性）が示されただけで，effectiveness（現実の場における有効性）が示されたわけではない．胸部単純X線撮影の読影は，卓越した解剖学的知識と経験が必要とされるものの，読影専門医制度を設けずに，検診が行われてしまった．また，有症状者や，肺がん治療例の再発確認など医療でカバーされるべきものが，実際の検診の現場では多く混入する．これでは集団としてみても到底肺がん死亡率の減少は期待できない．**死亡率減少を期待するのであれば，きちんとした精度管理システムを構築する必要がある．**

結論として，「肺がん検診を受けると，肺がん死亡率は減らせるのか？」という命題に対しては，きちんとした精度管理システムの元では集団としての死亡率は減少させることが可能であると考えられる．ただし個人単位に関しては，個人の年齢・性・喫煙歴等で左右される可能性があり，今後の研究成果を待たねばならない．

●参考文献

1) Tockman MS, et al：Screening and detection of lung cancer. In "Lung Cancer, Contemporary Issues in Clinical Oncology. Vol.3," ed. J Aisner, Churchill Livingstone, 25-40, 1985.
2) Melamed MR, et al：Memorial Sloan-Kettering Study. Screening for early lung cancer. Results of Memorial Sloan-Kettering in New York. Chest, 86：44-53, 1984.
3) Fontana RS, et al：Lung cancer screening：The Mayo Program. J Occup Med, 28：746-750, 1986.
4) Kubik A, et al：Lack of benefit from semi-annual screening for cancer of the lung：Follow-up report of a randomized controlled trial of a population of high-risk males in Czechoslovakia. Int J Cancer, 45：26-33, 1990.
5) Marcus PM, et al：Lung cancer mortality in the Mayo Lung Project：impact of extended follow-up. JNCI, 92(16)：1308-1316, 2000.
6) Sobue T, et al：A case control study for evaluating lung-cancer screening in Japan. Int J Cancer, 50：230-237, 1992.
7) Okamoto N, et al：Evaluation of a clinic-based screening program for lung cancer with a case-control design in Kanagawa, Japan. Lung Cancer, 25：77-85, 1998.
8) Nakayama T, et al：An evaluation of chest X-ray screening for lung cancer in Gunma prefecture, Japan. A population-based case-control study. Eur J Cancer, 38(10)：1380-1387, 2002.
9) Sagawa M, et al：A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. Cancer, 92(3)：588-594, 2001.
10) Nishii K, et al：A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer, 34：325-332, 2001.
11) Tsukada H, et al：An evaluation of screening for lung cancer in Niigata prefecture, Japan：a population-based case-control study. Br J Cancer, 85(9)：1326-1331, 2001.
12) 久道　茂：平成12年度厚生労働省老人保健事業推進費等補助金．がん検診の適正化に関する調査研究事業．新たながん検診手法の有効性の評価報告書．(財)日本公衆衛生協会，2001.
13) Humphrey LL, et al：Lung cancer screening with sputum cytologic examination, Chest radiography, and computed tomography：An update for the US preventive Service Task Force. Ann Intern Med, 140：740-753, 2004.

ORIGINAL INVESTIGATION

Computed Tomographic Screening for Lung Cancer

The Relationship of Disease Stage to Tumor Size

*The International Early Lung Cancer Action Program Investigators**

Background: The relationship of lung cancer stage to tumor diameter has been identified as a prognostic indicator. We report on the stage-size relationship of these asymptomatic, latent lung cancer cases diagnosed by computed tomographic screening.

Methods: Baseline and repeat screening of 28 689 people following the International Early Lung Cancer Action Program regimen of screening has resulted in 464 diagnoses of lung cancer. Each case was characterized according to tumor diameter, consistency (solid, part solid, or nonsolid), and the presence or absence of identifiable metastases (N0 M0) at the time of diagnosis, regardless of whether it was delayed.

Results: For the 436 non–small cell carcinomas, the percentages of cases with no metastases (N0 M0) were 91%, 83%, 68%, and 55% for the categories 15 mm or less, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater, respectively. The gradients in the successive percentages of N0 M0 cases were significantly different ($P=.02$, 1-sided), except between the last 2 categories, and held for solid nodules, were suggestive for part-solid ones, but were not suggestive for nonsolid ones. For the 28 small cell carcinomas, the percentages of N0 M0 cases were 67% and 23% ($P=.01$, 1-sided), respectively, for those 25 mm or less compared with those greater than 25 mm.

Conclusions: Lymph node status has a strong relationship to tumor diameter for non–small cell and small cell cancers. The percentages of N0 M0 cases in screen-diagnosed lung cancers are much higher than previously reported in the Surveillance, Epidemiology, and End Results registry. These results provide direct evidence of a stage-size relationship in a screened population.

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*Authors: The Writing Committee members for the International Early Lung Cancer Action Program (I-ELCAP) are Claudia I. Henschke, PhD, MD; David F. Yankelevitz, MD; and Olli S. Miettinen, MD, PhD.
Group Information: A complete list of the I-ELCAP investigators appears on page 325.

FOR STAGE I LUNG CANCER, tumor size has been identified as a prognostic indicator. It thus was incorporated into the International System for Staging Lung Cancer[1] classification in 1986. Cases without identifiable lymph node metastases (stage I cases) were subdivided into stage IA and stage IB, according to the tumor being less or more than 30 mm in diameter. This refinement in staging has been continued,[2] but all were based on registries of cases.

Since 1986, remarkable advances have occurred in computed tomography (CT) scanners. Submillimeter slicing can now be applied to the entire chest in a single breathhold; as a result, lung cancer is being detected at a smaller size than in cases diagnosed before 1986. Further size-based subdivisions of stage I cancer have been suggested, also based on registry cases.[3-6]

The introduction of CT screening leads to consideration of the prognostic value of tumor size in the context of diagnoses of asymptomatic (thus latent) lung cancers. Until now, registry data have been used to investigate disease stage in relation to tumor size for these smaller, latent cancers.[6] Registry cases, however, do not expressly reflect the stage-size relationship of asymptomatic cases; registry cases typically come to medical attention because of symptoms, possibly metastasis induced, whereas latent cases are found in asymptomatic people.

We report the stage-size relationship of latent lung cancers diagnosed in our International Early Lung Cancer Action Program (I-ELCAP), which is dedicated to research on CT screening for lung cancer.[7] These data provide for the first time, to our knowledge, direct evidence relevant to this issue.

METHODS

Following the I-ELCAP protocol,[8] 28 689 asymptomatic men and women were enrolled and received baseline screening at 38 institutions throughout the world; among them,

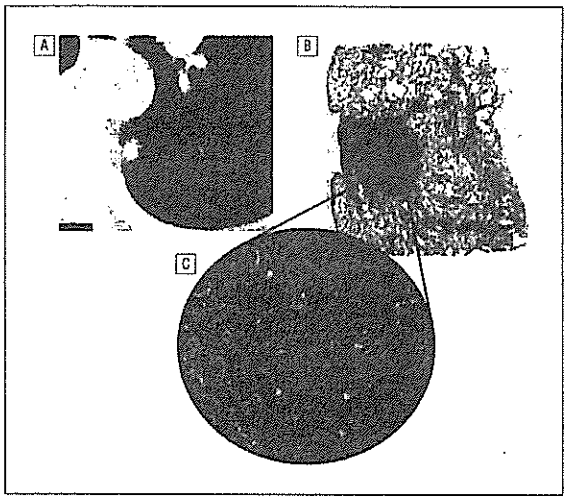

Figure 1. A computed tomographic image and biopsy specimen from a 72-year-old woman. High-resolution computed tomographic image shows a solid 7-mm left lower lobe nodule abutting the pleura (A). The diagnosis was solid adenocarcinoma with mucin, Noguchi D[6] (hematoxylin-eosin, original magnification ×2) (B). Magnified area shows that the tumor is composed of sheets of polygonal cells with enlarged vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. By definition, solid adenocarcinoma with mucin lacks acini, tubules, and papillae (as seen in this image) but contains mucin in at least 5 tumor cells in each of 2 high-power fields, confirmed by histochemical stains for mucin (not seen in this image) (hematoxylin-eosin, original magnification ×40) (C).

22 991 repeat screenings have been performed. At enrollment, the median age was 61 years, median pack-years of smoking was 30, and 58% of the study participants were men. Baseline screenings were conducted in 1993 to 2004 and repeat screenings in 1994 to 2004. All participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols.

The I-ELCAP protocol defined the initial low-dose, noncontrast CT test and its positive result at both baseline and repeat screening. It also defined the recommended diagnostic workup following a positive result. The actual workup, however, was left to the discretion of each participant and the referring physician, but it was documented in the Web-based ELCAP Management System.[7]

All screen-diagnosed cases of lung cancer are included in this report. They consist of cases in which the diagnostic workup was prompted by a positive result of the initial CT test on either the baseline or repeat screening, even if the interval to repeat screening was more than 12 months or the diagnostic workup was delayed, the latter by as much as 3 years. Thus, we excluded the interim-diagnosed cases, identified on the prompting of symptoms emerging between screenings. We focused on the first primary lung cancer that was diagnosed.

A total of 464 cases of lung cancer were screen diagnosed, 376 and 88 of the diagnoses prompted by a positive result of the initial CT test at baseline and on repeat screening, respectively. Each screen-diagnosed case of lung cancer was characterized according to tumor diameter, consistency, and the presence or absence of identifiable lymph node or distant metastases at the time of diagnosis by 1 of 3 experienced chest radiologists (C.I.H., D.F.Y., or Dorothy I. McCauley, MD) at the I-ELCAP Coordinating Center. Tumor diameter was derived as the average of its length and width measured on the pathologic specimen, if available; otherwise, it was measured on the CT images closest in time to diagnosis. Nodule consistency was classified as solid, part solid, or nonsolid on the basis of these same images.[9] It was defined as solid if the nodule obscured the entire lung parenchyma within it (**Figure 1**) or subsolid if it did not. We further subdivided subsolid nodules into part solid if it obscured part of the lung parenchyma within it (**Figure 2**) and nonsolid if it obscured none of the parenchyma within it (**Figure 3**).

Biopsy specimens were submitted to experts for independent reading: cytology specimens to an expert cytologist (Madeline Vazquez, MD) and histologic specimens to our 5-member Pathology Review Panel (Darryl Carter, MD, chair, Elizabeth Brambilla, MD, Adi Gazdar, MD, Masayuki Noguchi, MD, and William Travis, MD) for reading according to the I-ELCAP pathology protocol.[10] Histologic diagnosis superseded the cytologic one when both were available. For purposes of this report, we used the consensus diagnoses of these experts, following the 2004 World Health Organization criteria.[11] Among the 464 cases, there were 436 diagnoses of non–small cell carcinoma and 28 diagnoses of small cell carcinoma.

Lymph node status was based on the surgical findings when available; otherwise, it was based on the CT (and positron emission tomography, if done) test performed closest in time to the recommendation for biopsy, identical to the reporting in the National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results (SEER) registry. Hilar and mediastinal lymph nodes were classified as metastatic if the short axis on CT was greater than 10 mm or the positron emission tomographic scan showed any uptake. It was classified as N0 (no metastases), N1 (only ipsilateral peribronchial, hilar, and/or intrapulmonary metastases), N2 (ipsilateral mediastinal and/or subcarinal metastases, no contralateral), or N3 (contralateral mediastinal and/or hilar, scalene, or supraclavicular metastases). Status of distant metastases was classified as M0 (absent) or M1 (present). Staging was based on the postsurgical findings in 368 (84%) of the 426 cases of non–small cell carcinoma and in 8 of the 28 cases of small cell carcinoma. For these 376 resected cases, the presurgical and postsurgical stages were identical for 335 (89%) of them. Of the 41 cases in which there was disagreement, 37 were presurgical N0 but postsurgical N1 to N3, and 4 were presurgical N1 to N2 but postsurgical N0.

We classified the tumors in the following categories of diameter: 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. We focused principally on the frequency of N0 M0 status in these categories. Because it is well established that the frequency of N0 M0 decreases with increasing tumor size, we used the 1-sided test for assessing significant differences between the size categories. Statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 gives lymph node status by tumor size for 436 diagnosed cases of non–small cell lung cancer. The proportions of cases with no metastases (N0 M0) were 85% overall and 91%, 83%, 68%, and 55% for the respective size categories of 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. The gradients in the successive percentages of N0 M0 were significantly different ($P=.02$, 1-sided), except between the last 2 categories. Of the 370 cases classified as N0 M0, 323 (87%) were based on postsurgical staging.

Table 2, like Table 1, addresses lymph node status in relation to tumor size in those 436 cases of non–small cell lung cancer, but separately according to nodule consistency. The declining trend in the frequency of N0 M0 status with increasing size of the tumor is evident for solid nodules, suggestive for part-solid ones, but not suggestive for nonsolid ones. All non–small cell patho-

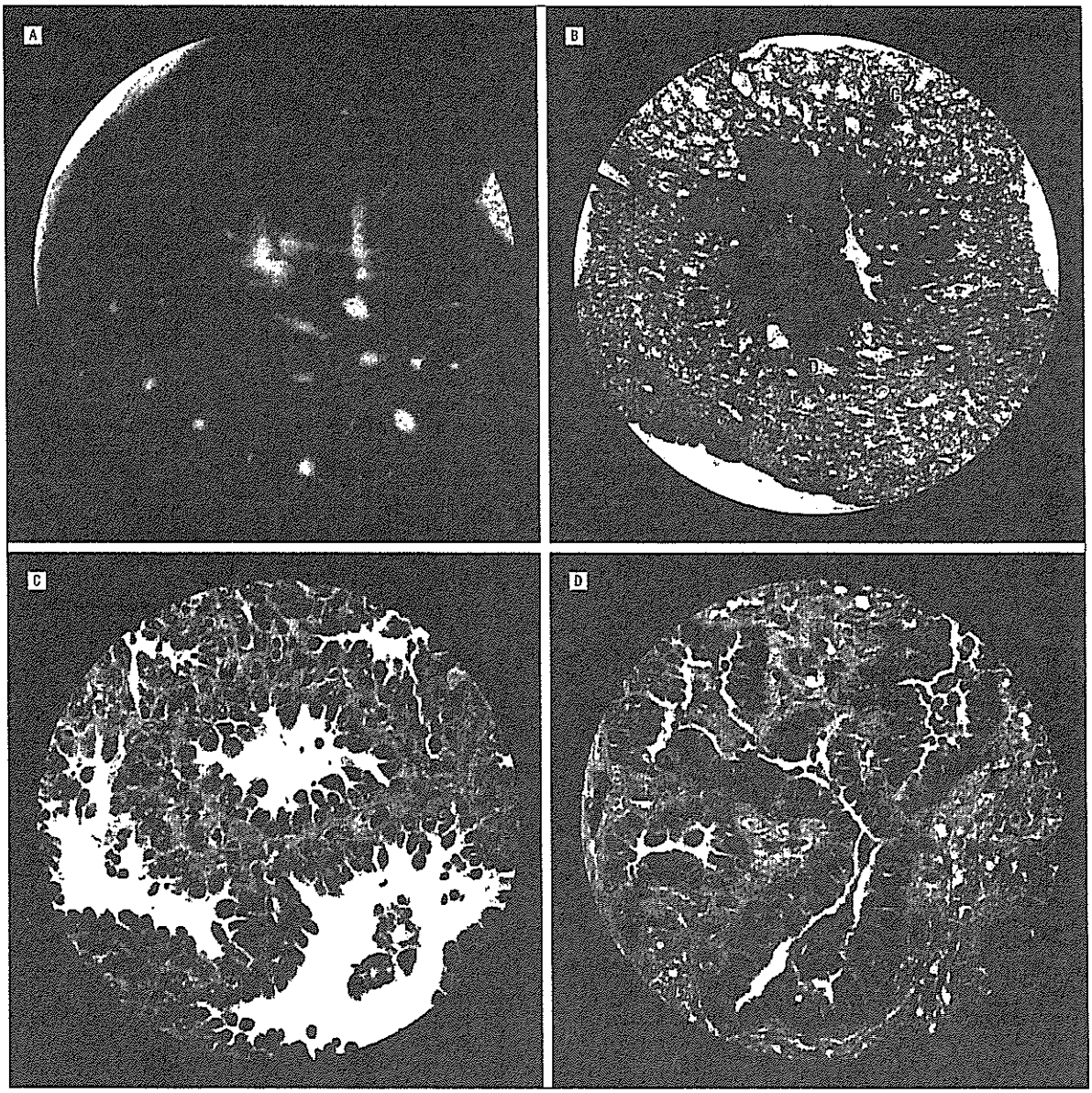

Figure 2. A computed tomographic image and biopsy specimen from a 48-year-old man. The high-resolution computed tomographic image shows a part-solid 15-mm right upper lobe pulmonary nodule; note the patent bronchus in the center of the nodule (A). The diagnosis was adenocarcinoma, mixed subtype, Noguchi C[6] (B) (hematoxylin-eosin, original magnification ×2). Arrowheads indicate magnified areas. Magnified areas show the peripheral noninvasive bronchioloalveolar subtype (C) and the central invasive acinar subtype (D) (hematoxylin-eosin, original magnification ×40).

logic classifications were represented by the cancers presenting in solid nodules, whereas only adenocarcinoma (bronchioloalveolar or mixed subtype) was found in those presenting as part-solid and nonsolid nodules. For solid nodules, the proportions of N0 M0 cases of adenocarcinoma and squamous cell carcinoma were not significantly different (81% vs 79%, respectively; $P=.69$).

For small cell lung cancers, all presenting as solid nodules, the trend in the percentage of N0 M0 status by tumor size is strongly apparent (**Table 3**). Because of the small number of cases, we pooled the data and compared only those 25 mm or less with those larger than 25 mm. The proportions of N0 M0 cases were significantly different: 67% (10/15) and 23% (3/13), respectively ($P=.01$, 1-sided).

COMMENT

Among cases of non–small cell lung cancer diagnosed in asymptomatic persons by CT screening, we find lymph node status to have a strong relationship to tumor diameter for cancers that present as solid nodules. Among the few cases of small cell lung cancer, all presenting as solid nodules, a relationship between lymph node status and tumor diameter was also seen.

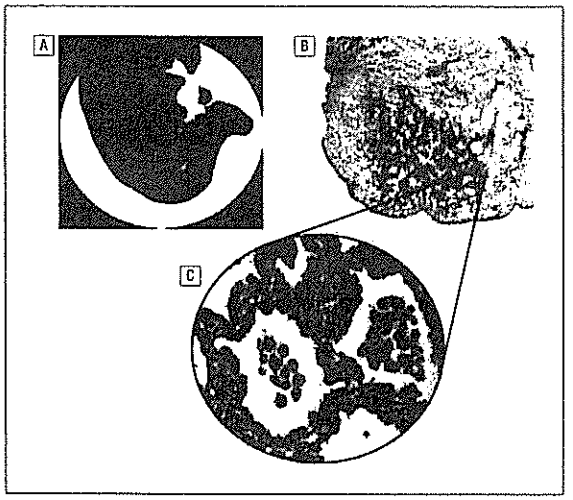

Figure 3. A computed tomographic image and biopsy specimen from a 66-year-old woman. High-resolution computed tomographic image shows a nonsolid 5-mm right lower lobe nodule abutting the pleura (A). The diagnosis was adenocarcinoma, nonmucinous bronchioloalveolar subtype, Noguchi A[5] (hematoxylin-eosin, original magnification ×2) (B). Magnified area shows a classic lepidic growth pattern lining the alveolar septa (hematoxylin-eosin, original magnification ×40) (C).

Table 1. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter*

Lymph Node†	Tumor Diameter, mm ≤15	16-25	26-35	≥36	Any
N0 M0	234	98	27	11	370
N1 M0	5	9	5	4	23
N2 M0	19	10	8	4	41
N3 M0/M1	0	1	0	1	2
Total (% of N0 M0)	**258 (91)**	**118 (83)**	**40 (68)**	**20 (55)**	**436 (85)**

*For tumor diameter ≤15 vs 16-25, $P = .02$; for 16-25 vs 26-36, $P = .02$; and for 26-35 vs ≥36, $P = .17$.

†Cancer stages are as follows: N0 M0, absence of identifiable metastases; N1 M0, peribronchial or hilar lymph nodes, no other metastases; N2 M0, ipsilateral mediastinal lymph nodes, no other metastases; N3, M0/M1, contralateral mediastinal lymph nodes, without or with other metastases.

The relationship of lymph node status to tumor size was not apparent for cancers that presented as nonsolid nodules, whereas it was suggestive for those that presented as part-solid nodules. Cancers that present as nonsolid nodules are noninvasive adenocarcinomas or adenocarcinoma–mixed subtype with a small invasive component and thus have not yet spread to the lymph nodes, as demonstrated by Noguchi et al.[12]

The percentages of N0 M0 cases specific to categories of tumor diameter for non–small cell lung cancer in this report are much higher than those reported from the SEER registry data, which were 54%, 46%, 34%, and 18%, respectively (**Figure 4**).[6] The trend, however, was evident in the SEER data as well. It was not apparent in the analysis of a much smaller registry[13] for reasons explained in subsequent publications.[14,15] Nevertheless, results from that same registry were used as part of the justification for performing a large randomized controlled trial.[16] We have now demonstrated the prognostic significance of tumor size directly.

Table 2. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter and Separately According to Nodule Consistency

Nodule Consistency and Lymph Node Status	Tumor Diameter, mm ≤15	16-25	26-35	≥36	All
Solid					
N0 M0*	146	65	18	6	235
Other	23	18	12	9	62
Total (% of N0 M0)	**169 (86)**	**83 (78)**	**30 (60)**	**15 (40)**	**297 (79)**
Part solid					
N0 M0*	48	22	5	2	77
Other	1	2	1	0	4
Total (% of N0 M0)	**49 (98)**	**24 (92)**	**6 (83)**	**2 (100)**	**81 (95)**
Nonsolid					
N0 M0*	40	11	4	3	58
Other	0	0	0	0	0
Total (% of N0 M0)	**40 (100)**	**11 (100)**	**4 (100)**	**3 (100)**	**58 (100)**

Absence of identifiable metastases.

Table 3. Lymph Node Status of 28 Cases of Small Cell Lung Cancer at Diagnosis by Tumor Diameter (All With Solid Consistency)

Lymph Node	Tumor Diameter, mm ≤15	16-25	26-35	≥36	Any
N0 M0*	6	4	2	1	13
Other	3	2	3	7	15
Total (% of N0 M0)	**9 (67)**	**6 (67)**	**5 (40)**	**8 (13)**	**28 (46)**

Absence of identifiable metastases.

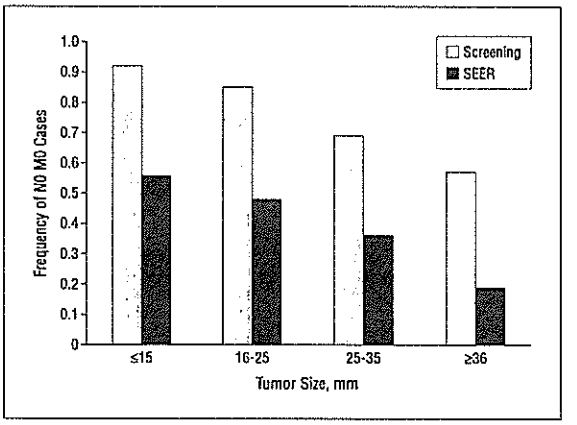

Figure 4. Frequency distribution of cases with absence of identifiable metastases (N0 M0) specific to categories of tumor diameter (≤15 mm, 16-25 mm, 26-35 mm, and ≥36 mm) for non–small cell lung cancer diagnosed as a result of screening and compared with the Surveillance, Epidemiology, and End Results (SEER) registry data.

The pattern confirmed herein suggests the usefulness of finding latent cancers at small sizes. Most lung cancers without evidence of lymph node metastases are curable, with the curability rate being higher at smaller sizes.[5,6] This suggests that tumor diameter also serves as a prognostic indicator for curability, perhaps even for micrometastases not detectable by our current techniques.

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Correspondence: Claudia I. Henschke, PhD, MD, Department of Radiology, New York Presbyterian Hospital–Weill Cornell Medical Center, 525 E 68th St, New York, NY 10021 (chensch@med.cornell.edu).
Author Contributions: Dr Henschke has full access to all data in this study and takes responsibility for the integrity of the data and accuracy of data analysis.
Group Members: The I-ELCAP Investigators were as follows: Joan & Sanford I. Weill Medical College of Cornell University, New York, NY: Claudia I. Henschke, PhD, MD, principal investigator, David F. Yankelevitz, MD, Dorothy I. McCauley, MD; Azumi General Hospital, Nagano, Japan: Shusuke Sone, MD, Takaomi Hanaoka, MD; City University of New York at Queens College, Queens, NY: Steven Markowitz, MD, Albert Miller, MD; Lungen-Zentrum Hirslanden, Zurich, Switzerland: Karl Klingler, MD, Thomas Scherer, MD, Rolf Inderbitzi, MD; H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla: Melvyn Tockman, MD; Hadassah Medical Organization, Jerusalem, Israel: Dorith Shaham, MD; Clinica Universitaria de Navarra, Pamplona, Spain: Javier Zulueta, MD, Gorka Bastarrika, MD, Maria D. Lozano, MD; Swedish Medical Center, Seattle, Wash: Kimball Rice, MD, Ralph Aye, MD; State University of New York at Stony Brook: Matthew Rifkin, MD, Edward Fiore, MD; National Cancer Institute Regina Elena, Rome, Italy: Salvatore Giunta, MD, Marcello Crecco, MD, Patrizia Pugliese, MD; Maimonides Medical Center, Brooklyn, NY: Samuel Kopel, MD; Roswell Park Cancer Institute, Buffalo, NY: Donald Klippenstein, MD, Alan Litwin, MD, Peter A. Loud, MD; Columbia University Medical Center, New York, NY: John H. M. Austin, MD, Gregory D. N. Pearson, MD; State University of New York, Upstate Medical University, Syracuse: Leslie J. Kohman, MD, Ernest M. Scalzetti, MD; Christiana Care, Helen F. Graham Cancer Center, Newark, Del: Thomas Bauer, MD, James Lally, MD; North Shore–Long Island Jewish Health System, New Hyde Park, NY: Arfa Khan, MD, Rakesh Shah, MD; New York University Medical Center, New York: David Naidich, MD, Georgeann McGuinness, MD; Georgia Institute for Lung Cancer Research, Atlanta: Michael V. Smith, MD, Hadyn T. Williams, MD, Louis Lovett, MD; Mount Sinai School of Medicine, New York, NY: David S. Mendelson, MD; University of Toronto, Princess Margaret Hospital, Toronto, Ontario: Heidi Roberts, MD, Demetris Patsios, MD; Memorial Sloan-Kettering Cancer Center, New York, NY: Robert T. Heelan, MD, Michelle S. Ginsberg, MD; Jackson Memorial Hospital, University of Miami, Miami, Fla: Richard Thurer, MD; Mount Sinai Comprehensive Cancer Center, Miami Beach, Fla: Shari-Lynn Odzer, MD; New York Medical College, Valhalla: Terence A. S. Matalon, MD; Eisenhower Lucy Curci Cancer Center, Rancho Mirage, Calif: Davood Vafai, MD; Our Lady of Mercy Medical Center Comprehensive Cancer Center, Bronx, NY: Peter H. Wiernik, MD; Karmanos Cancer Institute, Detroit, Mich: Harvey Pass, MD, Carmen Endress, MD; Evanston Northwestern Healthcare Medical Group, Evanston, Ill: Daniel Ray, MD; The Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, China: Xueguo Liu, MD; Greenwich Hospital, Greenwich, Conn: David Mullen, MD; Sharp Memorial Hospital, San Diego, Calif: Michael Kalafer, MD; Dorothy E. Schneider Cancer Center, Mills-Peninsula Health Services, San Mateo, Calif: Barry Sheppard, MD; Comprehensive Cancer Center, Desert Regional Medical Center, Palm Springs, Calif: Elber Camacho, MD; City of Hope National Medical Center, Duarte, Calif: Fred Grannis, MD, Arnold Rotter, MD. *Coordinating Center:* Joan & Sanford I. Weill Medical College of Cornell University: Claudia I. Henschke, PhD, MD, principal investigator; Nasser Altorki, MD, Ali Farooqi, MD, Jennifer Hess, MBA, Daniel Libby, MD, Dorothy I. McCauley, MD, Olli S. Miettinen, MD, PhD (also McGill University, Montreal, Quebec), Jamie Ostroff, PhD (Memorial Sloan-Kettering Cancer Center), Mark W. Pasmantier, MD, Anthony P. Reeves, PhD (also Cornell University), James P. Smith, MD, Madeline Vazquez, MD, David F. Yankelevitz, MD, Rowena Yip, MPH, Kimberly Agnello, BS, Arin Kramer, BS. *Pathology Review Panel:* Department of Pathology, Yale University School of Medicine, New Haven, Conn: Darryl Carter, MD, chairman; Department of Pathology, Centre Hospitalier Universitaire, Grenoble, France: Elizabeth Brambilla, MD; Department of Pathology, University of Texas Southwestern Medical Center, Dallas: Adi Gazdar, MD; Department of Pathology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan: Masayuki Noguchi, MD; Department of Pathology, Memorial Sloan-Kettering Cancer Center: William D. Travis, MD.
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REFERENCES

1. Mountain CF. A new international staging system for lung cancer. *Chest.* 1986; 89:225S-233S.
2. American Joint Committee on Cancer (AJCC). Lung. In: Fleming ID, Cooper JS, Hensen DE, et al, eds. *Cancer Staging Manual.* 5th ed. Philadelphia, Pa: Lippincott-Raven; 1997:127.
3. Buell PE. The importance of tumor size in prognosis for resected bronchogenic carcinoma. *J Surg Oncol.* 1971;3:539-551.
4. Riquet M, Manac'h D, Le Pimpec Barthes F, Dujon A, Debrosse D, Debesse B. Prognostic value of T and N in non small cell lung cancer three centimeters or less in diameter. *Eur J Cardiothorac Surg.* 1997;11:440-444.
5. Gajra A, Newman N, Gamble GP, et al. Impact of tumor size on survival in stage IA non-small cell lung cancer: a case for subdividing stage IA disease. *Lung Cancer.* 2003;42:51-57.
6. Wisnivesky JP, Yankelevitz DF, Henschke CI. The effect of tumor size on curability of Stage I non-small-cell lung cancers. *Chest.* 2004;126:761-765.
7. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. Screening for lung cancer: the Early Lung Cancer Action Approach. *Lung Cancer.* 2002;35:143-148.
8. International Early Lung Cancer Action Program protocol. Available at: www.IELCAP.org. Accessed December 1, 2005.
9. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley DI, Miettinen OS. CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol.* 2002;178:1053-1057.
10. Vazquez M, Flieder D, Travis W, et al. Early Lung Cancer Action Project Pathology Protocol Web site. Available at: www.IELCAP.org. Accessed December 1, 2005.
11. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon, France: IARC Press; 2004.
12. Noguchi M, Moricawa A, Kawasaki M, et al. Small adenocarcinoma of the lung: histologic characteristics and prognosis. *Cancer.* 1995;75:2844-2852.
13. Heyneman LE, Herndon JE, Goodman PC, Patz EF. Stage distribution in patients with a small (< or = 3 cm) primary nonsmall cell lung carcinoma: implication for lung carcinoma screening. *Cancer.* 2001;92:3051-3055.
14. Yankelevitz D, Wisnivesky JP, Henschke CI. Stage of lung cancer in relation to its size, I: insights. *Chest.* 2005;127:1132-1135.
15. Wisnivesky JP, Yankelevitz DF, Henschke CI. Stage of lung cancer in relation to its size, II: evidence. *Chest.* 2005;127:1136-1139.
16. Aberle DR, Black WC, Goldin JG, et al. American College of Radiology Imaging Network (ACRIN): Contemporary screening for the detection of lung cancer protocol. Available at: http://acrin.org/6654_protocol.html. Accessed December 4, 2005.

Women's Susceptibility to Tobacco Carcinogens and Survival After Diagnosis of Lung Cancer

International Early Lung Cancer Action Program Investigators*

Context It has been hypothesized that women are more susceptible to tobacco carcinogens than men, but after diagnosis of lung cancer, they have better survival rates than men.

Objective To add to the evidence on the lung cancer risk of women who smoke and their survival after diagnosis of lung cancer, conditional on other prognostic indicators and compared with men of the same age who smoke.

Design, Setting, and Participants Nonexperimental, etiologic study with prospective collection of data based on baseline computed tomographic screening for lung cancer and follow-up of diagnosed cases of lung cancer in North America in 1993-2005. A total of 7498 women and 9427 men were screened, all of whom were asymptomatic, aged at least 40 years, and had a history of cigarette smoking.

Main Outcome Measures Comparing women with men, the prevalence odds ratio (OR) for screen-detectable lung cancer (conditional on age and smoking history) and the hazard ratio of fatal outcome of lung cancer (conditional on smoking history, disease stage, tumor cell type, and resection).

Results Lung cancer was diagnosed in 156 women and 113 men (rates of 2.1% and 1.2%, respectively).The prevalence OR comparing women with men was 1.9 (95% confidence interval [CI], 1.5-2.5). The hazard ratio of fatal outcome of lung cancer comparing women with men was 0.48 (95% CI, 0.25-0.89).

Conclusion Women appear to have increased susceptibility to tobacco carcinogens but have a lower rate of fatal outcome of lung cancer compared with men.

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In 2006 in the United States, it is estimated that lung cancer will cause 73 020 deaths in women, proportionately only slightly fewer than the estimated 90 470 deaths in men.[1] Lung cancer now accounts for more deaths in women than any other cancer, more even than the second and third cancer killers (breast and colon cancer) combined.

Research to quantify the benefit of computed tomographic (CT) screening for lung cancer in preventing deaths is ongoing. We previously reported on the Early Lung Cancer Action Project (ELCAP) baseline screening study of 2490 high-risk persons, which indicated that women have a higher absolute risk for lung cancer than do men of the same age with the same history of smoking.[2] There have been other studies indicating that women have a higher relative risk of getting lung cancer than men[3-9]; other studies disagree,[10-12] the issue being the smoker vs nonsmoker risk ratio.

Sex differences in rates of survival following diagnosis of lung cancer have also been reported. Women have been reported to have higher survival rates regardless of the stage of the disease at diagnosis,[9,12-21] the most recent evidence in the United States derived from the national Surveillance, Epidemiology, and End Results (SEER) database[9] and a large cohort at the Mayo Clinic.[21]

For editorial comment see p 218.

Since our previous report, screening has continued at the original ELCAP institutions and has markedly expanded the amount of poolable data by institutions collaborating worldwide in the International Early Lung Cancer Action Project (I-ELCAP).[22] In this article, we again address the lung cancer risk of women compared with men, accounting for age and history of smoking, but herein we also compare the rate of fatal outcomes between sexes.

METHODS

In our previous report, we addressed the risk for lung cancer in 1202 women and 1288 men using New York City data undergoing baseline screening at Joan and Sanford I. Weill Medical College of Cornell University in 1993-1999 (series 1).[2] This report is based on a new

*Authors/Writing Committee and list of the International Early Lung Cancer Action Program Investigators appear at the end of this article.
Corresponding Author: Claudia I. Henschke, PhD, MD, Department of Radiology, Joan and Sanford I. Weill Medical College of Cornell University, New York Presbyterian Hospital, 525 E 68th St, New York, NY 10021 (chensch@med.cornell.edu).

series of 14 435 persons (6296 women and 8139 men) undergoing baseline CT screening for lung cancer in North America in 1999-2005 (series 2), and also on both series combined (7498 women and 9427 men). The comparison of women with men as to fatal outcome of cancer is based on cases from both screening series combined.

All of the screenees were asymptomatic volunteers with no history of cancer (other than nonmelanotic skin cancer) and fit to undergo thoracic surgery, were at least 40 years of age, and were past or current cigarette smokers. All of the participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols. The cohorts' distributions by age and history of smoking are shown in TABLE 1.

Information about smoking history was recorded at the time of the initial CT baseline screening. Participants were asked about the following by an interviewer: the age at which habitual smoking began and whether the habit had continued to the last month; if smoking had continued, the daily number of cigarettes smoked in that month; and if smoking had not continued, the typical number of cigarettes smoked per day and the duration of the smoking history. Pack-years of smoking was calculated as the product of the number of cigarettes smoked per day divided by 20 and the number of years of smoking.

The protocol specified a diagnostic workup following a positive result of the initial low-dose CT, ie, the identification of a specified pattern of noncalcified nodules. Although updated since our prior report, this workup has remained essentially unchanged in its indications for biopsy: demonstration of tumor growth on the CT scan, positive positron emission tomographic scan result, or CT 1 month after the initial scan not showing resolution after antibiotic treatment[23]; for nodules 15 mm or more in diameter, immediate biopsy was an option. A nodule's diameter was calculated as the average of its length and width in the image showing its largest cross-section in the CT scan closest to the time of diagnosis.

Table 1. Distribution of the 2 Series of Baseline Screenings by Age and History of Smoking

Characteristic	Series 1 (n = 2490)		Series 2 (n = 14 435)		Combined (N = 16 925)	
	Women	Men	Women	Men	Women	Men
Age, y						
Median	63	64	63	64	63	64
Mean	63	63	63	64	63	64
Pack-years of smoking, No.						
Median	36	42	40	40	39	40
Mean	40	47	42	44	42	45
Age at start of smoking, y						
Median	17	17	17	17	17	17
Mean	18	17	18	17	18	17

The consensus diagnoses by a panel of 5 experts on lung pathology, following the I-ELCAP pathology protocol[24,25] based on the 2004 World Health Organization criteria,[26] are used in this article. For patients undergoing resection, diagnoses were based on the histology of the surgical specimens; for other patients, diagnoses were based on the cytology of the biopsy specimens.

The women vs men incidence density ratio for lung cancer was the ratio of the corresponding prevalence odds ratio (OR) (cancer present vs cancer absent),[27] conditional on age and history of smoking. In logistic regression analysis (unconditional), with the dependent variate an indicator of cancer diagnosed (Y = 1 if diagnosed, 0 otherwise), we controlled for possible confounding by age by means of a single quantitative term, there being no apparent actual confounding (Table 1); we also used a single quantitative term for pack-years of smoking, which indicated a slight confounding (Table 1).

All cases of lung cancer diagnosed in the combined series have been followed up. In cases of known death, the date and cause of death were obtained from the patient's physician and/or family members. If the patient died as a result of the lung cancer treatment, it was also considered to be a lung cancer death. Follow-up time from diagnosis onward—to death from lung cancer, last contact, or March 15, 2006, whichever came first—was calculated for each case; it ranged from 1 to 117 months (median, 46 months).

The women vs men incidence density (hazard) ratio of fatal outcome of lung cancer in the combined cohort was addressed as the ratio of the respective risks, conditional on pack-years of smoking, disease stage, tumor cell type, and resection. This was performed using multivariate Cox proportional hazards regression analysis to test the independent effect of patient sex after accounting for pack-years of smoking at time of diagnosis, clinical stage of the disease (I, II+), cell type (adenocarcinoma, other non–small cell, small/large cell), and resection (yes, no).

All statistical analyses were performed using the SAS version 8.2 (SAS Institute Inc, Cary, NC) statistical package.

RESULTS

In the new series of 14 435 baseline screenings, lung cancer was diagnosed in 111 of 6296 women and 93 of 8139 men. Thus, for the crude women vs men prevalence OR, the point estimate was 1.6 (111/[6296 − 111]/[93/(8139 − 93)]; $P = .001$, 1-sided). TABLE 2 shows the corresponding result from the logistic regression discrimination between the case (N = 204) and the noncase (N = 14231 [14 435 − 204]) series, and also the result when controlling for age and pack-years of cigarette smoking. The OR for age and smoking was 1.7 (95% confidence interval [CI], 1.3-2.3). Combining the 2 series of baseline screenings, lung cancer was diagnosed in 269 cases

Table 2. Logistic Regression Analysis of 14 435 Baseline Screenings for Lung Cancer, Prevalence Odds Ratio, Women vs Men by Controlled Covariates

Covariates	Coefficient (SE)*	Odds Ratio (95% CI) Estimate	*P* Value†
None	0.44 (0.14)	1.6 (1.2-2.0)	.002
Age and smoking	0.54 (0.14)	1.7 (1.3-2.3)	<.001

Abbreviation: CI, confidence interval.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

Table 3. Distributions of Women and Men With Baseline Diagnosis of Lung Cancer According to Age, History of Smoking at Time of Diagnosis, Clinical Stage I of the Disease, and Resection*

Characteristic	Women (n = 156)	Men (n = 113)
Age, median (range), y	67 (47-84)	68 (49-83)
Pack-years of smoking, median (range), No.	47 (2-125)	64 (9-130)
Stage I disease	139 (89)	90 (80)
Underwent resection	125 (90)	79 (88)

*Data are reported as No. (%) of participants unless otherwise noted.

Table 4. Distributions of Cases of Baseline Diagnosis of Lung Cancer by Tumor Diameter

Tumor Diameter, mm	No. (%) Women (n = 156)	Men (n = 113)
<10	17 (11)	10 (9)
10-20	103 (66)	69 (61)
>20	36 (23)	34 (30)

(156/7498 women and 113/9427 men). The combined women vs men prevalence OR estimate, when controlling for age and pack-years of cigarette smoking, was 1.9 (95% CI, 1.5-2.5).

TABLE 3 shows that women diagnosed as having lung cancer were of a similar age as the men (67 vs 68 years) but had smoked considerably less (47 vs 64 pack-years, respectively). Also, the women were more frequently diagnosed as having clinical stage I disease (89% vs 80%), but when diagnosed as clinical stage I, women underwent resection only slightly more often than men (90% vs 88%). TABLE 4 shows the sex-specific frequency distribution of the diagnosed cases of lung cancer by tumor diameter to be quite similar. TABLE 5 provides the cell type distribution of the diagnosed cases. The proportions of adenocarcinoma among the women and men were 73% (114/156) and 59% (67/113), respectively (P=.01, 1-sided).

The incidence density (hazard) ratio of fatal outcome of lung cancer, women vs men, was 0.48 (95% CI, 0.25-0.89) (TABLE 6) when controlling for pack-years of smoking, disease stage, tumor cell type, and resection.

COMMENT

Following up on our previous study,[2] the findings reported herein again indicate that the risk of lung cancer is higher in women who smoke than in men of the same age who smoke the same amount.

The diagnoses were initially derived in the institutions in which the screenees were cared for, but in 222 of the 269 cases, the pathology specimens were independently reviewed by an expert panel of pulmonary pathologists. This panel confirmed all of the 222 cases as representing lung cancer, changing only the cell-type particulars in some of them. The low proportions of squamous and small cell carcinomas among the diagnosed cases were to be expected, as baseline screening less commonly leads to the detection of relatively fast-growing types, and also because there has been a shift to adenocarcinoma in cancer registry data in the United States and elsewhere.[9,13-15,28-31]

The results of our analysis do involve some residual confounding by age and/or smoking, despite the data in Table 1, but this confounding is negative, resulting in a diluted association (Table 2). As for potential confounding by other airborne carcinogens, the exposures presumably are more common and more pronounced among men, with the consequent bias again diluting rather than accentuating the apparent role of sex.

Our results also raise other questions. First, could the pursuit of malignancy diagnosis have been more vigorous with women screenees? We see no reason to presume this: not only was the diagnostic protocol the same for the 2 sexes, but its recommendations were followed equally. Had the reading of the images been biased in favor of more common nodule detection in the women, this would have accentuated the frequency of relatively small tumors among the diagnosed cases in the women (being that relatively small nodules are less readily detectable), but the proportions of tumors under 10 mm in diameter were quite similar for women and men (0.11 [17/156] vs 0.09 [10/113], respectively).

Second, could women more commonly have presented themselves for screening on the prompting not merely of risk, but also the presence of cancer-suggestive symptoms? Again, we see no reason to presume this. Nevertheless, if this was the case, the largest tumors would have been relatively more common in the cases diagnosed in the women (as larger cancers are more likely to be symptomatic). But the proportion of tumors more than 20 mm in diameter was actually lower in the women than in the men (0.23 [36/156] vs 0.30 [34/113], respectively). Thus, insofar as some of the diagnosed cases actually were symptomatic and differentially so between the sexes, this again more likely diluted rather than accentuated the apparent role of patient sex.

Third, could the higher prevalence of detected cancer in women have resulted from a generally lesser aggressiveness—lower rate of growth—of the women's cancers compared with those of the men? Referring to Table 5, we note that for the slowest-growing malignancies, typical carcinoids and adenocarcinomas of the bronchioloalveolar subtype, the proportions in women's and men's cases were 6% (9/156) and 4% (5/113), respectively. Also, for the fastest-growing type, small cell carci-

noma, the corresponding proportions were 3% (4/156) and 11% (12/113), respectively. The degree of aggressiveness of the women's cancers thus tended to be slightly lower than that of the men's. But if in 10% of the women's cases the growth rate was, for example, one half of that in the men's cases, this would have made the prevalence OR (incidence density) no higher than 1.1. Table 5 clearly indicates that insofar as a given level of smoking causes lung cancer more commonly in women than in men, the excess cases are principally adenocarcinomas, as has been shown in other studies.[9,13-15]

The hypothesis that women may be more susceptible to tobacco carcinogens is biologically plausible.[32,33] While evidence from some epidemiological cohort studies does not substantiate this idea,[10-12] a subsequent study based on the national SEER registry[9] again suggested the increased susceptibility of women. If additional studies add supporting evidence, the notion of women's susceptibility to tobacco carcinogens warrants serious consideration.

If lung cancer risk for women who smoke is indeed higher than the risk for men of the same age who smoke, as indicated by the evidence presented here, this suggests that antismoking efforts directed toward girls and women need to be even more serious than those directed toward boys and men. In the same vein, insofar as screening for lung cancer is practiced among smokers, female sex calls for screening at lower levels of smoking history than the corresponding indication threshold in men. Specifically, if men of a given age are to be screened if the number of pack-years of past smoking is at least X, the regression analysis of the 2 screening series combined suggests that the corresponding threshold for women would be X–0.662/0.0138=X–48 pack-years, where 0.662 and 0.0138 are the fitted coefficients of the indicator of female sex and pack-years of smoking; that is, that the screening threshold for women of a given age should be 50 pack-years lower than that for men of the same age.

Table 5. Cell Type Distribution of the Diagnosed Cases of Lung Cancer

Cell Type	No. (%) Women (n = 156)	Men (n = 113)	Total (N=269)
Carcinoid, typical	6 (4)	1 (1)	7 (3)
Adenocarcinoma (bronchioloalveolar)	3 (2)	4 (4)	7 (3)
Adenocarcinoma (other)	111 (71)	63 (56)	174 (64)
Squamous cell carcinoma	22 (14)	19 (17)	41 (15)
Non–small cell carcinoma, NOS	3 (2)	6 (5)	9 (3)
Carcinoid, atypical	2 (1)	0	2 (1)
Large cell carcinoma	5 (3)	4 (3)	9 (3)
Small cell carcinoma	4 (3)	12 (11)	16 (6)
Other	0	4 (3)	4 (2)

Abbreviation: NOS, not otherwise specified.

Table 6. Multivariate Cox Regression Analysis of 269 Baseline Diagnosed Cases of Lung Cancer for the Hazard Ratio of Fatal Outcome, Women vs Men by Controlled Covariates*

Covariates	Coefficient (SE)*	Hazard Ratio (95%CI) Estimate	*P* Value†
None	−1.12 (0.31)	0.33 (0.18-0.61)	<.001
Smoking, stage, cell type, and resection	−0.75 (0.32)	0.48 (0.25 0.89)	.02

Abbreviation: CI, confidence interal.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

It is well-established by the evidence accumulated over the past 20 years that women with lung cancer survive the disease better than men,[9,12-20] and that this difference is more pronounced when the cancer is diagnosed at an early stage.[18-20] Cancer stage at diagnosis, cell type, or treatment do not appear to be entirely explanatory of this difference.[21] As 85% (229/269) of the cases considered here were clinical stage I at diagnosis, the fatality hazard ratio in favor of women, conditional for pack-years of smoking, disease stage, tumor cell type, and resection was more pronounced than those reported by others.[21] Despite the conditionality, it is not clear whether this survival difference is because lung cancer in women tends to be more commonly curable or less malignant. If lung cancer is more commonly curable in women, then the need to screen women at a lower threshold than men is warranted. If lung cancer is less malignant in women, there may be less need to screen women at a lower threshold.

Author/Writing Committee Affiliations: Department of Radiology (Dr Henschke and Ms Yip), Department of Medicine (Dr Miettinen), Joan and Sanford I. Weill Medical College of Cornell University, New York, NY; Department of Epidemiology and Biostatistics and Department of Medicine, Faculty of Medicine, McGill University, Montreal, Quebec (Dr Miettinen).

Author Contributions: Dr Henschke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Henschke, Miettinen.
Acquisition of data: Henschke.
Analysis and interpretation of data: Henschke, Miettinen, Yip.
Drafting of the manuscript: Henschke, Miettinen, Yip.
Critical revision of the manuscript for important intellectual content: Henschke, Miettinen.
Statistical analysis: Henschke, Miettinen, Yip.
Administrative, technical, or material support: Henschke.
Study supervision: Henschke.
Financial Disclosures: None reported.

The I-ELCAP Investigators: *Joan & Sanford I. Weill Medical College of Cornell University, New York, NY:* Claudia I. Henschke, Principal Investigator, David F. Yankelevitz, Dorothy I. McCauley; *Azumi General Hospital, Nagano, Japan:* Shusuke Sone, Takaomi Hanaoka; *CBNS, City University of New York at Queens College, Queens, NY:* Steven Markowitz, Albert Miller; *LungenZentrum Hirslanden, Zurich, Switzerland:* Karl Klingler, Thomas Scherer, Rolf Inderbitzi; *Clinica Universitaria de Navarra, Pamplona, Spain:* Javier Zulueta, Gorka Bastarrika, Maria D. Lozano; *National Cancer Institute Regina Elena, Rome, Italy:* Salvatore Giunta, Marcello Crecco, Patrizia Pugliese; *H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla:* Melvyn Tockman; *Hadassah Medical Organization, Jerusalem, Israel:* Dorith Shaham; *Swedish Medical Center, Seattle, Wash:* Kim Rice, Ralph Aye; *University of Toronto, Princess Margaret Hospital, Toronto, Canada:* Heidi Roberts, Demetris Patsios; *Christiana Care, Helen F. Graham Cancer Center, Newark, Del:* Thomas Bauer, James Lally; *Columbia University Medical Center, New York, NY:* John H.M. Austin, Gregory D. N. Pearson; *New York University Medical Center, New York, NY:* David Naidich, Georgeann McGuinness; *State University of New York at Stony Brook, Stony Brook, NY:*

Matthew Rifkin, Edward Fiore; *Maimonides Medical Center, Brooklyn, NY:* Samuel Kopel; *Roswell Park Cancer Institute, Buffalo, NY:* Donald Klippenstein, Alan Litwin, Peter A. Loud; *State University of New York, Upstate Medical University, Syracuse, NY:* Leslie J. Kohman, Ernest M. Scalzetti; *North Shore-Long Island Jewish Health System, New Hyde Park, NY:* Arfa Khan, Rakesh Shah; *Georgia Institute for Lung Cancer Research, Atlanta, Ga:* Michael V. Smith, Hadyn T. Williams, Louis Lovett; *Mount Sinai School of Medicine, New York, NY:* David S. Mendelson; *Jackson Memorial Hospital, University of Miami, Miami, Fla:* Richard Thurer; *Memorial Sloan-Kettering Cancer Center, New York, NY:* Robert T. Heelan, Michelle S. Ginsberg; *Holy Cross Hospital Cancer Institute, Silver Spring, MD:* Frank Sullivan, Marlana Ottinger; *Eisenhower Lucy Curci Cancer Center, Rancho Mirage, Calif:* Davood Vafai; *New York Medical College, Valhalla, NY:* Terence A.S. Matalon; *Mount Sinai Comprehensive Cancer Center, Miami Beach, Fla:* Shari-Lynn Odzer; *The 5th Affiliated Hospital of Sun Yat-Sen University, Zhuhai, China:* Xueguo Liu; *Dorothy E. Schneider Cancer Center, Mills-Peninsula Health Services, San Mateo, Calif:* Barry Sheppard; *St Agnes Cancer Center, Baltimore, MD:* Enser Cole; *Our Lady of Mercy Medical Center, Bronx, NY:* Peter H. Wiernik; *Evanston Northwestern Healthcare Medical Group, Evanston, Ill:* Daniel Ray; *Karmanos Cancer Institute, Detroit, Mich:* Harvey Pass, Carmen Endress; *Greenwich Hospital, Greenwich, Conn:* David Mullen; *Sharp Memorial Hospital, San Diego, Calif:* Michael Kalafer; *City of Hope National Medical Center, Duarte, Calif:* Fred Grannis, Arnold Rotter; *ProHealth Care Regional Cancer Center, Waukesha & Oconomowoc Memorial Hospitals, Oconomowoc, Wis:* M. Kristin Thorsen, Richard Hansen; *Comprehensive Cancer Center, Desert Regional Medical Center, Palm Springs, Calif:* Elber Camacho; *St Joseph Health Center, St Charles, Mo:* Dan Luedke.

Coordinating Center, Joan and Sanford I. Weill Medical College of Cornell University: Claudia I. Henschke, PhD, MD, Principal Investigator; Nasser Altorki, MD, Ali Farooqi, MD, Jennifer Hess, MBA, Daniel Libby, MD, Dorothy I. McCauley, MD, Olli S. Miettinen, MD, PhD (also McGill University, Montreal, Canada), Jamie Ostroff, PhD (Memorial Sloan-Kettering Cancer Center), Mark W. Pasmantier, MD, Anthony P. Reeves, PhD (also Cornell University), James P. Smith, MD, Madeline Vazquez, MD, David F. Yankelevitz, MD, Rowena Yip, MPH, Kimberly Agnello, BS, Arin Kramer BS.

Pathology Review Panel: Darryl Carter, MD, Chairman, Department of Pathology, Yale University School of Medicine, New Haven, Conn; Elizabeth Brambilla, MD, Department of Pathology, Centre Hospitalier Universitaire, Grenoble, France; Adi Gazdar, MD, Department of Pathology, University of Texas Southwestern Medical Center, Dallas; Masayuki Noguchi, MD, Department of Pathology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan; William D. Travis, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY.

REFERENCES

1. American Cancer Society. Statistics for 2006: Cancer Facts & Figures 2006. http://www.cancer.org/docroot/STT/stt_0.asp. Accessibility verified June 13, 2006.
2. Henschke CI, Miettinen OS. Women's susceptibility to tobacco carcinogens. *Lung Cancer*. 2004;43:1-5.
3. Brownson RC, Chang JC, Davis JR. Gender and histologic type variations in smoking-related risk of lung cancer. *Epidemiology*. 1992;3:61-64.
4. McDuffie HH, Klaassen DJ, Dosman JA. Female-male differences in patients with primary lung cancer. *Cancer*. 1987;59:1825-1830.
5. Harris RE, Zang EA, Anderson HI, Wynder EI. Race and sex differences in lung cancer risk associated with cigarette smoking. *Int J Epidemiol*. 1993;22:592-599.
6. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ, Miller AB. Are female smokers at higher risk for lung cancer than male smokers? a case-control analysis by histologic type. *Am J Epidemiol*. 1993;138:281-293.
7. Osann KE, Anton-Culver H, Kurosaki R, Taylor T. Sex differences in lung-cancer risk associated with cigarette smoking. *Int J Cancer*. 1993;54:44-48.
8. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst*. 1996;88:183-192.
9. Fu JB, Kau Y, Severson RK, Kalemberian GP. Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database. *Chest*. 2005;127:768-777.
10. Kreuzer M, Boffetta P, Whitley E, et al. Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. *Br J Cancer*. 2000;82:227-233.
11. Thun MJ, Henley SJ, Calle EE. Tobacco use and cancer: an epidemiologic perspective for geneticists. *Oncogene*. 2002;21:7307-7325.
12. United States Public Health Service. *Reducing the Health Consequences of Smoking: 25 Years of Progress: A Report of the Surgeon General Office on Smoking and Health*. Washington, DC: US Public Health Service; 1989.
13. Ferguson MK, Skusey C, Hoffman PC, Golomb HM. Sex-associated differences in presentation, and survival in patients with lung cancer. *J Clin Oncol*. 1990;8:1402-1407.
14. Minami H, Yoshimura M, Tsubota N, et al. Lung cancer in women: sex-associated differences in survival of patients undergoing resection for lung cancer. *Chest*. 2000;118:1603-1609.
15. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage initial treatment and survival: population-based study of 20,561 cases. *Ann Oncol*. 2002;13:1087-1093.
16. Ouellette D, Desbiens G, Emond C, Beauchamp G. Lung cancer in women compared with men: stage, treatment, and survival. *Ann Thorac Surg*. 1998;66:1140-1144.
17. Ferguson MK, Wang J, Hoffman PC, et al. Sex-associated differences in survival of patients undergoing resection for lung cancer. *Ann Thorac Surg*. 2000;69:245-250.
18. de Perrot M, Licker M, Spiliopoulous A, et al. Sex differences in presentation, management and prognosis of patients with non-small cell lung carcinoma. *J Thorac Cardiovasc Surg*. 2000;119:21-25.
19. Alexiou C, Onyeaka CV, Beggs D, et al. Do women live longer following lung resection for carcinoma? *Eur J Cardiothorac Surg*. 2002;21:319-325.
20. Yoshino I, Baba H, Kukuyama S, et al. A time trend of profile and surgical results in 1123 patients with non-small-cell lung cancer. *Surgery*. 2002;131:S242-S248.
21. Visbal AL, Williams BA, Nichols MC, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg*. 2004;78:209-215.
22. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. Screening for lung cancer: the Early Lung Cancer Action approach. *Lung Cancer*. 2002;35:143-148.
23. International Early Lung Cancer Action Program protocol. www.IELCAP.org. Accessibility verified June 13, 2006.
24. Vazquez M, Flieder D, Travis W, et al. Early Lung Cancer Action Project pathology protocol. *Lung Cancer*. 2003;39:231-232.
25. Vazquez M, Flieder D, Travis W, et al. Early Lung Cancer Action Project Pathology Protocol. http://www.ielcap.org/pathology_protocol.pdf. Accessibility verified June 13, 2006.
26. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon, France: IARC Press; 2004.
27. Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol*. 1976;103:226-235.
28. Levi F, Franceschi S, La Vecchia C, Randimbison L, Te V. Lung carcinoma trends by histologic type in Vaud and Neuchatel, Switzerland, 1974-1994. *Cancer*. 1997;79:906-914.
29. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. *J Natl Cancer Inst*. 1984;73:383-389.
30. Beard CM, Jedd MB, Woolner LB, Richardson RL, Bergstralh EJ, Melton LJ III. Fifty-year trend in incidence rates of bronchogenic carcinoma by cell type I, Olmsted County, Minnesota. *J Natl Cancer Inst*. 1988;80:1404-1407.
31. Koyi H, Hillerdal G, Branden E. A prospective study of a total material of lung cancer from a county in Sweden 1997-1999: gender, symptoms, type, stage, and smoking habits. *Lung Cancer*. 2002;36:9-14.
32. Wei Q, Lie C, Amos CI, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst*. 2000;92:1764-1772.
33. Shriver SP, Bourdeau HA, Gubish CT, et al. Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer. *J Natl Cancer Inst*. 2000;92:24-33.

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Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

The members of the Writing Committee (Claudia I. Henschke, M.D., Ph.D., David F. Yankelevitz, M.D., Daniel M. Libby, M.D., Mark W. Pasmantier, M.D., and James P. Smith, M.D., New York Presbyterian Hospital–Weill Medical College of Cornell University, New York; and Olli S. Miettinen, M.D., Ph.D., McGill University, Montreal) of the International Early Lung Cancer Action Program assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Henschke at New York Presbyterian Hospital–Weill Medical College of Cornell University, 525 E. 168th St., New York, NY 10021, or at chensch@med.cornell.edu.

*The International Early Lung Cancer Action Program investigators are listed in the Appendix.

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In 1993, the Early Lung Cancer Action Project (ELCAP) initiated a study of the early diagnosis of lung cancer in cigarette smokers with the use of annual screening with spiral computed tomography (CT).[1,2] The principal finding was that more than 80% of persons given a diagnosis of lung cancer as a result of annual CT screening had clinical stage I cancer.[3] This result has been confirmed by others[4] who have adopted the updated protocol.[5,6] The question remains, however, whether early intervention in such patients is sufficiently effective to justify screening large asymptomatic populations who are at risk for lung cancer.[7,8] We report the results of all patients in the study with stage I lung cancer detected with the use of spiral CT screening, including those who underwent surgical resection.

METHODS

Screening was defined according to the International ELCAP (I-ELCAP) protocol[6] so that data from participating institutions could be pooled. Each institution was required to document the initiation of screening in each participant and all subsequent screenings of that participant for as long as the screening continued, transmit the data and images to the coordinating center at Weill Medical College of Cornell University by means of the study's Web-based management system for CT screening for lung cancer,[9] submit pathological specimens to the coordinating center, and follow quality-assurance procedures specified by the protocol. All participants gave written informed consent, and the institutional review board at each participating institution approved the protocols (Fig. 1).

The protocol specified a common regimen of screening but allowed each participating institution to specify its criteria for enrollment. The regimen included the technical variables for the initial low-dose spiral CT scan, which were the same for the baseline and annual screenings. However, the definition of a positive result on the initial CT scan and the diagnostic workup leading to a diagnosis of lung cancer were different for the baseline screening and annual screening.

For baseline screening, a positive result on the initial low-dose CT scan was defined as the identification of at least one solid or partly solid noncalcified pulmonary nodule 5 mm or more in diameter, at least one nonsolid noncalcified pulmonary nodule 8 mm or more in diameter, or a solid endobronchial nodule.[10] If none of the noncalcified nodules identified met the study criteria for a positive result or if the test was negative, CT was repeated 12 months later. The diameter of the nodule was defined as the average of the length and width of the cross-sectional area of the largest nodule in the CT images. The consistency of the nodule was defined as solid if the nodule obscured the entire lung parenchyma, partly solid if it obscured part of the lung parenchyma, and nonsolid if it obscured none of the parenchyma.[11] If the result was positive, the type of workup depended on the diameter of the largest nodule. For nodules 5 to 14 mm in diameter, the preferred option was to perform another CT at 3 months; if the images showed growth of the nodule,[12] then biopsy, ideally by fine-needle aspiration, was to be performed, whereas if there was no growth, the workup was stopped. The other option was to perform positron-emission tomography (PET) immediately, and if the results were positive, biopsy was to be performed; otherwise, CT was to be performed at 3 months. For nodules 15 mm in diameter or larger (whether solid, partly solid, or nonsolid), immediate biopsy was an option in addition to the options already specified for smaller nodules. When infection was suspected, a 2-week course of antibiotics followed 1 month later by CT was an alternative to all the options mentioned,[13] and if no resolution or growth was observed, biopsy was to be performed; otherwise, the workup was stopped. For all participants for whom the workup was stopped or for whom the biopsy did not lead to a diagnosis of lung cancer, CT was to be repeated 12 months after the baseline CT.

For annual screenings, a positive result was considered to be any newly identified noncalcified nodule, regardless of size. If no new nodule was identified, CT was to be repeated 12 months later. If one or more new nodules were identified, the workup depended on the diameter of the largest nodule. If all nodules were less than 3.0 mm in diameter, or if the largest nodule was more than 3.0 mm but less than 5.0 mm in diameter, CT 6 or 3 months later, respectively, was to be performed. If no growth was seen in any of the nodules, the workup was stopped. If at least one of the noncalcified nodules was 5.0 mm or larger in diameter, then an immediate 2-week course of a broad-spectrum antibiotic was prescribed, followed 1 month later by CT. If the nodules showed no

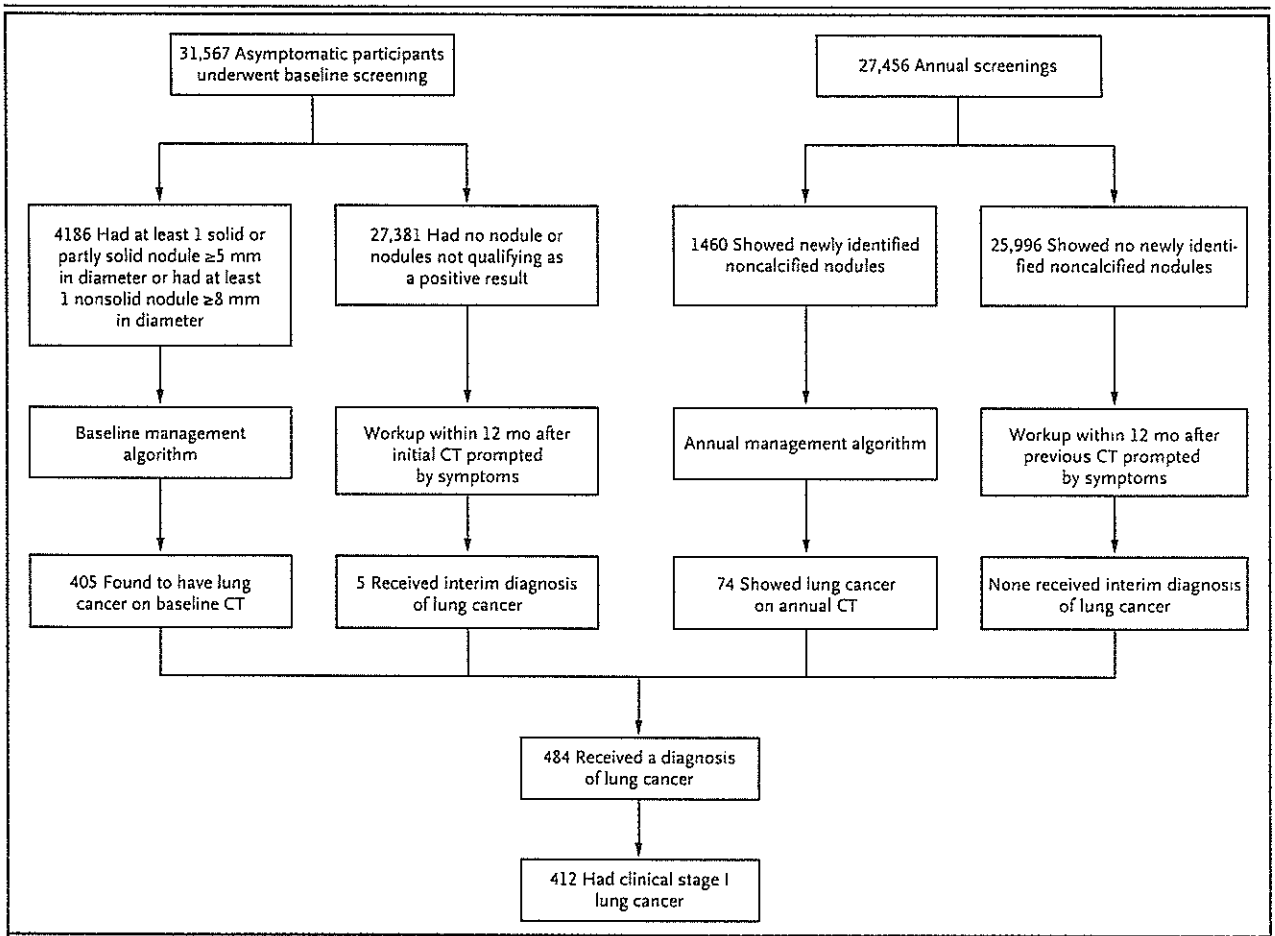

Figure 1. Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT.

A description of the I-ELCAP management algorithm for baseline CT and repeated CT screening is available in the study protocol.[6]

resolution or growth, biopsy was to be performed; otherwise, the workup was stopped. PET was an alternative to immediate biopsy; if the result was positive, biopsy was to follow. If the result was indeterminate or negative, CT was to be performed 3 months later, and if the scans showed growth, biopsy was to follow. Otherwise, the workup was stopped. For all patients for whom the workup was stopped or when biopsy did not result in a diagnosis of lung cancer, CT was to be repeated 12 months after the previous annual CT.

The protocol provided recommendations for the diagnostic workup in participants with a positive result on CT, with the decision regarding how to proceed left to each participant and the referring physician. The I-ELCAP protocol did not require that its recommendations for the workup of a nodule be followed, but it did require a firmly established final diagnosis of lung cancer and documentation of the workup in the management system. After the diagnosis of lung cancer was established, the type of intervention, if any, was left to the discretion of the participant and the physician. Documentation in the management system of the timing and type of intervention, if any, and follow-up with respect to manifestations of spread or death up to 10 years after diagnosis, were required.

A total of 31,567 asymptomatic men and women underwent baseline screening between 1993 and 2005 (median, 2001). The participants, who were 40 years of age and older, were at risk for lung cancer because of a history of cigarette smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to secondhand smoke without having smoked themselves; in Azumi, Japan, they participated as part of the annual health screening program (Table 1). All partici-

Table 1. I-ELCAP Participants, According to the Smoking Status, Exposure to Secondhand Smoke, and Occupational Exposures.

Program	Participants (N=31,567)
	no. (%)
Azumi Health Care Program in Japan	
Current or former smokers	3,087 (10)
Persons who had never smoked with exposure to secondhand smoke	3,299 (10)
Programs in the United States, Europe, Israel, and China	
Current or former smokers	23,052 (73)
Persons who had never smoked	
Occupational exposure*	1,690 (5)
Exposure to secondhand smoke with or without family history of lung cancer	439 (1)

* This category includes exposure to asbestos, beryllium, uranium, or radon.

pants were considered fit to undergo thoracic surgery. A total of 27,456 annual screenings were conducted between 1994 and 2005 (median, 2002), each of which was performed 7 to 18 months after the previous screening. At baseline, the median age of the participants was 61 years (range, 40 to 85), and the median number of pack-years of smoking was 30 (range, 0 to 141); on annual CT, the median values were an age of 62 years (range, 41 to 86) and 35 pack-years (range, 0 to 141). Among the participants, 13% (4186 of 31,567) who underwent baseline CT and 5% (1460 of 27,456) who underwent annual CT had a positive result that required immediate further workup. A biopsy of a pulmonary nodule as recommended in the protocol was performed in 535 of the participants with a positive result on the baseline or annual CT and led to a diagnosis of malignant disease in 492 of the participants (lung cancer was diagnosed in 479 and lymphoma or metastases from cancers other than lung cancer in 13) and no evidence of malignant disease in 43. The diagnosis was classified as having been identified during baseline screening when the nodule was first identified on the baseline CT, even for cases not meeting the criteria for a positive result, regardless of when the diagnosis was made. When the nodule was first identified on an annual CT, it was attributed to the annual screening. If the result on the baseline or annual CT was negative and a diagnostic workup was subsequently prompted by suggestive symptoms (or incidental findings) before the next scheduled annual CT, the finding was classified as an interim diagnosis. To fully document interim diagnoses of lung cancer, the protocol required that each enrolled participant who had not returned for the next scheduled screening be contacted 1 year after the previous screening. If contact could not be made either directly or through relatives of the participant, the referring physician was contacted to ascertain whether a diagnosis of lung cancer had been made.

We determined the distribution of the baseline and annual screenings and the resulting diagnoses according to age and median pack-years of cigarette smoking (Table 2). Each diagnosis of lung cancer was classified according to clinical stage with the use of standard criteria based on the clinical examination and the results of imaging.[24] The presence or absence of lymph-node (N) and distant metastases (M) was assessed on the most recent CT obtained before diagnosis and from PET (performed in 166 of the 484 participants who received a diagnosis of lung cancer). The cancer was classified as N0M0 if on CT the widths of all mediastinal lymph nodes were less than 10 mm and no hilar lymph nodes or distant metastases were identified (and PET, if performed, showed no abnormal uptake). For the purpose of this study, stage I cancers included those classified as N0M0 with more than 1 adenocarcinoma so long as all adenocarcinomas were 30 mm or less in diameter.[6]

The specimens obtained from participants who underwent surgical resection were examined at each institution according to the I-ELCAP pathology protocol,[15] which specified the preparation of the specimen and the findings that were to be documented by the pathologist at the hospital where the resection was performed. The protocol also specified the review process: a five-member pathology-review panel consisting of expert pulmonary pathologists was to reach a consensus diagnosis for each case of cancer and identify lymph-node involvement, additional cancers, and pleural, lymphatic, vascular, bronchial, and basement-membrane invasion by the cancer. For 22 of the 411 participants who underwent resection (5%), specimens could not be obtained from a nonparticipating hospital, and the panel therefore reviewed the detailed surgical and pathological reports for the relevant information.

All patients given a diagnosis of lung cancer were followed annually by the principal investigator and by the study coordinator at each participating institution, who submitted the information

Table 2. Frequency Distribution of Lung-Cancer Diagnoses on Baseline and Annual CT Screening, According to Age and Median Pack-Years of Cigarette Smoking.

Age	Baseline Screening			Annual Screening		
	Smoking History	No. Screened	Diagnosis of Lung Cancer	Smoking History	No. Screened	Diagnosis of Lung Cancer
	median pack-yr		*no. (%)*	*median pack-yr*		*no. (%)*
40–49 yr	15	4,066	8 (<1)	20	1,324	1 (<1)
50–59 yr	28	9,948	67 (1)	30	6,678	7 (<1)
60–69 yr	38	12,184	206 (2)	40	11,879	29 (<1)
70–79 yr	38	4,840	116 (2)	40	6,692	33 (<1)
80–86 yr	30	529	13 (2)	37	883	4 (<1)
Total	30	31,567	410 (1)*	35	27,456	74 (<1)

* The number includes five participants with interim diagnoses.

required by the protocol to the coordinating center. When a participant was known to have died, the date and cause were obtained from the participant's physician, family members, or both. Death resulting from treatment was considered to have been caused by lung cancer. Follow-up from diagnosis to death from lung cancer, the last contact, or May 30, 2006, whichever came first, was documented for each participant. The duration of follow-up ranged from 1 to 123 months (median, 40).

Kaplan–Meier curves were calculated for lung-cancer–specific survival as of the date of diagnosis, irrespective of the type of treatment, including no treatment, for all participants with lung cancer, irrespective of the stage of the cancer, and for the subgroup with clinical stage I cancer. Survival curves were also calculated for participants who underwent resection of clinical stage I cancer within 1 month after diagnosis and those who did not receive treatment. On the basis of these curves, we estimated the 10-year survival rates. The curves were constructed with the use of SAS statistical software (version 8), which also produced the standard error for the estimates.

RESULTS

Baseline screening of 31,567 asymptomatic persons who were at risk for lung cancer and annual screening of 27,456 resulted in the diagnosis of lung cancer in 405 and 74 participants, respectively (Fig. 1). Another five participants received interim diagnoses of lung cancer that were prompted by the development of symptoms within 12 months after the baseline screening. Of these 484 participants given a diagnosis of lung cancer, 411 underwent resection; 57 received radiation, chemotherapy, or both; and 16 received no treatment. Because survival rates among the participants who underwent baseline screening and those who underwent annual screening did not differ significantly, Kaplan–Meier estimates of lung-cancer–specific survival were calculated for all 484 participants (Fig. 2). The estimated 10-year survival rate for all participants, regardless of tumor stage and treatment, was 80% (95% confidence interval [CI], 74 to 85); as of May 2006, 75 of the 484 participants had died of lung cancer, including 2 who died within 4 weeks after surgery, yielding an operative mortality rate of 0.5% (2 of 411 participants).

Of the 484 participants who received a diagnosis of lung cancer, 412 (85%) had clinical stage I lung cancer. In this subgroup, the estimated 10-year survival rate regardless of treatment was 88% (95% CI, 84 to 91); as of May 2006, 39 of these 412 patients had died of lung cancer. Of these 412 participants, 375 had undergone surgical resection (284 lobectomy, 60 wedge resection, 21 segmentectomy, and 10 bilobectomy); 29 did not undergo resection but received chemotherapy, radiation, or both; and the remaining 8 did not receive treatment. Figure 2 also shows the lung-cancer–specific survival rate among the 302 participants who underwent resection within 1 month after diagnosis, among whom the estimated 10-year survival rate was 92% (95% CI, 88 to 95). All eight untreated patients died within 5 years after diagnosis.

Among the 412 participants with clinical

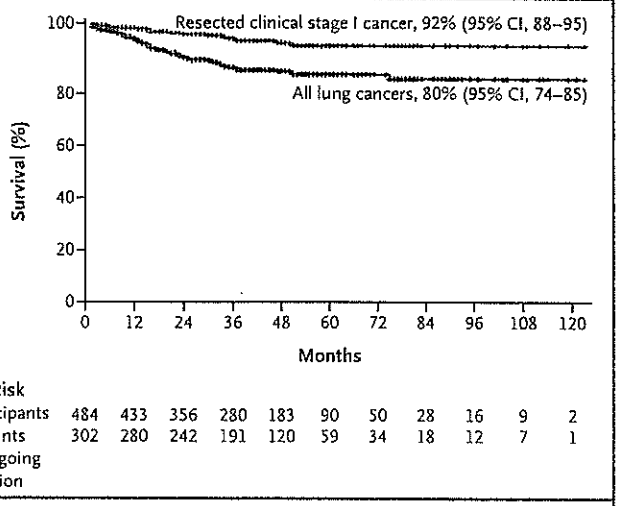

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

Table 3. Types of Cancer among 412 Participants with Clinical Stage I Lung Cancer Detected on Baseline or Annual CT Screening.

Type of Cancer	Diagnosed on Baseline Screening (N=348)	Diagnosed on Annual Screening (N=64)
	no. of participants	
Adenocarcinoma		
Bronchioloalveolar subtype	20	1
Other subtypes	243	30
Squamous cell	45	14
Adenosquamous	3	0
Non–small-cell*	5	2
Neuroendocrine		
Atypical carcinoid	2	1
Large cell	15	8
Small cell	9	7
Other	6	1

* If this cell type cannot be differentiated, the category is known as "not otherwise specified."

stage I cancer, the distribution according to the type of cell is shown in Table 3. The median tumor diameter was 13 mm at baseline and 9 mm on annual CT. The pathology-review panel confirmed the diagnosis of clinical stage I cancer in the specimens obtained from the 375 participants who underwent resection according to World Health Organization criteria of 2004.[16] With regard to spread or invasion (Table 4), the panel identified lymph-node metastases (hilar or ipsilateral mediastinal) in 28 participants (7%) and more than one cancer, either in the same or in different lobes, in another 35 (9%). Among the remaining participants, each with a solitary cancer, the panel identified invasion of the pleura in 62 (17%); bronchial, vascular, or lymphatic invasion or a combination in another 28 (7%); invasion of the basement membrane alone in 203 (54%), and no invasion in the remaining 19 (5%). (Because of rounding, percentages may not total 100.) Thus, of the 375 participants who underwent resection, 347 had pathological stage I cancer, and their estimated 10-year survival rate was 94% (95% CI, 91 to 97).

DISCUSSION

In making decisions about instituting CT screening for lung cancer, a major consideration is the outcome of treating a cancer detected on screening. In our study, the estimated 10-year lung-cancer–specific survival rate among the 484 participants with disease diagnosed on CT, regardless of the stage at diagnosis or type of treatment (including no treatment), was 80% (95% CI, 74 to 85) (Fig. 2). Among the 412 participants with clinical stage I lung cancer — the only stage at which cure by surgery is highly likely — the estimated 10-year survival rate was 88% (95% CI, 84 to 91), and among those with clinical stage I lung cancer who underwent surgical resection within 1 month after the diagnosis, the rate was 92% (95% CI, 88 to 95). The diagnosis of lung cancer of one type or another was verified by a panel of five expert pulmonary pathologists. In our series, the operative mortality rate was low — 0.5% — and was less than the 1.0% reported with lobectomy in a large cooperative study.[17]

Sobue et al.[18] reported a 5-year survival rate of 100% in their series of 29 patients who underwent resection after pathological stage I cancer was detected on CT. Before CT screening, reports based on registries showed 10-year survival rates of 80% among 17 patients with pathological stage I lung cancer 20 mm or less in diameter[19] and 93% among 35 patients with pathological stage I cancer less than 10 mm in diameter.[20] The National Cancer Institute's Surveillance, Epidemiology, and End

Table 4. Extent of Spread of Cancer in 375 Participants Who Underwent Resection of Clinical Stage I Lung Cancer According to Whether Cancer was Detected on Baseline or Annual CT Screening.

Extent of Spread	Diagnosed on Baseline Screening (N=320)	Diagnosed on Annual Screening (N=55)
	no. of participants	
Metastases to lymph nodes	22	6
No metastases to lymph nodes		
More than 1 cancer	29	6
Solitary cancer with invasion		
Pleural invasion	51	11
No pleural invasion but lymphatic, vascular, or bronchial spread (or a combination)	24	4
Basement membrane only	175	28
Solitary cancer without invasion	19	0

Results (SEER) registry, the largest U.S. cancer registry, reported an 8-year survival rate of 75% among patients with pathological stage I cancer with nodules less than 15 mm in diameter who had undergone resection.[8] Although the lung cancers in these three series were not detected on CT screening, most were presumably incidentally detected on imaging performed for other reasons in people who had no symptoms of lung cancer.

CT screening according to the I-ELCAP regimen can detect clinical stage I lung cancer in a high proportion of persons when it is curable by surgery. In a population at risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer. In comparison, in the United States at present, annually approximately 173,000 persons are diagnosed with lung cancer and 164,000 deaths are attributed to this disease,[21] so that approximately 95% of those who are diagnosed with lung cancer die from it.

Are these results sufficiently effective to justify screening people who are at risk of lung cancer? As compared with mammographic screening for breast cancer, for lung cancer the rates of detection among the participants in this study who were 40 years of age and older were 1.3% on baseline CT screening and 0.3% on annual screening (Table 2), values that were slightly higher than those for the detection of breast cancer (0.6 to 1.0% on baseline screening) and similar to those for annual screening (0.2 to 0.4%) among women 40 years of age and older.[22] The rate of cancer detection depends on the risk profile of those undergoing screening; the higher the risk, the more productive the screening. Thus, as expected, CT screening of the original participants in ELCAP, who were former and current smokers 60 years of age and older,[1,2] was more productive in detecting lung cancer (detection rates, 2.7% on baseline screening and 0.6% on annual screening) than among participants in the expanded study. The cost of low-dose CT is below $200,[23-26] and surgery for stage I lung cancer is less than half the cost of late-stage treatment.[26,27] Using the original ELCAP data and the actual hospital costs for the workup, we found CT screening for lung cancer to be highly cost-effective.[23] Other estimates of the cost-effectiveness of CT screening for lung cancer for various risk profiles[24-26,28] are similar to that for mammography screening.[29,30]

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No potential conflict of interest relevant to this article was reported.

APPENDIX

The following investigators participated in I-ELCAP: *Joan and Sanford I. Weill Medical College of Cornell University, New York:* C.I. Henschke (principal investigator), D.F. Yankelevitz, D.I. McCauley; *Azumi General Hospital, Nagano, Japan:* S. Sone, T. Hanaoka; *Center for the Biology of Natural Systems, City University of New York at Queens College, Queens:* S. Markowitz, A. Miller; *LungenZentrum Hirslanden, Zurich:* K. Klingler, T. Scherer, R. Inderbitzi; *Clinica Universitaria de Navarra, Pamplona, Spain:* J. Zulueta, L. Montuenga, G. Bastarrika; *National Cancer Institute Regina Elena, Rome:* S. Giunta, M. Crecco, P. Pugliese; *H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL:* M. Tockman; *Hadassah Medical Organization, Jerusalem, Israel:* D. Shaham; *Swedish Medical Center, Seattle:* K. Rice, R. Aye; *University of Toronto, Princess Margaret Hospital, Toronto:* H. Roberts, D. Patsios; *Christiana Care Helen F. Graham Cancer Center, Newark, DE:* T. Bauer, J. Lally; *Columbia University Medical Center, New York:* J.H.M. Austin, G.D.N. Pearson; *New York University Medical Center, New York:* D. Naidich, G. McGuinness; *State University of New York at Stony Brook, Stony Brook:* M. Rifkin, E. Fiore; *Maimonides Medical Center, Brooklyn, NY:* S. Kopel; *Roswell Park Cancer Institute, Buffalo, NY:* D. Klippenstein, A. Litwin, P.A. Loud; *State University of New York Upstate Medical University, Syracuse:* L.J. Kohman, E.M. Scalzetti; *North Shore–Long Island Jewish Health System, New Hyde Park, NY:* A. Khan, R. Shah; *Georgia Institute for Lung Cancer Research, Atlanta:* M.V. Smith, H.T. Williams, L. Lovett; *Mount Sinai School of Medicine, New York:* D.S. Mendelson; *Jackson Memorial Hospital, University of Miami, Miami:* R. Thurer; *Memorial Sloan-Kettering Cancer Center, New York:* R.T. Heelan, M.S. Ginsberg; *Holy Cross Hospital Cancer Institute, Silver Spring, MD:* F. Sullivan, M. Ottinger; *Eisenhower Lucy Curci Cancer Center, Rancho Mirage, CA:* D. Vafai; *New York Medical College, Valhalla:* T.A.S. Matalon; *Mount Sinai Comprehensive Cancer Center, Miami Beach, FL:* S.-L. Odzer; *Fifth Affiliated Hospital (Zhuhai Hospital), of Sun Yat-Sen University, Zhuhai, China:* X. Liu; *Dorothy E. Schneider Cancer Center, Mills-Peninsula Health Services, San Mateo, CA:* B. Sheppard; *St. Agnes Cancer Center, Baltimore:* E. Cole; *Our Lady of Mercy Medical Center, Bronx, NY:* P.H. Wiernik; *Evanston Northwestern Healthcare Medical Group, Evanston, IL:* D. Ray; *Karmanos Cancer Institute, Detroit:* H. Pass, C. Endress; *Greenwich Hospital, Greenwich, CT:* D. Mullen; *Sharp Memorial Hospital, San Diego, CA:* M. Kalafer; *City of Hope National Medical Center, Duarte, CA:* F. Grannis, A. Rotter; *ProHealth Care Regional Cancer Center, Waukesha and Oconomowoc Memorial Hospitals, Oconomowoc, WI:* M.K. Thorsen, R. Hansen; *Comprehensive Cancer Center, Desert Regional Medical Center, Palm Springs, CA:* E. Camacho; *St. Joseph Health Center, St. Charles, MO:* D. Luedke; **Coordinating Center:** C.I. Henschke, N. Altorki, A. Farooqi, J. Hess, D. Libby, D.I. McCauley, O.S. Miettinen, J. Ostroff, M.W. Pasmantier, A.P. Reeves, J.P. Smith, M. Vazquez, D.F. Yankelevitz, R. Yip, L. Zhang, K. Agnello; **Pathology Review Panel:** D. Carter, E. Brambilla, A. Gazdar, M. Noguchi, W.D. Travis.

REFERENCES

1. 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.
2. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screening. Cancer 2001;92:153-9.
3. Henschke CI, Yankelevitz DF, Smith JP, et al. CT screening for lung cancer: assessing a regimen's diagnostic performance. Clin Imaging 2004;28:317-21.
4. Henschke CI, Yankelevitz DF, Miettinen OS, I-ELCAP Investigators. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. Arch Intern Med 2006;166:321-5.
5. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS, ELCAP Group. Screening for lung cancer: the Early Lung Cancer Action approach. Lung Cancer 2002;35:143-8.
6. International Early Lung Cancer Action Program protocol. (Accessed September 29, 2006, at http://www.IELCAP.org.)
7. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. The use of spiral CT in lung cancer screening. In: DeVita VT, Hellman S, Rosenberg SA, eds. Progress in oncology 2002. Sudbury, MA: Jones and Barlett, 2002.
8. Henschke CI, Wisnivesky JP, Yankelevitz DF, Miettinen OS. Screen-diagnosed small stage I cancers of the lung: genuineness and curability. Lung Cancer 2003;39:327-30.
9. Reeves AP, Kostis WJ, Yankelevitz DF, Henschke CI. A Web-based data system for multi-institutional research studies on lung cancer. Presented at the 87th annual meeting of the Radiologic Society of North America, Chicago, November 25–30, 2001. abstract.
10. Henschke CI, Yankelevitz DF, Naidich D, et al. CT screening for lung cancer: suspiciousness of nodules at baseline according to size. Radiology 2004;231:164-8.
11. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley DI, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053-7.
12. Kostis WJ, Yankelevitz DF, Reeves AP, Fluture SC, Henschke CI. Small pulmonary nodules: reproducibility of three-dimensional volumetric measurement and estimation of time to follow-up CT. Radiology 2004;231:446-52.
13. Libby DM, Wu N, Lee IJ, et al. CT screening for lung cancer: the value of short-term CT follow-up. Chest 2006;129:1039-42.
14. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.
15. Vazquez M, Flieder D, Travis W, et al. Early Lung Cancer Action Project pathology protocol. Lung Cancer 2003;39:231-2.
16. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, eds. World Health Organization classification of tumours: pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon, France: IARC Press, 2004.
17. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ASOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-20.
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;20:911-20.
19. Buell PE. The importance of tumor size in prognosis for resected bronchogenic carcinoma. J Surg Oncol 1971;3:539-51.
20. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120-9.
21. Cancer facts and figures: statistics. 2005. Atlanta: American Cancer Society, 2005. (Also available at http://www.cancer.org.)
22. Quality determinants of mammography. In: Clinical practice guideline no. 13. Rockville, MD: Agency for Health Care Policy and Research, 1994:82-6. (Publication no. 95-0632.)
23. Wisnivesky JP, Mushlin A, Sicherman N, Henschke CI. Cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest 2003;124:614-21.
24. Miettinen OS. Screening for lung cancer: can it be cost-effective? CMAJ 2000;162:1431-6.
25. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. Lung Cancer 2001;32:227-36.
26. *Idem.* Economic decision analysis model of screening for lung cancer. Eur J Cancer 2001;37:1759-67.
27. Riley GF, Potosky AL, Lubitz JD, Kess-

ler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. Med Care 1995;33:828-41.
28. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. Chest 2002;121:1507-14.
29. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. JAMA 1995;274:881-4. [Erratum, JAMA 1996;275:112.]
30. Rosenquist CJ, Lindfors KK. Screening mammography beginning at age 40 years: a reappraisal of cost-effectiveness. Cancer 1998;82:2235-40.