

January 2007

**LUNG
CANCER****FRONTIERS****STUDY SUPPORTS EARLY
SCREENING FOR
LUNG CANCER**

Comments may be
submitted to:

**Lung Cancer
Frontiers**

899 Logan, Suite 103
Denver, CO 80203

or by email to:

tlpdoc@aol.com

Lung Cancer Frontiers is published by The Snowdrift Pulmonary Conference and supported by a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the next series of issues will help to disseminate knowledge based on our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado.

"The purpose of **Lung Cancer Frontiers** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated."

The Editorial Board calls everyone's attention that all issues of **Lung Cancer Frontiers** beginning with their inception in 1996 are available on the internet at www.lungcancerfrontiers.org.

Lung Cancer Frontiers has long been an advocate for early screening for lung cancer particularly in high risk patients. Now, new research, published recently in the *New England Journal of Medicine* adds to a growing body of evidence that screening can find early stage lung cancer in stages where the cure rate is as high as 88%.

Survival of patients with stage 1 lung cancer detected on CT screening.

N Engl J Med 2006;355:1822-1824

International Early Lung Cancer Action Program Investigators: Henschke CI, Yankelevitz DF, Libby DM, et al

New York Presbyterian Hospital-Weill Medical College of Cornell University, New York 10021, USA. chensch@med.cornell.edu

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%

The Forum for Early Diagnosis and Treatment of Lung Cancer

Lung Cancer Frontiers Editorial Board

Thomas L. Petty M.D.
Editor-in-Chief
President of Snowdrift
Pulmonary Conference
Denver, CO

Robert L. Keith M.D.
Deputy Editor
University of Colorado
Health Sciences Center
Denver, CO

York E. Miller M.D.
Deputy Editor
Veterans Administration
Medical Center
Denver, CO

Paul Baas M.D., Ph.D.
Dept of Thoracic Surgery
The Netherlands Cancer
Institute
Amsterdam, The
Netherlands

Joel J. Bechtel M.D.
St. Mary's Hospital
and Medical Center
Grand Junction, CO

Eric S. Bensadoun M.D.
University of Kentucky
Lexington, KY

Elisabeth Brambilla M.D.
Hopital Albert Michallon
Grenoble Cedex France

Denis A. Cortese M.D.
Mayo Clinic
Rochester, MN

**Fred W. Hetzel
J.D., Ph.D.**
University of Colorado
Health Science Center
Denver, CO

**Fred R. Hirsch M.D.,
PhD**
University of Colorado
Cancer Center
Denver, CO

James R. Jett M.D.
Mayo Clinic
Rochester, MN

**Michael R. Johnston
M.D.**
University of Toronto
Toronto, Ontario,
Canada

Steinn Jonsson M.D.
Landspítali University
Hospital
Reykjavik, Iceland

**Harubumi Kato M.D.,
Ph.D.**
Tokyo Medical College
Tokyo, Japan

**Timothy C. Kennedy
M.D.**
HealthONE Alliance
Denver, CO

Stephen Lam M.D.
University of British
Columbia
Vancouver, BC,
Canada

**Richard A. Matthay
M.D.**
Yale University
New Haven, CT

**James L. Mulshine
M.D.**
Rush-Presbyterian-St.
Luke's Medical Center
Chicago, IL

Shreedhar Nair M.D.
Norwalk Hospital
Norwalk, CT

**Patrick Nana-Sinkam,
M.D.**
Ohio State University
Columbus, OH

**Louise M. Nett R.N.,
R.R.T.**
Snowdrift Pulmonary
Conference
Denver, CO

Thomas Sutedja M.D.
VC Medical Center
Amsterdam
The Netherlands

**Melvyn S. Tockman
Ph.D., M.D.**
H. Lee Moffitt
Cancer Center and
Research Institute
Tampa, FL

*Comments may be submitted to:
Lung Cancer Frontiers, 899
Logan St., Suite 103 Denver,
CO 80203
or by email at: tlpdoc@aol.com*

Lung Cancer Screening is Becoming the Standard of Care

The Early Lung Cancer Action Program (ELCAP), reported in the New England Journal of Medicine, is the latest of many peer reviewed studies which establish that early cancer can be diagnosed by CT, which results in cure in most cases. As reported in *LCF No. 26*, experts are recommending CT screening become a standard public health measure (Mulshine JL: *Oncology* 2006;12:1632). Thus with the emergence of these new data and rapid practice changes in the community, screening will rapidly become established practice, even before American Cancer Society and the National Cancer Institute abandon their reactionary stance on lung cancer screening. Soon there will be law suits brought for failure to diagnose lung cancer in smokers, particularly in those with the highest risk factors which are airflow obstruction, family history and occupational risks. It is a pity when we have to go to the courthouse to educate physicians about advances in outcomes in lung cancer treatment through screening.



(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. Copyright 2006 Massachusetts Medical Society.

Editorial Comment (TLP): This is the largest study of its kind published so far. The yield in screening was 1.3% which is about twice as high as is achieved in breast cancer screening and the results of treatment were at least equal to that achieved in breast cancer and colon cancer where screening is strongly recommended. Robert A. Smith, Director of Screening for the American Cancer Society, said his group could ultimately reconsider its neutral stance on screening for lung cancer. Why wait?

Critics of this study continue to put forth the lame argument that no randomized control group was followed. This argument is becoming particularly ludicrous now that the clear benefits from early identification and treatment are being realized all over the world. It is important to remember that all of medicinal practice is not based upon controlled clinical trials. In fact, it is not known by many that there have never been controlled clinical trials that show that PAP smears in women improve the survival of cervical cancer. Such controlled clinical trials were not in fashion in the early years when Dr. Papanicolaou introduced his technique of screening for occult uterine cancer. The acceptance of the "PAP test" resulted in dramatically reducing uterine cancer morbidity. A controlled trial was unnecessary and, in fact, not ethical. The same is the case with lung cancer today.

The Grand Junction Study in Perspective

The yield of 1.3% in the ELCAP study is quite high in screening when compared with breast and colon cancers. But an even more efficient approach would be in patients who first had spirometry to identify the fact of airflow obstruction. It is well established that if airflow obstruction is present, lung cancer is four to six times more common, than if airflow is normal with all other factors including smoking, family history and occupational risks being equal. In Grand Junction, Colorado, we showed that a lung cancer can be found at a cost of approximately \$12,000 (Bechtel JJ, Kelley WA, Coons TA, Klein MG, Slagel DD, Petty TL: Lung cancer detection in patients with airflow obstruction identified in a primary care outpatient practice. Chest 2005;127:1140-1145). All of these early stage cancers were cured at five years. Thus, as a

country we need to decide to promote widespread screening or more targeted screening, for which abundant evidence exists. It is time for the American Cancer Society and National Cancer Institute to get line to support the early identification of lung cancer.

Recommendations For Spirometry

The National Lung Health Education Program (NLHEP) consensus recommendation is to perform simple office spirometry in all current or former smokers, age 45 or older. Spirometry is also recommended for all individuals with chronic cough, mucus hypersecretion, wheeze or dyspnea on exertion. (Ferguson GT, Enright PL, Buist AS, Higgins MW: Office Spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program—Chest 2000;117:1146-61).

Simple spirometry will identify persons with COPD, asthma, and restrictive lung disease and those at highest risk of lung cancer. Spirometry should be available in all primary care physicians' offices.

IASLC: Moderate Dysplasia Plus Abnormal FISH Increases Lung Cancer Risk

By Peggy Peck, Managing Editor, MedPage Today

Reviewed by: Zalman S. Agus, MD, Emeritus Professor at the University of Pennsylvania School of Medicine



Steinn Jonsson, M.D.,
of the University of
Colorado Health
Sciences Center in
Aurora, Colorado

Chicago, Nov. 3 – Abnormal fluorescence in situ hybridization (FISH) probe results significantly increase the risk of invasive lung cancer in smokers with severe or moderate dysplasia on bronchial biopsy, researchers reported here.

Action Points

Explain to interested patients that this study suggests that biomarkers assessed in bronchial biopsies may help refine lung cancer risk in individual smokers.

This report is based on a presentation at a meeting. These data and conclusions should be considered preliminary as they have not yet been reviewed and published in a peer-reviewed publication.

An abnormal FISH analysis was associated with five times the risk of developing invasive lung cancer, said Steinn Jonsson, M.D., of the University of Colorado Health Sciences Center in Aurora, Colorado, at the International Society for the Study of Lung Cancer symposium on malignancies of the chest and head and neck.

Not surprisingly when bronchoscopy detected carcinoma in situ the risk was even greater – a 35-fold increase for invasive lung cancer (OR: 35.2, 95% CI: 5.3-223), he said.

But there was no increased risk associated with angiogenic squamous dysplasia, Dr. Jonsson said.

Dr. Jonsson and colleagues analyzed aneurysomy, angiogenesis and histology from bronchial biopsies of 106 smokers (83 men) with a mean age of 63 and a mean smoking history of 62.8 pack years. The population included 83 males and 23 females.

They used 4-color FISH probe targeting centromere 6, 5p15.2, EGFR and CMYC. Three or more copies for two or more of these DNA targets indicated presence of an aneusomic cell.

At the time of biopsy, 30 patients had lung cancer—two incident cases and 28 prevalent cases. Fourteen subjects had carcinoma in situ, 42 had severe dysplasia, and 50 had moderate dysplasia.

FISH analysis was abnormal in 12 patients with mild dysplasia and in 15 with severe dysplasia. Abnormal FISH results were also found in two patients with CIS and 18 patients with lung cancer.

Among patients who were free of lung cancer at the time of the biopsy, an abnormal FISH analysis was associated with an OR of 5.04 for invasive lung cancer (95% OR 1.8-14.5.), which suggested the need for close monitoring of these patients, he said.

Selected Peer-Reviewed Literature:

1.
Outcome in patients with lung cancer invisible on chest roentgenogram but detected only by helical computed tomography.

Respirology 2006;11:592-597

Kashiwabara K, Kohshi S

Respiratory Department, Taragi Municipal Hospital, 4210 Taragi-machi, Kuma-gun, Kumamoto 868-0501, Japan.
cbi54000@pop02.odn.ne.jp

The aim of this study was to evaluate the prognosis for patients with lung cancer detected by helical CT but not by CXR. One hundred and thirty-seven asymptomatic patients with lung cancer diagnosed by annual mass screening of the chest were enrolled over a 7-year period. Five-year survival rates in patients with lung cancer detected only by helical CT (n = 19: CT-only detection group) and in patients with lung cancer visible by both CXR and helical CT (n = 118: control group) were evaluated, and clinical variables were examined as possible predictors of survival time using the Cox proportional-hazards model. There was a significant difference between the 5-year survival rates in the CT-only detection group and in the control group (80% vs. 39%, log rank: P = 0.0171). The risk of death decreased 77% in CT-only detectable lung cancer (hazard ratio: 0.219, 95% confidence interval: 0.057-0.845, P = 0.0275). Lung cancer could not be seen by CXR because nodules were small or faint (n = 11) or overlapping a shadow of thoracic components (n = 8). The percentage of subsolid nodules

(classified as either part-solid or non-solid nodules) was higher in the subgroup with small or faint nodules (82% vs. 25%, P = 0.0423). Helical CT has the ability to detect early lung cancer before the small or faint nodules increase to a size visible on CXR, and patients with lung cancer detected only by helical CT have a better prognosis.

Editorial Comment (TLP): This is still another article that emphasizes that CT scanning is more effective in diagnosing early stage lung cancer than standard chest x-rays. Even though the new NCI controlled trials are proving this point, final results are still incomplete. But no longer is there any question about the advantages of CT screening (see below).

2.
Baseline findings of randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute

Chest 2004;126:114-121

Gohagan J, Marcus P, Fagerstrom R, et al

BACKGROUND: Low-radiation-dose spiral CT (LDCT) scanning is capable of detecting lung neoplasms in asymptomatic individuals. To determine whether such detection can reduce lung cancer mortality, a randomized controlled trial (RCT) of LDCT scanning is

...and patients with lung cancer detected only by helical CT have a better prognosis.

One hundred and thirty-seven asymptomatic patients with lung cancer diagnosed by annual mass screening of the chest were enrolled over a 7-year period.

CT-only detectable lung cancer (hazard ratio: 0.219, 95% confidence interval: 0.057-0.845, P = 0.0275).

During the fall of 2000, six PLCO screening centers recruited a total of 3,318 heavy or long-term smokers who were not participants in the PLCO trial and randomized them to receive either a screening LDCT scan . . .

Thirty lung cancers in subjects in the LDCT arm and 7 lung cancers in patients in the CXR arm were diagnosed following a positive screening result.

Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was initiated in 1992 to examine cause-specific mortality reduction from screening for these four cancers in men and women.

necessary. **METHODS:** The feasibility of conducting an RCT in asymptomatic individuals who are at high risk for lung cancer was explored in the Lung Screening Study (LSS), a 12-month special project of the ongoing Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. During the fall of 2000, six PLCO screening centers recruited a total of 3,318 heavy or long-term smokers who were not participants in the PLCO trial and randomized them to receive either a screening LDCT scan (1,660 participants) or screening posteroanterior view chest radiograph (CXR) [1,658 participants]. **RESULTS:** The screens were completed on 96% of subjects in the LDCT scan arm and 93% of subjects in the CXR arm. A total of 20.5% of screened subjects in the LDCT scan arm and 9.8% of those in the CXR arm had findings that were suspicious for lung cancer. Thirty lung cancers in subjects in the LDCT arm and 7 lung cancers in patients in the CXR arm were diagnosed following a positive screening result. Additional data from the LSS indicated that, among persons who were at elevated risk for lung cancer, CT scan use was not pervasive, interest in participating in an RCT of LDCT scanning was strong, and few subjects randomized to CXR either refused their examination or sought a CT scan after their study CXR. **INTERPRETATION:** The results of the LSS demonstrated convincingly the feasibility of an RCT of LDCT scanning in the United States.

Editorial Comment (TLP): It is the opinion of the editor that the issue

of mortality is rapidly becoming moot in view of the ELCAP study and other data cited in this and other issues of *LCF*. Early identification and intervention in lung cancer improves survival. Isn't survival the flip side of mortality?

3. Baseline chest radiograph for lung cancer detection in the randomized Prostate, Lung, Colorectal and Ovarian Cancer Screen Trial

J Nat Cancer Inst 2005;97:1805

Oken MM, Marcus PM, Hu P, et al

Hubert H. Humphrey Cancer Center, North Memorial Medical Center, Robbinsdale, MN 55422, USA.

martin.oken@northmemorial.com

BACKGROUND: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was initiated in 1992 to examine cause-specific mortality reduction from screening for these four cancers in men and women. We report lung cancer detection results of the baseline screening round. **METHODS:** Of the 154,942 participants enrolled, who were aged 55-74 years with no history of PLCO cancers, 77,465 were randomly assigned to the intervention arm. Current or former smokers and never smokers in this arm received an initial single-view posterior-anterior chest radiograph. **RESULTS:** In the initial screen, 5991 (8.9%, 95% confidence interval [CI] = 8.7% to 9.2%) of radiographs were suspicious for lung cancer: 8.2% (95% CI = 7.9%

The positive predictive value was 2.1% (95% CI = 1.7% to 2.5%), and 1.9 lung cancers were detected per 1000 screens.

In the baseline screen, nearly half the cancers were stage I. Whether this experience results in a reduction in lung cancer mortality is yet to be seen.

Lung cancer was diagnosed in 156 women and 113 men (rates of 2.1% and 1.2%, respectively).

to 8.5%) for women and 9.6% (95% CI = 9.3% to 10.0%) for men. Rates were highest for older age groups and for smokers. Among those 5991 participants with a positive screen, 206 (3.4%, 95% CI = 3.0% to 3.9%) underwent biopsy examination, 126 (61.2%, 95% CI = 54.5% to 67.8%) of whom were diagnosed with lung cancer within 12 months of the screen (59 in women and 67 in men). The positive predictive value was 2.1% (95% CI = 1.7% to 2.5%), and 1.9 lung cancers were detected per 1000 screens. Among these cancers, 44% (95% CI = 35% to 52%) were stage I non-small-cell lung cancer. High rates of lung cancer were found in current smokers (6.3 per 1000 screens) and in former smokers who had smoked within the past 15 years (4.9 per 1000 screens). The lung cancer detection rate among never smokers was 0.4 per 1000 screens; this group accounted for 11% (95% CI = 5.6% to 16.6%) of the cancers identified. CONCLUSIONS: In the baseline screen, nearly half the cancers were stage I. Whether this experience results in a reduction in lung cancer mortality is yet to be seen.

Editorial Comment (TLP): This study preceded the NCI controlled trial of CT versus chest x-rays in cancer detection. The two articles that appear in this issue of *LCF* demonstrate the clear superiority of CT screening for lung cancer.

4.

Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer.

JAMA 2006;296:180-184

International Early Lung Cancer Action Program Investigators:

Henschke CI, Yip R, Miettinen OS

Department of Radiology, Joan and Sanford I. Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, NY 10021, USA.

chensch@med.cornell.edu

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

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

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.

Editorial Comment (TLP): The results of this study are not surprising since a growing body of evidence indicates that women are more susceptible to the harmful effects of tobacco smoke than men. Thus if they are amongst the approximate 20% of patients who are going to get airflow obstruction from smoking often with associated lung cancer, they will do so at an earlier age and with a lower degree of smoking intensity.

5.
Wedge Resection for Non-small Cell Lung Cancer in Patients with Pulmonary Insufficiency: Prospective Ten-Year Survival

J Thorac Oncol 2006;1:960-964

Griffin JP, Eastridge CE, Tolley EA, et al

Background: Possibility of curative resection by lobectomy for non-small cell lung cancer is often denied patients with compromised pulmonary reserve. Analysis of survival of such patients treated by wedge resection was compared with that of patients treated by standard resection, with both groups followed for 10 years. Design: a prospective 5-year cohort study.

Methods: From 1988 to 1992, an observational cohort of 127 consecutive resected patients at Memphis VA Medical Center was divided into those receiving lobectomy in 81 cases and pneumonectomy in 15

cases (group I) versus 31 patients with compromised pulmonary reserve (group II), who had complete tumor excision by wedge resection. Preoperative clinical staging was corrected to surgical-pathological staging after demonstration of its superiority. Survival estimates were obtained by Kaplan-Meier method with curves compared by log rank tests, with all-cause mortality calculated from date of surgery. Results: Extent of disease in group I was 58% stage I, 19% stage II, and 23% stage III. In group II, extent of disease was 84% stage I, 3% stage II, and 14% stage III. Group I median survival was 26 months with 30% 5-year survival; for group II, median survival was 30 months and 32%. Kaplan-Meier survival plots showed similar curves in groups I and II. Realizing less extent of disease in group II, another Kaplan-Meier plot restricted to stage I and II patients showed overlapping survival curves for groups I and II. Conclusion: Survival during 10-year observation was similar for patients with pulmonary insufficiency treated by wedge resection to that of patients receiving standard resection in this single-institution consecutive cohort.

Editorial Comment (TLP): The use of limited or “wedge resection” has been used by experienced surgeons for many years in an attempt to spare lung tissue. But the emergence of lung volume reduction surgery, also aimed at removing nodules within the lobe, might also be effective in maintaining or actually improving lung function.

Possibility of curative resection by lobectomy for non-small cell lung cancer is often denied patients with compromised pulmonary reserve.

Survival during 10-year observation was similar for patients with pulmonary insufficiency treated by wedge resection to that of patients receiving standard resection . . .