PMID: 11687005]
  30. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20:21-35. [PMID: 11306229]
  31. Cole P, Morrison AS. Basic issues in population screening for cancer. *J Natl Cancer Inst*. 1980;64:1263-72. [PMID: 6767876]
  32. Fletcher RH, Fletcher SW, Wagner EH. *Clinical Epidemiology, The Essentials*. 3rd ed. Baltimore: Williams & Wilkins; 1996:128.
  33. Dales LG, Friedman GD, Collen MF. Evaluating periodic multiphasic health checkups: a controlled trial. *J Chronic Dis*. 1979;32:385-404. [PMID: 109452]
  34. Friedman GD, Collen MF, Fireman BH. Multiphasic Health Checkup Evaluation: a 16-year follow-up. *J Chronic Dis*. 1986;39:453-63. [PMID: 3711252]
  35. Brett GZ. The value of lung cancer detection by six-monthly chest radiographs. *Thorax*. 1968;23:414-20. [PMID: 5664703]
  36. Brett GZ. Earlier diagnosis and survival in lung cancer. *Br Med J*. 1969;4:260-2. [PMID: 5345935]
  37. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. *Chest*. 1984;86:44-53. [PMID: 6734291]
  38. Frost JK, Ball WC Jr, Levin ML, Tockman MS, Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir Dis*. 1984;130:549-54. [PMID: 6091505]
  39. Fontana RS, Sanderson DR, Taylor WF, Woolner LB, Miller WE, Muhm JR, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis*. 1984;130:561-5. [PMID: 6091507]
  40. Kubik A, Polak J. Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. *Cancer*. 1986;57:2427-37. [PMID: 3697941]
  41. Ebeling K, Nischan P. Screening for lung cancer—results from a case-control study. *Int J Cancer*. 1987;40:141-4. [PMID: 3610384]
  42. Okamoto N, Suzuki T, Hasegawa H, Gotoh T, Hagiwara S, Sekimoto M, et al. Evaluation of a clinic-based screening program for lung cancer with a case-control design in Kanagawa, Japan. *Lung Cancer*. 1999;25:77-85. [PMID: 10470841]
  43. Sobue T. A case-control study for evaluating lung cancer screening in Japan. *Cancer*. 2000;89:2392-6. [PMID: 11147617]
  44. Sagawa M, Tsubono Y, Saito Y, Sato M, Tsuji I, Takahashi S, et al. A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. *Cancer*. 2001;92:588-94. [PMID: 11505403]
  45. Tsukada H, Kurita Y, Yokoyama A, Wakai S, Nakayama T, Sagawa M, et al. An evaluation of screening for lung cancer in Niigata Prefecture, Japan: a population-based case-control study. *Br J Cancer*. 2001;85:1326-31. [PMID: 11720469]
  46. Nishii K, Ueoka H, Kiura K, Kodani T, Tabata M, Shibayama T, et al. A case-control study of lung cancer screening in Okayama Prefecture, Japan. *Lung Cancer*. 2001;34:325-32. [PMID: 11714529]
  47. Wilde J. A 10 year follow-up of semi-annual screening for early detection of lung cancer in the Erfurt County, GDR. *Eur Respir J*. 1989;2:656-62. [PMID: 2776873]
  48. Weiss W, Boucot KR, Cooper DA. The Philadelphia pulmonary neoplasm research project. Survival factors in bronchogenic carcinoma. *JAMA*. 1971;216:2119-23. [PMID: 5108675]
  49. Weiss W, Boucot KR. The Philadelphia Pulmonary Neoplasm Research Project. Early roentgenographic appearance of bronchogenic carcinoma. *Arch Intern Med*. 1974;134:306-11. [PMID: 4843198]
  50. An evaluation of radiologic and cytologic screening for the early detection of lung cancer: a cooperative pilot study of the American Cancer Society and the Veterans Administration. *Cancer Res*. 1966;26:2083-121. [PMID: 5922259]
  51. Hayata Y, Funatsu H, Kato H, Saito Y, Sawamura K, Furose K. Results of lung cancer screening programs in Japan. *Recent Results Cancer Res*. 1982;82:163-73. [PMID: 7111839]
  52. Nash FA, Morgan JM, Tomkins JG. South London Lung Cancer Study. *Br Med J*. 1968;2:715-21. [PMID: 5690439]
  53. Diederich S, Wormanns D, Semik M, Thomas M, Lenzen H, Roos N, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. *Radiology*. 2002;222:773-81. [PMID: 11867800]
  54. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. 1999;354:99-105. [PMID: 10408484]
  55. Henschke CI, Yankelevitz DF, Libby DM, McCauley D, Pasmantier M, Altorki NK, et al. Early lung cancer action project: annual screening using single-slice helical CT. *Ann N Y Acad Sci*. 2001;952:124-34. [PMID: 11795431]
  56. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest*. 2002;122:15-20. [PMID: 12114333]
  57. Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet*. 1998;351:1242-5. [PMID: 9643744]
  58. Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. *Br J Cancer*. 2001;84:25-32. [PMID: 11139308]
  59. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol*. 2002;20:911-20. [PMID: 11844811]
  60. Jett JR. Spiral computed tomography screening for lung cancer is ready for prime time [Editorial]. *Am J Respir Crit Care Med*. 2001;163:812; discussion 814-5. [PMID: 11282745]
  61. Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes AM, et al. Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med*. 2002;165:508-13. [PMID: 11850344]
  62. Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, et al. Lung cancer screening with CT: Mayo Clinic experience. *Radiology*. 2003;226:756-61. [PMID: 12601181]
  63. Flehinger BJ, Melamed MR, Zaman MB, Heelan RT, Perchick WB, Martini N. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. *Am Rev Respir Dis*. 1984;130:555-60. [PMID: 6091506]
  64. Martini N. Results of the Memorial Sloan-Kettering study in screening for early lung cancer. *Chest*. 1986;89(4 Suppl):S325.
  65. Heelan RT, Flehinger BJ, Melamed MR, Zaman MB, Perchick WB, Caravelli JF, et al. Non-small-cell lung cancer: results of the New York screening program. *Radiology*. 1984;151:289-93. [PMID: 6324279]
  66. Melamed M, Flehinger B, Miller D, Osborne R, Zaman M, McGinnis C, et al. Preliminary report of the lung cancer detection program in New York. *Cancer*. 1977;39:369-82. [PMID: 837325]
  67. Melamed MR. Lung cancer screening results in the National Cancer Institute New York study. *Cancer*. 2000;89:2356-62. [PMID: 11147612]
  68. Berlin NI, Buncher CR, Fontana RS, Frost JK, Melamed MR. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: Introduction. *Am Rev Respir Dis*. 1984;130:545-9. [PMID: 6548343]
  69. Stitik FP, Tockman MS. Radiographic screening in the early detection of lung cancer. *Radiol Clin North Am*. 1978;16:347-66. [PMID: 746141]
  70. Baker RR, Tockman MS, Marsh BR, Stitik FP, Ball WC Jr, Eggleston JC, et al. Screening for bronchogenic carcinoma: the surgical experience. *J Thorac Cardiovasc Surg*. 1979;78:876-82. [PMID: 502570]
  71. Levin ML, Tockman MS, Frost JK, Ball WC Jr. Lung cancer mortality in males screened by chest X-ray and cytologic sputum examination: a preliminary report. *Recent Results Cancer Res*. 1982;82:138-46. [PMID: 7111836]
  72. Tockman M. Survival and mortality from lung cancer in a screened population: The Johns Hopkins study. *Chest*. 1986;89(Suppl):325s-326s.
  73. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm

- JR, et al. Screening for lung cancer. A critique of the Mayo Lung Project. *Cancer*. 1991;67:1155-64. [PMID: 1991274]
74. **Fleehinger BJ, Kimmel M, Polyak T, Melamed MR.** Screening for lung cancer. The Mayo Lung Project revisited. *Cancer*. 1993;72:1573-80. [PMID: 8394199]
75. **Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR.** Lung cancer screening: the Mayo program. *J Occup Med*. 1986;28:746-50. [PMID: 3528436]
76. **Woolner LB, Fontana RS, Sanderson DR, Miller WE, Muhm JR, Taylor WF, et al.** Mayo Lung Project: evaluation of lung cancer screening through December 1979. *Mayo Clin Proc*. 1981;56:544-55. [PMID: 6267386]
77. **Taylor WF, Fontana RS, Uhlenhopp MA, Davis CS.** Some results of screening for early lung cancer. *Cancer*. 1981;47:1114-20. [PMID: 6263442]
78. **Taylor WF, Fontana RS.** Biometric design of the Mayo Lung Project for early detection and localization of bronchogenic carcinoma. *Cancer*. 1972;30:1344-7. [PMID: 5083070]
79. **Sanderson D, Fontana R.** Results of Mayo lung project: an interim report. *Recent Results Cancer Res*. 1982;82:179-86. [PMID: 6287546]
80. **Marcus PM, Bergstralh EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF, et al.** Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst*. 2000;92:1308-16. [PMID: 10944552]
81. **Marcus PM, Prorok PC.** Reanalysis of the Mayo Lung Project data: the impact of confounding and effect modification. *J Med Screen*. 1999;6:47-9. [PMID: 10321372]
82. **Muhm JR, Miller WE, Fontana RS, Sanderson DR, Uhlenhopp MA.** Lung cancer detected during a screening program using four-month chest radiographs. *Radiology*. 1983;148:609-15. [PMID: 6308709]
83. **Fontana TR, Sanderson DR, Woolner LB, Miller WE, Bernatz PE, Payne WS, et al.** The Mayo Lung Project for early detection and localization of bronchogenic carcinoma: a status report. *Chest*. 1975;67:511-22. [PMID: 1126186]
84. **Kubik A, Parkin DM, Khat M, Erban J, Polak J, Adamec M.** Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. *Int J Cancer*. 1990;45:26-33. [PMID: 2404878]
85. **Kubik AK, Parkin DM, Zatloukal P.** Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. *Cancer*. 2000;89:2363-8. [PMID: 11147613]
86. **Diederich S, Lenzen H.** Radiation exposure associated with imaging of the chest: comparison of different radiographic and computed tomography techniques. *Cancer*. 2000;89:2457-60. [PMID: 11147626]
87. **Osann KE, Anton-Culver H, Kurosaki T, Taylor T.** Sex differences in lung-cancer risk associated with cigarette smoking. *Int J Cancer*. 1993;54:44-8. [PMID: 8386708]
88. **McDuffie HH, Klaassen DJ, Dosman JA.** Men, women and primary lung cancer—a Saskatchewan personal interview study. *J Clin Epidemiol*. 1991;44:537-44. [PMID: 2037858]
89. **Nesbitt JC, Lee JL, Komaki R, Roth JA.** Cancer of the lung. In: Holland JF, Bast RC Jr., Morton DL, Frei E 3rd, Kufe DW, Weichselbaum RR, eds. *Cancer Medicine*. Baltimore: Williams & Wilkins; 1997.
90. **Cotran RS, Kumar V, Robbins SL, Schoen FJ.** Robbins' Pathologic Basis of Disease. 5th ed. Philadelphia: WB Saunders; 1994.
91. **Weiss NS, McKnight B, Stevens NG.** Approaches to the analysis of case-control studies of the efficacy of screening for cancer. *Am J Epidemiol*. 1992;135:817-23. [PMID: 1595681]
92. **Weiss NS.** Application of the case-control method in the evaluation of screening. *Epidemiol Rev*. 1994;16:102-8. [PMID: 7925719]
93. **Moss SM.** Case-control studies of screening. *Int J Epidemiol*. 1991;20:1-6. [PMID: 2066205]
94. **Bernard A.** Resection of pulmonary nodules using video-assisted thoracic surgery. The Thorax Group. *Ann Thorac Surg*. 1996;61:202-4; discussion 204-5. [PMID: 8561553]
95. **Schmuecking MW, Baum RP, Leonhardi J, Pichta K, Bonnet R, Presselt N.** Evaluation of solitary pulmonary nodules: diagnostic accuracy of F-18 FDG PET in clinical routine [Abstract]. *Radiology*. 2000;217(Suppl):469.
96. **Ostroff JS, Buckshee N, Mancuso CA, Yankelevitz DF, Henschke CI.** Smoking cessation following CT screening for early detection of lung cancer. *Prev Med*. 2001;33:613-21. [PMID: 11716658]
97. **Pigula FA, Keenan RJ, Ferson PF, Landreneau RJ.** Unsuspected lung cancer found in work-up for lung reduction operation. *Ann Thorac Surg*. 1996;61:174-6. [PMID: 8561548]
98. **Black WC.** Overdiagnosis: An underrecognized cause of confusion and harm in cancer screening [Editorial]. *J Natl Cancer Inst*. 2000;92:1280-2. [PMID: 10944539]
99. **Lindgren A.** Autopsy and cause of death in randomized mammography studies. *Qual Assur Health Care*. 1993;5:303-7. [PMID: 8018887]
100. **Black WC, Haggstrom DA, Welch HG.** All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst*. 2002;94:167-73. [PMID: 11830606]
101. **McFarlane MJ, Feinstein AR, Wells CK.** Clinical features of lung cancers discovered as a postmortem "surprise". *Chest*. 1986;90:520-3. [PMID: 3757562]
102. **Austin JH, Romney BM, Goldsmith LS.** Missed bronchogenic carcinoma: radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. *Radiology*. 1992;182:115-22. [PMID: 1727272]
103. **Quekel LG, Kessels AG, Goei R, van Engelsloven JM.** Miss rate of lung cancer on the chest radiograph in clinical practice. *Chest*. 1999;115:720-4. [PMID: 10084482]
104. **Bernard A, Bouchot O, Hagry O, Favre JP.** Risk analysis and long-term survival in patients undergoing resection of T4 lung cancer. *Eur J Cardiothorac Surg*. 2001;20:344-9. [PMID: 11463555]
105. **Vaporciyan AA, Merriman KW, Ece F, Roth JA, Smythe WR, Swisher SG, et al.** Incidence of major pulmonary morbidity after pneumonectomy: association with timing of smoking cessation. *Ann Thorac Surg*. 2002;73:420-5; discussion 425-6. [PMID: 11845853]
106. **Romano PS, Mark DH.** Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest*. 1992;101:1332-7. [PMID: 1582293]
107. **Myrdal G, Gustafsson G, Lambe M, Horte LG, Stahle E.** Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. *Eur J Cardiothorac Surg*. 2001;20:694-9. [PMID: 11574210]
108. **Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B.** Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest*. 1994;106:329S-330S. [PMID: 7988256]
109. **Battafarano RJ, Piccirillo JF, Meyers BF, Hsu HS, Guthrie TJ, Cooper JD, et al.** Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2002;123:280-7. [PMID: 11828287]
110. **Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB.** The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med*. 2001;345:181-8. [PMID: 11463014]
111. 1989 survey of physicians' attitudes and practices in early cancer detection. *CA Cancer J Clin*. 1990;40:77-101. [PMID: 2106372]
112. **Gohagan JK, Prorok PC, Hayes RB, Kramer BS.** The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials*. 2000;21:251S-272S. [PMID: 11189683]
113. **Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al.** Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21:273S-309S. [PMID: 11189684]
114. National Lung Screening Trial (NLST) 2002. National Institutes of Health. Available at [clinicaltrials.gov/ct/gui/show/NCT00047385;jsessionid=20DAB829F5C5A123FB490104A003A4BA?order=1](http://clinicaltrials.gov/ct/gui/show/NCT00047385;jsessionid=20DAB829F5C5A123FB490104A003A4BA?order=1).
115. **Tockman MS, Gupta PK, Myers JD, Frost JK, Baylin SB, Gold EB, et al.** Sensitive and specific monoclonal antibody recognition of human lung cancer antigen on preserved sputum cells: a new approach to early lung cancer detection. *J Clin Oncol*. 1988;6:1685-93. [PMID: 2846790]
116. **Mao L, Hruban RH, Boyle JO, Tockman M, Sidransky D.** Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. *Cancer Res*. 1994;54:1634-7. [PMID: 8137272]
117. **Palmisano WA, Divine KK, Saccomanno G, Gilliland FD, Baylin SB, Herman JG, et al.** Predicting lung cancer by detecting aberrant promoter methylation in sputum. *Cancer Res*. 2000;60:5954-8. [PMID: 11085511]
118. **Tsou JA, Hagen JA, Carpenter CL, Laird-Offringa IA.** DNA methylation analysis: a powerful new tool for lung cancer diagnosis. *Oncogene*. 2002;21:5450-61. [PMID: 12154407]

119. **Gazdar AF, Minna JD.** Molecular detection of early lung cancer [Editorial]. *J Natl Cancer Inst.* 1999;91:299-301. [PMID: 10050857]
120. **Patz EF Jr, Goodman PC, Bepler G.** Screening for lung cancer. *N Engl J Med.* 2000;343:1627-33. [PMID: 11096172]
121. **Fong KM, Sekido Y, Minna JD.** Molecular pathogenesis of lung cancer. *J Thorac Cardiovasc Surg.* 1999;118:1136-52. [PMID: 10595998]
122. **Tockman MS, Mulshine JL.** Sputum screening by quantitative microscopy: a new dawn for detection of lung cancer? [Editorial]. *Mayo Clin Proc.* 1997;72:788-90. [PMID: 9276609]
123. **Mulshine JL, Tockman MS, Smart CR.** Considerations in the development of lung cancer screening tools. *J Natl Cancer Inst.* 1989;81:900-6. [PMID: 2659802]
124. **Rizvi N, Hayes DF.** A "breathalyser" for lung cancer? *Lancet.* 1999;353:1897-8. [PMID: 10371562]
125. **Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR.** Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA.* 2003;289:313-22. [PMID: 12525232].

## APPENDIX. U.S. PREVENTIVE SERVICES TASK FORCE QUALITY RATING CRITERIA

For randomized, controlled trials, the criteria are as follows.

1. Initial assembly of comparable groups: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.

2. Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination).

3. Levels of follow-up: differential loss between groups; overall loss to follow-up.

4. Measurements: equal, reliable, and valid, including masking of outcome assessment.

5. Clear definition of interventions.

6. Important outcomes considered.

7. Analysis: intention to treat.

Definition of ratings are as follows, based on these criteria.

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

In a **Fair** study, comparable groups are generally 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 are 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 randomized, controlled trials.

In a **Poor** study, 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 is not masked; and key confounders are given little or no attention. For randomized, controlled trials, intention-to-treat analysis is not performed.

For case-control studies, the criteria are as follows.

1. Accurate ascertainment of case-patients.

2. Nonbiased selection of case-patients and controls with exclusion criteria applied equally to both.

3. Response rate.

4. Diagnostic testing procedures applied equally to each group.

5. Measurement of exposure accurate and applied equally to each group.

6. Appropriate attention to potential confounding variables.

Definition of ratings are as follows, based on these criteria.

A **Good** study has appropriate ascertainment of case-patients

## Appendix Table 1. Search Strategy

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)

and nonbiased selection of case and control participants; exclusion criteria are applied equally to case-patients and controls; response rate is at least 80%; diagnostic procedures and measurements are accurate and are applied equally to case-patients and controls; and appropriate attention is paid to confounding variables.

In a **Fair** study, there is appropriate ascertainment of case-patients and controls and exclusion criteria is applied equally to case-patients and controls, without major apparent selection or diagnostic work-up bias; response rate is less than 80%; or attention is paid to some but not all important confounding variables.

A **Poor** study has major selection or diagnostic work-up biases; response rates are less than 50%; or no attention is paid to confounding variables.

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Appendix Table 2. Cohort Studies of Lung Cancer Screening with Chest Radiography\*

Study, Year (Reference)	Study Sample	Intervention	Malignant Disease	Resectable Tumors	Survival Rate
			<i>n</i> (%)	%	
Philadelphia Neoplasm Research Project, 1951 (48, 49)	6136 men age $\geq 45$ y	Photofluorography and questionnaires every 6 mo for 10 y	Prevalence: 84 (1.37)	35	8 (5 y)
Tokyo Metropolitan Government Study, 1953 (51)	1 871 374 men and women, all ages	Intermittent CXR over 26 y (sputum cytologic examination in some)	Incidence: 121 193 (0.01)	56	44 (5 y for resectable tumors) (usual survival at that time, 20)
Veterans Administration Trial, 1958 (50)	141 607 men; median age, 62.8 y	CXR and sputum cytologic examination	73 (0.052)	36	17 (32 mo)
South London Cancer Study, 1959 (52)	67 400 men age $\geq 45$ y	CXR every 6 mo	234 (0.35)	56	18% (4 y) (usual survival at that time, 9)

\* CXR = chest radiography.