CORRESPONDENCE

CT Screening for Lung Cancer

TO THE EDITOR: The survival data from the International Early Lung Cancer Action Program (I-ELCAP) study of computed tomographic (CT) screening for lung cancer, as reported by Henschke et al. (Oct. 26 issue), are misleading.[1] These estimates of survival are potentially confounded by lead-time and overdiagnosis biases of unknown magnitude and therefore defy meaningful interpretation. Although the authors claim to report 10-year lung-cancer–specific survival rates, the median follow-up was only 40 months, and less than 20% of the subjects were observed for more than 5 years. This time horizon is probably not sufficient to assess the behavior of screening-detected lung cancers, 85% of which were detected on baseline screening. Previous research has shown that lung cancers identified on baseline screening are often indolent or very slowly progressive.[2-4] In the absence of screening, at least some patients who had screening-detected cancers would die with lung cancer rather than from lung cancer. Before rushing to embrace CT screening for lung cancer, both patients and clinicians should await publication of less biased data from randomized, controlled trials.

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1. The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
2. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 2000;73:1252-9.
3. Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. AJR Am J Roentgenol 2000;174:763-8.
4. Bach PB, Kelley MJ, Tate RC, McCrory DC. Screening for lung cancer: a review of the current literature. Chest 2003;123:Suppl:72S-82S.

TO THE EDITOR: The I-ELCAP investigators report an estimated 10-year survival rate of 88% among patients with stage I lung cancer. Their claim that "screening could prevent some 80% of deaths from lung cancer" is misleading. The survival estimates misrepresent the benefit owing to the effects of overdiagnosis, lead-time bias, and length bias.[1] Furthermore, the I-ELCAP trial had no comparison group, and the investigators provided inadequate information on several important variables: the pathological stage of tumors at the time of the prevalence and incidence screening, the absolute number of advanced-stage cancers, the completeness of follow-up across the entire cohort, and the total number of lung cancers (not only nodule-based tumors). The lack of evidence re-

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garding the benefits of screening would be less important if the interventions resulting from screening were harmless; however, two deaths were related to surgery. Furthermore, although no complications from interventions for non–lung-cancer findings are reported, with more widespread screening, deaths would also occur from such interventions for ultimately benign disease. The National Lung Screening Trial, an ongoing randomized study with results expected by 2009, will assess the benefits and harms of CT and chest radiography for lung-cancer screening.

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Dr. Aberle reports serving as an expert witness in a tobacco-litigation case during the past 6 years.

1. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA 2000; 283:2975-8.

TO THE EDITOR: The study by Henschke et al. ensured that survival of their subjects would be superior to that of epidemiologic cohorts because the investigators compared lung-cancer–specific survival in the screened subjects (for whom only deaths from lung cancer were counted) with overall survival among subjects in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry (for whom all deaths were counted). Henschke et al. ignored lead time and length biases, which inflate survival among screened subjects without altering mortality,[1] and did not account for enhanced survival of subjects who were treated in high-volume academic institutions; most screened subjects received care at such institutions, but most patients with lung cancer do not.[2,3] What result in the study by Henschke et al. would have suggested that screening might not reduce mortality from lung cancer?

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1. Bach PB, Kelley MJ, Tate RC, McCrory DC. Screening for lung cancer: a review of the current literature. Chest 2003;123: Suppl:72S-82S.
2. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. Chest 1998;114:675-80.
3. 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.

TO THE EDITOR: The results reported by the I-ELCAP investigators represent a real achievement in demonstrating the effectiveness of the described regimen of CT screening for the detection of genuinely cancerous lung lesions while they are still curable. In view of this, steering committees that are involved in ongoing randomized clinical trials will surely question whether it remains ethical for people at risk for lung cancer to be randomly assigned to something other than CT imaging. Since the participants in current trials will become aware of these results, it is very likely that CT imaging will be adopted by many subjects who have been randomly assigned to the control group.

The National Lung Screening Trial[1] now has the opportunity to do the right thing: offer the I-ELCAP regimen of CT screening to all trial participants.[2] Public trust in clinical research will be enhanced, and the results reported by the I-ELCAP investigators will be subject to repetition, which is a requirement of scientific research. We hope that the many years of struggle and controversy over the interpretation of findings from trials of screening mammography may thereby be avoided.

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1. Cancer.gov. National Lung Screening Trial. Bethesda, MD: National Cancer Institute, 2006. (Accessed January 25, 2007, at http://www.nci.nih.gov/NLST.)
2. Miettinen OS. Screening for lung cancer: do we need randomized trials? Cancer 2000;89:Suppl:2449-52.

TO THE EDITOR: Henschke et al. show that annual screening with CT can identify a substantial proportion of patients with stage I lung cancer who can be cured by surgical resection. However, two pieces of information were not reported in the study that may be informative to readers. First,

biopsies were performed in 535 of the 5646 participants (9.5%) with positive results on chest CT. It would be of interest to know the fate of the large majority of patients who did not undergo biopsy. Second, the authors report that none of the eight untreated patients survived for more than 5 years after diagnosis, in striking contrast to the 10-year survival rate of 92% among patients who underwent resection within 1 month. Although the outcome for patients with unresected early-stage lung cancer is poor,[1] the authors do not state whether these untreated patients died from lung cancer or from competing causes.

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1. 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. Cancer 1992;69:685-92.

TO THE EDITOR: The I-ELCAP investigators screened 31,567 subjects but reported on the outcomes of only 412 (1.3%). Such selective reporting is not acceptable. In the I-ELCAP study, the important question is not disease-specific survival in a highly selected subgroup but the number of deaths from lung cancer that were avoided in the entire population. However, the investigators do not report how many deaths from lung cancer occurred or describe the outcomes of the 72 subjects with screening-detected lung cancer whom they dropped from their analyses because they did not have the most favorable possible prognosis.

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TO THE EDITOR: The numbers of subjects screened and of cancers treated and the length of follow-up in the study by Henschke et al. support the use of CT screening to increase the 5-year survival rate among patients with lung cancer from 15 to 85%.

Among the questions raised by clinicians is the practicability of the I-ELCAP protocol in nonacademic settings. The majority of the I-ELCAP sites are recognized academic institutions, and the others are regional centers. In our program — which is part of I-ELCAP, funded by the Department of Energy, and administered in New York — further evaluation and treatment of patients were in the hands of local physicians and hospitals in smaller communities in Tennessee, Kentucky, and Ohio. We screened 6220 subjects and oversaw the treatment of 45 patients with lung cancer. Input from relevant specialties and the availability and quality of diagnostic and treatment approaches were similar to those at major centers. Our experience reflects the medical resources available in the United States and validates the view that CT screening for lung cancer should be widely adopted.

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TO THE EDITOR: If 74 lung cancers were detected from 27,456 annual CT screenings in the I-ELCAP study, as reported by Henschke et al., the annual incidence of lung cancer would be 269 cases per 100,000 persons at risk. Although we acknowledge that the study involved participants from several continents, for 2005, the Centers for Disease Control and Prevention reported an annual incidence of 62.8 cases per 100,000 men and 52.7 per 100,000 women.[1] Is CT screening "overdetecting" lung cancer, by approximately 200 cases, and should these cases of lung cancer therefore be considered clinically insignificant? If so, early detection alone, without treatment, will proportionately increase the cure rate by 74%.

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1. Lung cancer: statistics. Atlanta: Centers for Disease Control and Prevention. (Accessed January 25, 2007, at http://www.cdc.gov/cancer/lung/statistics/.)

TO THE EDITOR: However promising the outcome of the I-ELCAP study appears to be, I have some

reservations about routine annual spiral CT screening for patients at risk for stage I lung cancer. My first concern is that the authors conclude that the screening is cost-effective on the basis of studies performed in 2000, 2001, and 2003. The result is that their assumed average cost for spiral CT screening is half what more recent studies suggest.[1,2] Another concern is that the data used to calculate the cost of surgical treatment at an early stage, as compared with that at a late stage, are from a 1995 Medicare payment schedule. Considering that any change in the recommendations of the Preventive Services Task Force will take into account cost-effectiveness, I hope that future dialogue will include a more thorough and up-to-date assessment of the issue. In a society in which more than 45 million people lack basic health insurance,[3] such questions cannot be ignored, regardless of the potential benefits of a novel screening tool.

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1. Kent MS, Korn P, Port JL, Lee PC, Altorki NK, Korst RJ. Cost effectiveness of chest computed tomography after lung cancer resection: a decision analysis model. Ann Thorac Surg 2005;80:1215-22.
2. Korst RJ, Gold HT, Kent MS, Port JL, Lee PC, Altorki NK. Surveillance computed tomography after complete resection for non-small cell lung cancer: results and costs. J Thorac Cardiovasc Surg 2005;129:652-60.
3. Overview of the uninsured in the United States: an analysis of the 2005 Current Population Survey. ASPE issue brief. Washington, DC: ASPE Office of Health Policy, September 22, 2005. (Accessed January 25, 2007, at http://aspe.hhs.gov/health/reports/05/uninsured-cps/ib.pdf.)

THE AUTHORS REPLY: Gould asserts that our estimates of survival were potentially confounded by lead-time, length, and overdiagnosis biases, so that the estimates preclude a meaningful interpretation. This criticism is echoed by Berg and Aberle and by Bach.

Screening for cancer is supposed to provide for lead time in diagnosis and treatment. A bias is introduced when one compares relatively short-term survival rates as of diagnosis to assess the effectiveness of treatment with lead time relative to treatment without lead time. We did not do this.

The longer the latent stage is for a subtype of cancer, the more prevalent the subtype is in baseline screening. Cancers that are diagnosed at baseline thus tend to grow more slowly than does the subtype in general; they also grow more slowly than do tumors that are diagnosed in repeated screenings. This fact does not introduce a bias, but it may call for making a distinction between baseline screening and repeated screening. Likewise, a timing bias is not introduced by the diagnosis of cancers later in their latent course at baseline than at repeated screenings.

As for the question of whether overdiagnosis introduced a bias in our survival rates, the diagnoses we reported were confirmed by an expert panel of pulmonary pathologists; 95% of the surgical specimens obtained from patients with clinical stage I tumors were classified by the panel as invasive. All eight patients with untreated stage I disease died of lung cancer within 5 years after screening.

Berg and Aberle remark that our study had no comparison group, but unlike interventional research, diagnostic research does not inherently require a comparison, much less a comparison group. The attainable frequency of diagnoses of stage I tumors can be assessed only in the framework of screening, and our principal diagnostic result was the 85% frequency of diagnoses of clinical stage I tumors among all diagnoses. The principal interventional result was the 92% cause-specific 10-year survival rate after prompt treatment of stage I tumors. The relevant comparison group would consist of patients who received early diagnoses but were treated late, principally to learn about the timing of deaths from lung cancer.

Bach incorrectly states that we compared lung-cancer–specific survival with overall survival in the SEER database. The article we cited reported lung-cancer–specific deaths. To answer his question, the absence of a reduction in mortality would have been suggested if the overall 10-year cause-specific survival rate had been close to the rate of 5 to 10% seen without screening.

With regard to the comments of Yee and Lynch: every instance of a positive or negative result of the initial CT screening was followed through all screenings and for 18 months after the last screening. Thus, all cases of lung cancer that were diagnosed during that time were identified.

With regard to the comments of Silvestri: we focused on the outcome of the 412 patients with stage I tumors because the aim of the screening

was to detect cancer in stage I, but we also reported on the outcomes of all 484 patients who received a diagnosis of lung cancer. We agree with Miller and colleagues that CT screening for lung cancer should not be practiced without the accessibility and collaboration of all relevant specialties and that such services can be found outside major medical centers. With regard to the comments of Sutedja et al.: since lung-cancer screening reflects selectivity with respect to age and smoking status, the frequency of diagnosis associated with screening is higher than that in the general population. We agree with Dehavenon that the most up-to-date and appropriate cost figures should be used for a meaningful assessment of cost-effectiveness, but the costs he cites are not those of CT screening.

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Ranibizumab for Neovascular Age-Related Macular Degeneration

TO THE EDITOR: The results of the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) study and the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) study (Oct. 5 issue)[1,2] show the remarkable and reassuring safety of ranibizumab in the treatment of neovascular age-related macular degeneration. We are concerned, however, by the low reported rate of arterial thromboembolic events in both ranibizumab groups (4.6% over a period of 2 years among patients receiving 0.3 mg or 0.5 mg) and sham injection (3.8%) in the MARINA study, since patients with age-related macular degeneration may have an increased risk of stroke.[3]

In the population-based Blue Mountains Eye Study,[4] conducted from 1992 through 1994 and involving 3654 adults over the age of 49 years, we observed 19 arterial thromboembolic events (incident nonfatal stroke, nonfatal myocardial infarction, and deaths from stroke or coronary heart disease) among 49 subjects with neovascular age-related macular degeneration after 5 years of follow-up, an incidence of 38.8% (Table 1). Although we are comparing data from a 2-year clinical trial with those from a 5-year observational trial, the annualized incidence rate for arterial thromboembolic events in our study (7.8%) was more than three times the rates in the MARINA trial (1.9%

Table 1. Cardiovascular Risk Factors and Arterial Thromboembolic Events among Patients with Neovascular Age-Related Macular Degeneration in the MARINA Trial and the Blue Mountains Eye Study.*

Risk Factor or Event	MARINA Trial		Blue Mountains Eye Study (N=49)†
	Sham Injection (N=238)	Ranibizumab (N=238)‡	
Age — yr			
Mean ±SD	77±7	77±8	80±8
Range	56–94	52–95	60–96
Male sex — no. (%)	159 (66.8)	153 (64.3)	34 (69.4)
White race — no. (%)§	231 (97.1)	229 (96.2)	49 (100)
History of angina, myocardial infarction, or stroke — no. (%)	NA	NA	15 (30.6)
Hypertension — no. (%)	NA	NA	30 (61.2)
Current smoker — no. (%)	NA	NA	9 (18.4)
Diabetes — no. (%)	NA	NA	5 (10.2)
Incident arterial thromboembolic events — no. (%)	9 (3.8)§	11 (4.6)¶	19 (38.8)‖

* NA denotes not available.
† In this study, neovascular age-related macular degeneration was defined as previously reported.[4] Arterial thromboembolic events were documented on the basis of physicians' notes and hospital records; results of electrocardiography, computed tomography, and magnetic resonance imaging; and data linkage with the Australian National Death Index database (to determine the number of deaths from coronary heart disease and stroke).[5]
‡ Results are given for the patients who received 0.3 mg of ranibizumab. Results were similar for the patients who received 0.5 mg of ranibizumab.
§ Race was reported by means of a questionnaire administered by an examiner.
¶ Data are for 2 years of follow-up.
‖ Data are for 5 years of follow-up.