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ORIGINAL REPORT

Estimate of Lung Cancer Mortality From Low-Dose Spiral Computed Tomography Screening Trials: Implications for Current Mass Screening Recommendations

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ABSTRACT

Purpose
Low-dose computed tomography (CT) has been suggested for lung cancer screening. Several observational trials have published their preliminary results, and some investigators suggest that this technique will save lives. There are no mortality statistics, however, and the current study used published data from these trials to estimate the disease-specific mortality in this high-risk population.

Patients and Methods
Two nonrandomized CT screening trials were selected from the literature for analysis. The number of trial participants, the number of lung cancers diagnosed per year, and stage distribution of the cancers was recorded. Previously published 5-year survival data were used to calculate the number of predicted lung cancer deaths and estimate the overall lung cancer mortality per 1,000 person-years among participants screened. These statistics were then compared to the previous Mayo Lung Project, which used chest radiographs and sputum cytology for screening high-risk individuals.

Results
This study estimates the lung cancer mortality is 4.1 deaths per 1,000 person-years in the Mayo Clinic CT screening trial, and is 5.5 deaths per 1,000 person-years in the Early Lung Cancer Action Program trial. These data are similar to the lung cancer mortality of 4.4 deaths per 1,000 person-years in the interventional arm, and 3.9 deaths per 1,000 person-years in the usual-care arm of the previous Mayo Lung Project.

Conclusion
These data suggest that CT screening could produce similar outcomes to prior chest radiographic trials in this high-risk group. Results from randomized trials are required, however, before the true utility of mass screening with CT for lung cancer can be determined.

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INTRODUCTION

Lung cancer continues to be a worldwide epidemic and major public health issue. More than 150,000 patients die in the United States each year from this disease, and the overall mortality has not significantly changed in decades.[1] There have been many different strategies used to improve outcomes, including recent efforts focusing on lung cancer screening with low-dose helical computed tomography (CT).[2-6]

The rationale for using CT as a screening modality is that it can detect small pulmonary nodules in asymptomatic individuals, and that a larger percentage of these nodules will be earlier-stage lung cancer than with chest radiograph or no screening. It is hypothesized that the use of CT will ultimately reduce the number of patients who die from this disease. The initial CT screening trials are nonrandomized observational studies with no control group. While tremendous amounts of data concerning pulmonary nodules have been generated, and some investigators have already speculated that this technology will save lives, there are currently no published mor-

tality data—the ultimate measure of a screening trial. Thus, the current investigation designed a model that uses the published results of the only two trials in high-risk individuals with prevalence and at least 1-year annual repeat follow-up data to estimate the lung cancer mortality when screening is performed with low-dose helical CT.

PATIENTS AND METHODS

Trial Data Analyzed

We performed a comprehensive review of the current literature and found only two CT screening trials that had published at least the prevalence of lung cancer at initial screening and the first annual repeat screen. Entrance criteria for both studies included the following: all participants had a significant smoking history, there was no prior malignancy, participants were potentially operable, and all individuals were older than age 50 years. These trials included studies from Mayo Clinic and the Early Lung Cancer Action Program (ELCAP) study.[2,3,7] While there are several other observational studies being conducted, to our knowledge to date, none have published data beyond the prevalence year.[8] Several studies from Japan were not included because they enrolled smokers and never smokers.[4-6,9]

Analysis Scheme

The Mayo Clinic and ELCAP trials were analyzed independently. The number of trial participants, the number of diagnosed lung cancers, and the stage distribution of the tumors were available for the prevalence year (or initial screening), and each of three subsequent annual incidence follow-up years for the Mayo Clinic trial. Similar information was available for the prevalence screening and the initial annual repeat screening for the ELCAP trial. For subsequent follow-up assessments in the ELCAP trial, the number of lung cancers diagnosed and their stage was estimated assuming drop-out and diagnostic patterns similar to those seen during the first repeat assessment. Analyses assume that all patients were followed for 5 years after completion of the third and final annual repeat assessment.

To predict each study's expected mortality, the number of lung cancer deaths and the number of person-years at risk of developing lung cancer need estimation. To accomplish this task, the expected number of lung cancer deaths and the expected number of person-years were initially calculated within three cohorts of patients: patients identified with lung cancer at the initial screening, patients identified with lung cancer at each of three follow-up repeat screenings, and patients who were not identified as having lung cancer. Based on stage-specific 5-year survival estimates published by Mountain,[10] the expected number of lung cancer deaths among patients diagnosed with lung cancer at each of four screenings (initial, and three follow-up) was calculated (Table 1).

This calculation assumed that lung cancer deaths occurred only during the first 5 years of follow-up, and that no patient died as a result of lung cancer subsequently. The expected number of lung cancer deaths among patients who completed all screenings without identification of lung cancer was estimated from the mortality rate reported by Marcus for the usual care arm.[11] Between screening assessments, some patients determined not to have lung cancer did not participate in subsequent screenings and became drop-outs. For the purposes of these calculations, it is assumed that drop-outs constituted a random sample of patients determined not to have lung cancer at a particular assessment. To account for these random drop-outs, the overall number of lung cancer deaths expected within the original sample was estimated as a weighted sum of cohort-specific estimates, where the weight was a function of the inverse of the proportion of patients who were drop-outs.

Table 1. 5-Year Survival Rates for Non–Small-Cell Lung Cancer

Clinical Stage	5-Year Survival
IA	0.61
IB	0.38
IIA	0.34
IIB	0.24
IIIA	0.13
IIIB	0.05
IV	0.01

For each cohort of patients diagnosed with lung cancer, the expected number of person-years at risk of lung cancer death was calculated. For a patient diagnosed with lung cancer, that patient's contribution to expected person-years was the sum of the expected survival time and the time between the initial screening and the diagnosis of lung cancer.

The mortality rate was then calculated as the ratio of the expect number of lung cancer deaths and the expected person-years at risk of lung cancer death (per 1,000 person-years).[11]

RESULTS

Mayo Clinic CT Screening Trial

The number of patients enrolled and rescreened at the annual visits is presented in Tables 2, 3, and 4. The number of lung cancer and stage distribution for each year is also presented in Tables 2 through 4. The estimated lung cancer mortality in the Mayo CT screening trial is 4.1 deaths per 1,000 person-years.

ELCAP CT Screening Trial

The number of patients enrolled and rescreened at the annual visits is presented in Tables 5, 6, and 7. The number of lung cancer and estimated stage distribution for each year is also presented in Tables 5 through 7. The estimated lung cancer mortality in the ELCAP study is 5.5 per 1,000 person-years.

Table 2. Stage Distribution: Mayo Computed Tomography Screening Trial

Year	No. of Pts Screened	No. With Cancer	Stage Distribution						
			IA	IB	IIA	IIB	IIIA	IIIB	IV
Prevalence	1,520	10	6	0	2	0	2	0	0
1	1,478	10	7	1	1	1	0	0	0
2	1,441	16	11	1	1	0	2	0	1
3	1,407	14	9	0	1	0	1	2	1

Abbreviation: Pts, patients.

Table 3. Estimated Deaths and Person-Years: May Computed Tomography Screening Trial

Estimated No. of Pts With No Lung Cancer	Estimated No. of Deaths in Cohort	Estimated No. of Person-Years in Cohort	Deaths in Cohort Without Lung Cancer	Person-Years in Cohort Without Lung Cancer
1,510	5.40	63.80		
1,468	4.77	70.46		
1,425	8.30	119.70		
1,393	7.93	112.00		
1,393			27.1635	12.537

Abbreviation: Pts, patients.

The results for both CT screening trials are similar to the lung cancer mortality of 4.4 deaths per 1,000 person-years (95% CI, 3.9 to 4.9) in the interventional arm and 3.9 deaths per 1,000 person-years (95% CI, 3.5 to 4.4) in the usual-care arm of the Mayo Lung Project.

DISCUSSION

While lung cancer continues to be a significant diagnostic and therapeutic challenge, it more importantly remains a devastating disease to patients and their families. Despite significant research efforts and advances in an understanding of tumor biology, there has been no impact on mortality during the last several decades.[1]

Many different tactics are being explored simultaneously to improve the outcomes from this disease. Some investigators are attempting to reduce the number of individuals who develop lung cancer, with smoking cessation programs; others, meanwhile, are pursuing chemoprevention trials.[12-14] Unfortunately, these are more long-term efforts, and clinically applicable strategies are needed at this time.

The primary focus of several groups has been screening and early detection. It has been postulated for decades that if lung cancer can be found at a small size in an asymptomatic individual, then this will represent early-stage disease, which will result in improved outcomes. It is clear that asymptomatic patients diagnosed with early-stage disease do better than symptomatic patients with more advanced disease, but this a very different scenario than screening participants, finding small nodules, assuming a small pulmonary nodule represents early stage, and translating this into a mortality reduction. This screening hypothesis with imaging depends only on size and sometimes growth characteristics, and does not incorporate the fundamental genetic composition of the tumor. Just because chest radiographs or CT scans can detect a small lesion, it still remains unproven that there will be a change in the course of this disease.[15]

The theory of lung cancer screening was tested initially in multiple trials using a combination of chest radiographs and sputum cytology.[16-20] These prior screening studies detected an increased number of early-stage disease, found more resectable cases of lung cancer, and showed an improved 5-year survival, but extended follow-up could find no difference in mortality between the control and screened groups. While some argue that these statistics may be of patient benefit, without reducing the number of patients who die from this disease, no official organization could recommend chest radiographic screening for lung cancer.

With the superior sensitivity of CT, it has again been suggested that if tumors can be detected at an even smaller size (millimeter range), more asymptomatic patients should be diagnosed at an earlier stage. Therefore fewer patients should have advanced-stage disease, and this "stage shift" should produce a reduction in lung cancer mortality. While the current CT trials have indeed reported that a

Table 4. Estimated Mortality: Mayo Computed Tomography Screening Trial

Cumulative No. of Deaths	Cumulative Person-Years	Adjustment Factor	Mortality
5.4000	63.80	1.0000	
10.2733	135.79	1.02165	
18.9119	260.37	1.04079	
27.2709	378.43	1.05411	
55.9042	13,593.79	1.05411	4.11248

Table 5. Stage Distribution: Early Lung Cancer Action Program Computed Tomography Screening Trial

Year	No. of Pts Screened	No. With Cancer	Stage Distribution						
			IA	IB	IIA	IIB	IIIA	IIIB	IV
Prevalence	1,000	27	22	1	1	0	2	1	0
1	841	8	5	0	0	1	1	0	0
2*	720	7	4	0	0	1	1	0	0
3*	616	6	4	0	0	1	0	0	0

Abbreviation: Pts, patients.
*The numbers of repeat years 2 and 3 are estimated values assuming drop-out and diagnostic patterns similar to that seen during the first repeat assessment.

Table 6. Estimated Deaths and Person Years: Early Lung Cancer Action Program Computed Tomography Screening Trial

Estimated No. of Pts With No Lung Cancer	Estimated No. of Deaths in Cohort	Estimated No. of Person-Years in Cohort	Deaths in Cohort Without Lung Cancer	Person-Years in Cohort Without Lung Cancer
973	17.95	178.35		
833	5.31	53.38		
713	4.69	51.31		
610	3.74	48.00		
610			11.8950	5,490

Abbreviation: Pts, patients.

relatively greater percentage of all patients diagnosed with lung cancer have stage I disease, this is a misleading statistic in the absence of a control group. If the number of patients diagnosed with advanced-stage disease in the CT trials are normalized, and compared with the prior chest radiographic studies, the number of individuals with late-stage disease per 1,000 trial participants does not seem to have decreased as the theory would predict.[15] Without this required concomitant reduction in late-stage disease, it is unlikely a meaningful decrease in mortality can ever be achieved.

Because of the reported percentage increase in stage I disease, CT screening for lung cancer seems to be an attractive immediate option to offer high-risk individuals. Unfortunately, it must be understood that this is based on theory and incomplete data from observational trials alone, and a number of other issues have not been adequately addressed. In one trial, more than 70% of participants had at least one indeterminate pulmonary nodule on CT dictating further evaluation, while approximately 2% are expected to have lung cancer.[2] With the addition of thinner sections and computer-aided diagnosis, even more nodules are being detected.[21,22] Most of these lesions are followed up in order to determine growth, as there is currently no other way to identify the cancers in this enormous pool of indeterminate nodules. Even growth characteristics are suboptimal, as in one study, 22% of tumors grew so slowly that the doubling times were considered in the benign range, and an additional 11% of lesions proven to be cancer actually decreased in size.[23]

Table 7. Estimated Mortality: Early Lung Cancer Action Program Computed Tomography Screening Trial

Cumulative No. of Deaths	Cumulative Person-Years	Adjustment Factor	Mortality
12.5500	178.35	1.00000	
18.6934	240.11	1.15696	
24.9712	308.79	1.33853	
30.7656	383.16	1.54931	
49.1946	8,888.86	1.54931	5.53441

Since the entire premise of screening is based on detecting tumors at a small size and early stage, the current data in the best possible trials find that the vast majority of patients will not have their tumor diagnosed until they are almost 10 mm—the size of a lesion visible on most chest radiographs. In addition, almost 25% of nodules seen on incidence studies were missed by experienced readers on the initial studies, and in some studies, as many as 25% of lesions resected were benign, with the certain small, but real issue of morbidity and mortality from unnecessary surgery.[2,3,9] While some of these limitations may be acceptable risks, one must also consider that initial protocols used a significant amount of radiation estimated an exposure doses equivalent to approximately 1,000 chest radiographs, or 60 mammograms, per year for evaluation, which is by no means a low-dose to the patient.[24] These findings do not even factor the cost, estimated to around $115 billion—an enormous burden on the health care system in the absence of any complete trial demonstrating patient benefit.[25]

Therefore, the purpose of the current analysis was intended to critically examine all relevant published data from these CT trials in order to estimate the overall mortality from lung cancer, the primary objective and end point in a screening program. The results from the current study were indeed sobering, as this model predicted that the mortality from CT trials was not statistically different from those of the prior Mayo Lung Project with chest radiographs and sputum cytology (and those trials were not significantly different from "usual care" control groups). One should recognize that to calculate this estimate, we needed to make many assumptions, including number of incident cases in subsequent years and survival statistics. We made every attempt to construct a conservative model that should, if anything, underestimate the true mortality. We assumed that screening would take place for 4 years, and after this, no other participants would develop lung cancer. We also did not take into account deaths due to interventions for lung cancer or surgery for benign or malignant disease; more than 70% of high-risk patients having a false-positive finding is a considerable factor. And finally, we did not include in the estimate those patients diagnosed with small cell lung

cancer, which contribute to the overall mortality, but are not typically considered for early detection in screening trials.

While this study uses all of the available data from uncontrolled CT screening trials to date to estimate mortality, we recognize that this model makes many assumptions, and suggest that these trials remain incomplete. In addition, the true mortality still needs to be determined. A large multi-institutional randomized National Lung Screening Trial (NLST) has recently begun to address this issue.[26] The results from the current analysis, however, are troublesome, and mass screening for lung cancer should not be recommended to the general public until the appropriate trials show a benefit to the patient.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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