



Gary Ernest Smith. *Blue Shadows*. Oil on canvas, 16" × 20". Courtesy of Raymond E. Johnson's Overland Gallery of Fine Art, Scottsdale, Arizona.

The potential place of computed tomography as a tool for improving lung cancer outcomes is reviewed.

A Systematic Review and Lessons Learned From Early Lung Cancer Detection Trials Using Low-Dose Computed Tomography of the Chest

Gerold Bepler, MD, PhD, Dawn Goodridge Carney, MSPH, Benjamin Djulbegovic, MD, PhD, Robert A. Clark, MD, MBA, and Melvyn Tockman, MD, PhD

Background: Computed tomography (CT) screening of the chest has shown promise for early detection of lung cancer, but evidence for a reduction in lung cancer mortality by CT screening is not available.

Methods: We reviewed 208 articles to synthesize available evidence for efficacy of CT screening in detecting potentially curative stages of lung cancer and for evidence in reducing lung cancer mortality. Other outcomes of interest included detection rate of cancer and of suspicious lesions, histology and stage of cancer at detection, screening-related morbidity, and the identification of populations uniquely suited for CT screening. We identified eight papers that reported the outcomes for CT of the chest in lung cancer screening.

Results: Since none of the studies utilized a control group, quantitative pooling was not done. In two studies, both CT and chest radiography (CXR) were used as screening tools in the same cohorts. A total of 19,107 subjects were screened using CT. The detected prevalence rate for lung cancer ranged from 0.40% to 13.6% and was a function of the subjects' age and smoking history. CT screening resulted in a 3-fold higher detection rate and a 5-fold increase in the rate of resectable cancers compared to CXR. Data on lung cancer and overall mortality and screening-related morbidity and mortality were incomplete. CT screening resulted in selective detection of adenocarcinomas with an approximately 2- to 3-fold oversampling of this histologic subtype. The positive predictive value of CT screening was highest for subjects in the 8th decade of life, and it was virtually nil for those in their 5th decade.

Conclusions: Evidence regarding lung cancer screening by CT shows that this technology detects earlier-stage and smaller lung cancers with greater frequency than other screening methods. To date, no trials have demonstrated that CT screening leads to a reduction in lung cancer mortality. Until mortality trials are completed, low-dose CT screening should be considered an investigative tool rather than the standard of care.

From the Thoracic Oncology Program (GB, DGC), Malignant Hematology Program (BD), Radiology Program (RC), and Molecular Screening Program (MT) at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, Florida.

Submitted February 26, 2003; accepted May 20, 2003.

Address reprint requests to Gerold Bepler, MD, PhD, H. Lee Moffitt

Cancer Center & Research Institute, Thoracic Oncology Program, 12902 Magnolia Drive, MRC-MOLONC, Tampa, FL 33612. E-mail: bepler@moffitt.usf.edu

No significant relationship exists between the authors and the companies/organizations whose products or services are referenced in this article.

Introduction

Lung cancer accounts for one third of cancer deaths in men and one fourth of cancer deaths in women in the United States, despite advances in the treatment and prevention of this disease.¹ The disease-specific mortality is declining in most age groups, except in women 65 to 74 years of age, where death rates continue to rise.² Without the development of efficacious primary prevention, the number of people diagnosed with lung cancer is expected to double in the next 50 years. Former smokers maintain lung cancer incidence rates that are greater than comparable never smokers, and these rates will increase substantially as they age.

Lung cancer treatment and survival are functions of disease stage at presentation. As stage I and II tumors rarely cause symptoms, the disease is usually diagnosed in advanced stages (stage III and IV) when potentially curative therapy is often beyond the reach of physicians' present capabilities. As a result, the overall 5-year lung cancer survival rate is only 14%, with 22% to 67% for stage I and II lung cancer and 1% to 25% for advanced stages.³ Based on these survival results and the assumption that 5-year survival is equal to cure, the hypothesis that "early detection by screening asymptomatic individuals will result in a decline in overall and disease-specific mortality from lung cancer" has been formulated. However, none of the professional health organizations and task forces currently endorse screening for lung cancer with radiologic imaging techniques. This is a result of 3 large randomized trials that were

conducted in the United States and Europe between 1960 and 1980.^{4,6} These trials used frequent (every 4 to 6 months for 3 to 6 years) two-dimensional chest radiography (CXR) as a screening tool, and details are provided in Table 1. Cancers were detected at earlier stages, more cancers were resectable, and 5-year survival rates were significantly better in the screened groups compared to the control groups. However, mortality rates from lung cancer, overall mortality, and the number of unresectable cases were not significantly reduced on final evaluation. These results may be explained by lead-time bias, length-time bias, overdiagnosis, and the finding that many people in the "control group" actually had frequent CXR, which may have skewed the controls toward relatively early diagnosis of lung cancer. The impact of these biases has been explained, reviewed, and discussed elsewhere.⁷⁻⁹

Computed tomography (CT) of the chest has been reported to be superior to CXR in detecting pulmonary nodules.¹⁰ This implies that an increase in the detection rate of putatively surgically curable lung cancers and a concomitant decline in incurable late-stage disease (ie, a stage shift) as a result of CT screening should lead to a decline in lung cancer-specific mortality, which is the ultimate goal of all early detection trials. However, whether CT screening will result in a reduction of lung cancer mortality is not known. The question of CT screening efficacy is paramount, since at least one economic analysis has shown that screening with CT is cost-effective compared to other methods of screening for lung cancer.¹¹ However, a recent decision

Table 1. — Summary of Eligibility Criteria and Results From Lung Cancer Screening Trials With Chest Radiography

Reference	No. of Patients	Sex	Age	Exposure (Cigarette Smoking Active or Past)	Detected Cases of Lung Cancer on Prevalence Screen	Operable Cases on Prevalence Screen	Lung Cancer Mortality in Screened Group	Lung Cancer Mortality in Control Group	Overall Mortality in Screened Group	Overall Mortality in Control Group
Brett ⁴ (1968)	55,034 (29,416*)	M=100%	≥40	88% PY = NS	51 (0.09%)	31 (0.06%)	N=82 (0.28%) at 3 years of follow-up	N=68 (0.27%) at 3 years of follow-up	NS	NS
Fontana ⁵ (1986)	10,933 (4,618*)	M=100%	≥45	100% PY = NS	74 (0.68%)**	33 (0.30%)	N=122 (2.64%) 3 years of median follow-up	N=115 (1.82%) 3 years of median follow-up	24.8% per 1,000 person-years	24.6% per 1,000 person-years
Kubik ⁶ (1986)	6,364 (3,171*)	M=100%	≥40	100% (all active) ≥20 PY	19 (0.30%)	NS	N=85 (2.68%) ≥5 years of follow-up	N=67 (2.10%) ≥5 years of follow-up	N=341 (10.75%) ≥5 years of follow-up	N=293 (9.18%) ≥5 years of follow-up

* Number of subjects in the screening cohort.
 ** Cases detected by chest radiography; cases detected by sputum cytology only are excluded (N=17).
 PY = pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked)
 NS = not specified

and economic analysis has suggested that the incremental cost-effectiveness associated with screening a population of current and former smokers over the age of 60 years is between \$116,300 and \$2,322,700 per quality-adjusted life-year gained.¹²

We have undertaken a systematic review of available studies to obtain evidence if screening by CT is able to (1) detect smaller cancers than traditional screening methods, (2) determine whether shifting the distribution toward earlier stage at detection occurs, and (3) determine if there is evidence for a decrease in lung cancer mortality.

Methods

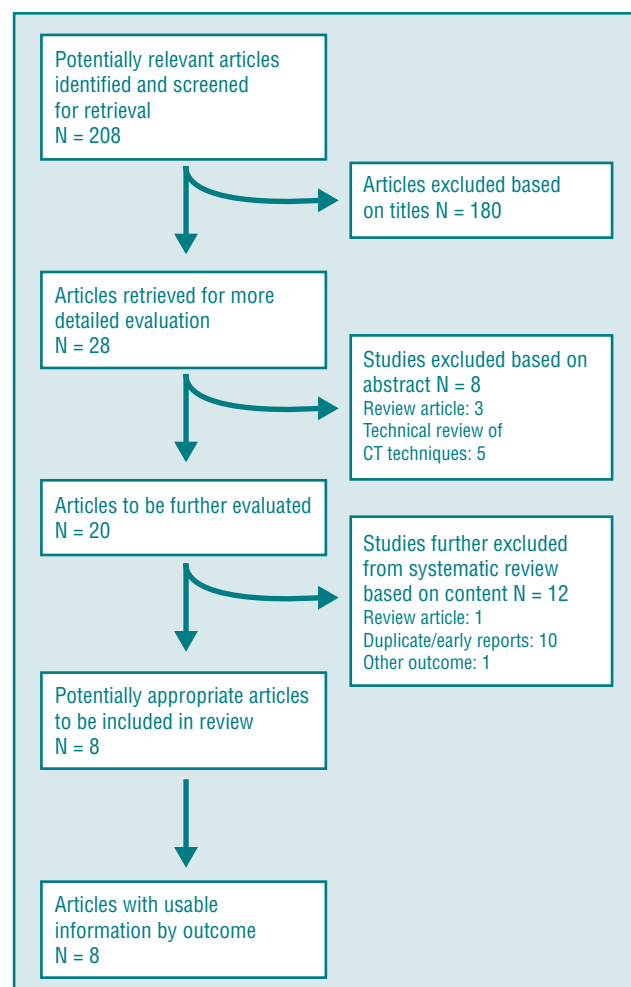
Search Methods

Searches of MEDLINE and CancerLit databases from 1988 to August 2002 were undertaken using “lung neoplasms [MeSH] and (tomography [MeSH] OR tomography scanners, x-ray computed [MeSH]) and

mass screening [MeSH]” as the search terms. The bibliographies of selected references were also searched.

Study Selection

All observational studies and randomized, controlled trials (RCTs) of screening vs no screening with chest CT were eligible for this review. Studies utilizing screening via CT vs some other screening method or no screening at all were eligible for inclusion. For the RCTs, any method of randomization was eligible. Trials of screening alone and screening followed by treatment were also included. Papers were not excluded based on language. A flow diagram of the search strategy is illustrated in the Figure. Initially, 208 articles were identified for possible retrieval. After further review, we excluded 200 articles that were review articles containing no primary data, duplicate studies, preliminary reports later available as full reports, or technical reviews of methods. Eight papers published as full reports were used for data extraction. The data extracted were focused on the results from prevalence screening, and the respective data variables are shown in Tables 2 and 3.



Flow diagram of search results.

Outcomes

The main outcomes of interest were detection rate of cancer, stage of cancer at detection, and lung cancer mortality. Other outcomes of interest included detection rate of suspicious lesions, overall mortality, histology of detected cancers, as well as screening-related morbidity and surgeries. The specific assessment questions were: What is the detection rate of screening CT for lung cancer in asymptomatic individuals, what is the stage distribution of detected lung cancers, and what is the disease-specific mortality? For analysis, data were extracted from the publications and tabulated. Specific attention was given to the demographic characteristics and potential exposures of the respective cohorts studied as well as the criteria used to evaluate the CT scans and to initiate subsequent workups.

Results and Discussion

Overview

An electronic search of the literature and hand-searched review of selected bibliographies resulted in 8 papers published as full reports that were used for data extraction.¹³⁻²⁰ None of the identified papers were randomized, controlled trials. While two of the papers used same patient comparisons with concurrent CXR as the control,^{14,18} the remaining were single-arm prospective cohort studies without explicit historical controls.

The largest and smallest reported sample sizes in these studies were 7,956 and 118, respectively.^{13,17} A total of 19,107 subjects were screened using CT. Overall, the reported gender distribution showed 69.6% were men and 30.4% were women. Gender was not reported for 118 subjects. The estimated median age in these studies was 60 years (range 38 to 85 years).

Table 2 itemizes the demographics and study characteristics on the 19,107 subjects who underwent lung cancer screening by CT. Except for two studies,^{15,17} nearly all subjects were current or former smokers (86% to 100%). Asbestos exposure was reported in three studies,^{14,16,20} and evidence for asbestos-related lung disease was a requirement for study participation in one study.²⁰ This is the only study in which comor-

bid conditions of subjects are specifically reported. The study by Matsumoto et al¹³ was a pilot study to assess the feasibility of using a mobile CT scanner for early lung cancer detection in Japan. This was a small study with 118 participants and limited available information. Because of these limitations, this study is not included in the description and discussion of reported results on CT as a screening tool for lung cancer.

Detection Rate of Lung Cancer and Factors Associated With Risk

Among all studies, the detected prevalence for lung cancer using CT ranged from 0.40%¹⁵ to 2.70%¹⁴ (Table 3). All studies were conducted in comparable yet dis-

Table 2. — Demographics and Characteristics

Reference	No. of Patients	Sex	Age	Comorbid Conditions	Exposure	Study Design	Comment
Matsumoto ¹³ (1995)	118	Not available	Not available	Not available	Not available	Prospective cohort without historical control	Abstract only; a pilot study with limited information.
Henschke ¹⁴ (1999)	1,000	M = 540 F = 460	≥60 Median 67	NR	Smokers 100% ≥10 PY Median 45 PY Asbestos 14%	Prospective cohort with same patient comparison	Radiography served as control. Final results were reported in 2001.*
Sone ¹⁵ (2001)	5,483	M = 2,971 F = 2,512	≥40 Mean 64 Range 40-74	NR	Smokers or former smokers 46.1% ≥1 PY	Prospective cohort without historical control	
Diederich ¹⁶ (2002)	817	M = 588 F = 229	≥40 Median 53 Range 40-79	NR	Smokers 100% ≥20 PY Median 45 PY Range 20-166 PY Asbestos 2.4%	Prospective cohort without historical control	
Nawa ¹⁷ (2002)	7,956	M = 6,319 F = 1,637	≥50 Range 50-69	NR	Smokers or former smokers 62.1%	Prospective cohort without historical control	All participants were members of a single health insurance group.
Sobue ¹⁸ (2002)	1,611	M = 1,415 F = 196	≥40 Range 40-79	NR	Smokers or former smokers 86%	Prospective cohort with same patient comparison	Radiography served as control. All participants were members of a for-profit lung cancer screening association. Results from 1,320 participants were reported in 2000.**
Swensen ¹⁹ (2002)	1,520	M = 785 F = 735	≥50 Mean 59 Range 50-85	NR	Smokers 100% ≥20 PY Median 45 PY Range 20-230 PY	Prospective cohort without historical control	
Tiitola ²⁰ (2002)	602	M = 591 F = 11	Mean 63 Range 38-81	Asbestosis and/or bilateral pleural plaques	Smokers 96.7% ≥10 PY Mean 24 PY Asbestos 100%	Prospective cohort/case series without historical control	
NR = not reported PY = pack-years * Henschke CI, Naidich DP, Yankelevitz DF, et al. Early lung cancer action project: initial findings on repeat screenings. <i>Cancer</i> . 2001;92:153-159. ** Kaneko M, Kusumoto M, Kobayashi T, et al. Computed tomography screening for lung carcinoma in Japan. <i>Cancer</i> . 2000;89 (11 suppl):2485-2488.							

tinctly unique populations. Comparable features included a relatively strong smoking history of most participants and age above 40 years. Age was a strong risk factor for lung cancer, with combined detection rates of 0.25% in the youngest participants to 1.40% in the oldest participants (Table 4). In four studies,^{14,16,19,20} nearly 100% of participants were active or former smokers. In three studies,^{14,16,19} the median number of pack-years smoked was 45; however, they differed in their age eligibility criteria. Henschke et al¹⁴ required participants to be ≥60 years of age and the lung cancer detection rate was 2.70%, while Diederich et al¹⁶ reported a detection rate of 1.35% in participants over

the age of 40 years, and Swensen et al¹⁹ reported a rate of 1.38% in participants over the age of 50 years. This illustrates that the difference in lung cancer detection rates among these three studies can be explained by the age difference in the respective cohorts. In contrast, in the study by Tiitola et al,²⁰ participants had a median cigarette consumption of 24 pack-years and the lung cancer detection rate was 0.40% despite the added risk of asbestos exposure. The mean age in this group was 63 years (range 38 to 81 years), which is similar to the mean age of 59 years (range 50 to 85 years) in the study by Swensen and colleagues with a lung cancer detection rate of 1.38%. This suggests that a doubling

Table 3. — Selected Outcomes Based on Prevalence Screening Results

Reference	No. of Patients	Noncalcified Pulmonary Nodules	Detected Cases of Lung Cancer	Disease Stage	Histology	Lung Cancer Mortality	Overall Mortality (including lung cancer mortality)
Matsumoto ¹³ (1995)	118	Any: Not available ≥5 mm: N=43 (36.4%)	16 (13.6%)	I: N=9 IIIA: N=1 NR: N=6	Not available	Not available	Not available
Henschke ¹⁴ (1999)	1,000	Any: N=233 (23.3%) ≥5 mm: N=97 (9.7%)	27* (2.7%)	IA: N=22 IB: N=1 IIA: N=1 IIB: N=0 IIIA: N=2 IIIB: N=1	Adeno N=22 Squamous N=1 Adeno-squamous N=4 Carcinoid N=1	NR	NR
Sone ¹⁵ (2001)	5,483	Any: N=279 (5.1%) ≥3 mm: N=170 (3.1%)	22** (0.4%)	IA: N=21 IB: N=2 II: N=0 III: N=0	Adeno N=19 Squamous N=4	N=1	N=2
Diederich ¹⁶ (2002)	817	Any: N=409 (50.1%) >5 mm: N=154 (18.8%)	11* (1.35%)	IA: N=5 IB: N=1 IIA: N=1 IIB: N=1 IIIA: N=2 IIIB: N=1	Adeno N=6 Squamous N=4 Small cell N=1	N=3 at 2-40 months of follow-up	N=4 at 2-40 months of follow-up
Nawa ¹⁷ (2002)	7,956	Any: N=2,099 (26.4%) ≥8 mm: N=541 (6.8%)	36* (0.45%)	IA: N=28 IB: N=3 IIA: N=3 IIB: N=1 IIIA: N=1	Adeno N=35 Large cell N=1 Carcinoid N=1	NR	NR
Sobue ¹⁸ (2002)	1,611	Any: N=186 (11.5%) ≥5 mm: NR	13** (0.81%)	IB: N=1 IA: N=9 IIIA: N=2 IIIB: N=1	Adeno N=10 Squamous N=3	NR	NR
Swensen ¹⁹ (2002)	1,520	Any: N=782 (51.4%) ≥4 mm: N=475 (31.3%)	21** (1.38%)	IA: N=13 IB: N=1 IIA: N=4 IIB: N=0 IIIA: N=2 Limited: N=2	Adeno N=15 Squamous N=4 Large cell N=1 Small cell N=2	N=1 at 1 year of follow-up	N=9 at 1 year of follow-up
Tiitola ²⁰ (2002)	602	Any: N=111 (18.4%) ≥5 mm: N=48 (8.0%)	5 (0.83%)	I: N=0 IIA: N=1 IIIB: N=2 IV: N=2	Adeno N=2 Squamous N=1 Large cell N=1 "Cancer" N=1	N=6-7 at 2.5 years of follow-up	NR

* One patient had 2 primary lung cancers.
** One additional case was discovered by sputum cytology only.
NR = not reported

Table 4. — Prevalence Rate of Lung Cancer (LC) by Age Group and Lung Cancer Risk

Age	Sobue ¹⁸ No. LC / No. Screened	Sone ¹⁵ No. LC / No. Screened	Diederich ¹⁶ No. LC / No. Screened	Nawa ¹⁷ No. LC / No. Screened	Combined No. LC / No. Screened	Relative Lung Cancer Risk*
40-49	0 / 258	2 / 238	0 / 298	NA / NA	2 / 794 (0.25%)	1.0
50-59	2 / 521	5 / 771	3 / 313	27 / 6082	37 / 7687 (0.48%)	1.9
60-69	9 / 630	9 / 1474	7 / 167	9 / 1874	34 / 4145 (0.82%)	3.3
70-79	3 / 202	7 / 471	0 / 39	NA / NA	10 / 712 (1.40%)	5.6

* The relative risk for lung cancer by age groups is provided by comparing the frequency of CT screening-detected lung cancers in age group 40-49 years with those in the older age groups. Studies that did not specifically report detection rates by age decades are not listed.

in cigarette consumption (24 to 45 pack-years) is associated with a 2- to 3-fold increase in lung cancer risk. This assumption is underlined by the studies of Sone et al.¹⁵ and Sobue et al.¹⁸ In the former study, 46% of participants were smokers and the lung cancer detection rate was 0.40%, while in the latter study, 86% were smokers and the detection rate was 0.81%. None of the studies provided data on the amount of cigarettes smoked per day, the smoking duration, and the age of first smoking of participants. Thus a more detailed analysis on the impact of smoking behavior on CT-detected lung cancer prevalence rates in asymptomatic individuals is not possible. The relative contribution of gender to lung cancer risk cannot be assessed from the studies reviewed, although it appears that women were at an equal or perhaps slightly increased risk for lung cancer,^{15,17} which is consistent with numerous epidemiologic reports.²¹ It can thus be concluded that the detected lung cancer prevalence in asymptomatic individuals is a function of participants' age and smoking history.

Detection Rate of Lung Cancer on CT and CXR

Two studies^{14,18} found that when comparing low-dose CT with CXR, CT screening detected more lung cancers (27 by CT vs 7 by CXR in one study, and 13 by CT vs 5 by CXR in the second). The prevalence detection rates for CXR (0.70% and 0.31%) are equivalent to those reported from the randomized lung cancer screening trials in comparable study populations conducted in the 1970s⁵ and 1980s⁶ of 0.68% and 0.30%, respectively. These comparable prevalence detection rates by CXR in studies that are two decades apart is remarkable, given the advances in radiography equipment and the shift in lung cancer histology from squamous cell carcinoma as the most frequent subtype in the 1970s to adenocarcinoma as the most frequent current subtype. It can thus be concluded that screening of asymptomatic individuals for lung cancer with low-dose CT results in an approximately 3-fold higher detection rate than screening with CXR.

Stage of Cancer at Detection

With regard to stage distribution in all CT screening studies, the number of stage I or II lung cancer cases was 119, compared to 18 for stage III or IV (including small-cell lung cancer cases). The stage distribution in the screened cohorts of the previously referenced early detection trials with CXR was 155 resectable and 174 unresectable cases. A clear comparison of these data is difficult for several reasons: (1) the differences in the terms *resectable* and *unresectable* in stage I/II vs stage III/IV, (2) a change in the staging system, (3) the development of more sensitive tests to detect metastases, and (4) the frequent use of surgical staging in the recent CT screening studies. These developments have resulted in up-staging rather than down-staging of newly detected lung cancer cases. Thus, cases that might have been staged as resectable in the 1970s are more likely to have been staged as unresectable in the 1990s. In addition, two of the recent CT screening studies also used CXR screening for comparison. In these studies, the combined CT- vs CXR-detected lung cancer cases were stage I in 33 vs 7 cases, stage II in 1 vs 1 case, and stage III in 6 vs 4 cases. This suggests that the higher detection rate of lung cancers by CT compared to CXR is mainly a result of an increased number of cancers detected in stage I of the disease. It appears that the increase of cases with stage I is not accompanied by a decrease in the number of cases with inoperable stages of lung cancer. If this observation is confirmed in the ongoing and planned randomized early detection trials with CT, then it is unlikely that a decrease in lung cancer mortality will occur. A decrease in lung cancer mortality would require a stage shift in the screening detected cases, ie, a decrease in inoperable cases and an increase in operable cases. If only an increase in operable cases is observed, then an increase in lung cancer incidence will occur, likely as a result of overdiagnosis. Measurement of 5-year survival as an outcome parameter for screening trials is an insufficient parameter of screening efficacy. This is exemplified by the referenced CXR-based screening trials, where 5-year survival was increased in the screened cohorts yet not accompanied by a decrease in mortality. It can thus be concluded that screening of asymptomatic

Table 5. — Positive Predictive Value of Noncalcified Pulmonary Nodules (NCPN) for Lung Cancer by Age Group

Age	Sobue ¹⁸	Diederich ¹⁶	Nawa ¹⁷	Combined	Positive Predictive Value
	No. NCPN / No. Screened	No. NCPN / No. Screened	No. NCPN / No. Screened	No. NCPN / No. Screened	No. LC / No. NCPN
40-49	23 / 258	134 / 298	NA / NA	157 / 556 (28.2%)	0 / 157 0.000
50-59	58 / 521	155 / 313	1566 / 6082	1779 / 6916 (25.7%)	69 / 1779 0.039
60-69	73 / 630	95 / 167	533 / 1874	701 / 2671 (26.2%)	59 / 701 0.084
70-79	32 / 202	25 / 39	NA / NA	57 / 241 (23.7%)	3 / 57 0.053

individuals for lung cancer with low-dose CT may result in an up to 5-fold increase in the rate of resectable cases compared to screening with CXR, provided that CT screening is performed on participants who are medically operable. A conclusion whether or not CT screening results in a decrease of unresectable cases of lung cancer cannot be reached at this time.

Lung Cancer Mortality and Overall Mortality

Data on disease-specific and overall mortality are provided in Table 3. These data are incomplete and do not allow for a conclusion regarding the impact of CT screening on these crucial determinants of screening efficacy. First and foremost, a clear impact of screening on mortality can come only from randomized, controlled trials such as those originally conducted to assess the efficacy of CXR. Second, the reported follow-up periods on the referenced CT screening trials are too short for a meaningful comparison with global age-adjusted lung cancer mortality data, and 5-year survival results are insufficient to show screening efficacy because of the inherent biases of such data. Third, participants in the reported CT screening trials represent special populations, and therefore the results obtained are not necessarily applicable to the population at large. Notably, the study that included asbestos workers had the highest lung cancer and overall mortality rates,²⁰ which can be explained by the comorbidities of the study participants. A conclusion on the efficacy of CT screening on disease-specific and overall mortality cannot be reached from the available data.

Screening-Related Morbidity and Mortality

No screening-related deaths were reported. Only one of three studies that reported surgery-related deaths incurred an actual death,²⁰ and there was no surgery-related morbidity or mortality reported by other studies. A conclusion on screening-related morbidity and mortality cannot be reached based on the reported results.

Histology of Detected Lung Cancers

The predominant histology of lung cancers detected in the CT screening trials was adenocarcinoma, accounting for 109 (79.6%) of the 137 lung cancers. Only 17 cases (12.4%) of squamous cell carcinoma and 11 (8.0%) of other subtypes were reported. These numbers are clearly divergent from the numbers reported in the Surveillance, Epidemiology, and End Results (SEER) database for a comparable time period (ie, lung cancer cases from 1983 to 1992), where adenocarcinoma accounted for 34.9%, squamous cell carcinoma for 31.4%, and all others for 33.7% of lung cancers. This strongly suggests that CT screening as a tool for secondary prevention of lung cancer preferentially detects adenocarcinomas and may not be sufficiently sensitive to detect squamous and small-cell carcinomas. Thus, it can be concluded that CT screening as a tool for early detection of lung cancer results in over-sampling for adenocarcinomas by a factor of 2 or more.

Detection Rate of Suspicious Abnormalities (Noncalcified Pulmonary Nodules)

The rate of noncalcified pulmonary nodules (NCPNs) ranged from 5.1% to 51.4% (Table 3), and the smallest diameter of detectable lesions was below 3 mm. Thus, the positive predictive value (proportion of lung cancers among those with suspicious lesions) of CT scanning for lung cancer was variable (0.02 to 0.12). This range is comparable to that of mammography in breast cancer screening or fecal occult blood testing in colorectal cancer screening.^{22,23} Neither the specificity nor the sensitivity of CT scanning for lung cancer detection can be assessed because the proportion of individuals “truly negative” for lung cancer at the time of testing is unknown. Given the discrepancy in the distribution of histologic subtypes of lung cancers detected by CT compared to those reported nationwide, it is reasonable to assume that the false-negative rate of CT scanning for lung cancer may be substantial. An estimate is reported by Sone et al¹⁵ with a sensitivity (proportion of lung cancers determined by CT among all participants who have lung cancer) ranging from

55% to 83% and a specificity (proportion of non-lung cancers by CT among all participants who do not have lung cancer) of 95% to 97%. For obvious reasons, CT scanning will be most efficacious in populations where CT scanning provides the highest possible positive predictive value. Table 5 summarizes the available results from the reported trials. It is noteworthy that the rate of NCPNs does not increase with age after 40 years of age (column 5 in Table 5), while the lung cancer risk increases with age. As a result, the positive predictive value of CT for lung cancer detection is best for subjects over the age of 60 years (~0.08), it is low (~0.04) for subjects between 50 and 59 years, and it is vanishingly small (~0.00) for subjects less than 50 years of age. These numbers apply to populations with low or minimal comorbidity such as those found in the reported screening cohorts and for prevalence screening only.

Quality Assessment

After reviewing the articles for quality, we found that available evidence on the role of CT screening in early detection of lung cancer is limited and that the reported results may be biased. Some are as follows:

- Less than half of the articles reviewed used a broad spectrum of patients or described the selection criteria of their subjects. As a result of the differences in demographic and clinical features between populations, measures of diagnostic accuracy may be confounded by biologic differences in population disease frequency, resulting in spectrum bias.

- Most studies used consensus among readers to resolve disagreement for questionable results. However, it is unclear if the readers were blinded to patient information or to the results of other tests, thus raising the potential for review (detection) bias.^{24,25}

- In many of the studies, patients received a different reference test to verify the results of the CT screen. This is likely to result in partial verification bias.^{24,25}

- Finally, none of the articles addressed how withdrawals or losses to follow-up were handled in analysis, which can lead to biased estimates of test performance.²⁶

Conclusions

Two decades of trials with CT scanning for secondary prevention of lung cancer have taught us many valuable lessons on how to best deploy this

powerful technique. Given its exquisite sensitivity in detecting radiographic pulmonary abnormalities, CT scanning is best suited in populations with a low probability of benign pulmonary abnormalities (eg, histoplasmosis, tuberculosis, and interstitial pneumonitis). In such a population, the highest positive predictive value for lung cancer will be in persons above 60 years of age. This is exemplified by the Early Lung Cancer Action Project (ELCAP) study, which enrolled patients above the age of 60 with a history of moderate cigarette use and no other significant comorbidities (participants had to be asymptomatic and medically fit for surgery). The rate of NCPNs in this study was 23.3%, the rate of cancers was 2.7%, and the positive predictive value was 0.116, which is the highest of all reported studies. Currently available results are encouraging for a possible future utility of this method in combating lung cancer mortality. Demonstrating a longer survival is a certainty for this technology and easily explained by lead-time bias.

History has taught us a lesson; hopes were high in the 1960s, when pilot trials with CXR showed promising results akin to those described here for CT. It is our obligation as highly trained academicians and physicians to individuals at risk and to future generations to complement the CT pilot studies with definitive, prospective, unbiased, and population-wide trials in order to either accept or reject the working hypothesis that early detection of lung cancer by CT screening will reduce lung cancer mortality.

References

1. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. *CA Cancer J Clin*. 2003;53:5-26.
2. Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on the US cancer burden. *Cancer*. 2002;94:2766-2792.
3. Mountain CF. Revisions in the international system for staging lung cancer. *Chest*. 1997;111:1710-1717.
4. Brett GZ. The value of lung cancer detection by six-monthly chest radiographs. *Tborax*. 1968;23:414-420.
5. Fontana RS, Sanderson DR, Woolner LB, et al. Lung cancer screening: the Mayo program. *J Occup Med*. 1986;28:746-750.
6. Kubik A, Polak J. Lung cancer detection: results of a randomized prospective study in Czechoslovakia. *Cancer*. 1986;57:2427-2437.
7. Eddy DM. Screening for lung cancer. *Ann Intern Med*. 1989;111:232-237.
8. Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. *N Engl J Med*. 2000;343:1627-1633.
9. Strauss GM. The Mayo lung cohort: a regression analysis focusing on lung cancer incidence and mortality. *J Clin Oncol*. 2002;20:1973-1983.
10. Milla N, Ito K, Ikeda M, et al. Fundamental and clinical evaluation of chest computed tomography imaging in detectability of pulmonary nodule. *Nagoya J Med Sci*. 1994;57:127-132.
11. Chirikos TN, Hazelton T, Tockman MD, et al. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. *Chest*. 2002;121:1507-1514.
12. Mahadevia PJ, Fleisher LA, Frick KD, et al. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA*. 2003;289:313-322.

13. Matsumoto M, Horikoshi H, Moteki T, et al. A pilot study with lung-cancer screening CT (LSCT) at the secondary screening for lung cancer detection. *Nippon Igaku Hoshasen Gakkai Zasshi*. 1995;55:172-179.
14. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. 1999;354:99-105.
15. Sone S, Li F, Yang ZG, 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.
16. Diederich S, Wormanns D, Semik M, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. *Radiology*. 2002;222:773-781.
17. Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest*. 2002;122:15-20.
18. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol*. 2002;20:911-920.
19. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med*. 2002;165:508-513.
20. Tiitola M, Kivisaari L, Huuskonen MS, et al. Computed tomography screening for lung cancer in asbestos-exposed workers. *Lung Cancer*. 2002;35:17-22.
21. Bepler G. Lung cancer epidemiology and genetics. *J Thorac Imaging*. 1999;14:228-234.
22. Eddy DM. Screening for breast cancer. *Ann Intern Med*. 1989;111:389-399.
23. Eddy DM. Screening for colorectal cancer. *Ann Intern Med*. 1990;113:373-384.
24. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282:1061-1066.
25. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem*. 2003;49:7-18.
26. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA*. 2001;285:1987-1991.