

April 2006

**LUNG  
CANCER****FRONTIERS**

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## CT: A PUBLIC HEALTH MEASURE IN LUNG CANCER CONTROL

**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](http://www.lungcancerfrontiers.org).

James Mulshine, M.D., noted oncologist at the National Cancer Institute for 25 years and now Provost for Research at Rush University, presented an exciting new concept at the second annual Swedish Hospital Lung Cancer Program in Denver, Colorado on March 4, 2006. Mulshine likened the role of CT screening for asymptomatic lung cancer to x-ray screening for tuberculosis in the previous era. Certainly, imaging was a major factor in the identification of unsuspected tuberculosis and, coupled with effective drugs for treatment, has greatly reduced the impact of tuberculosis in this country and in other advanced nations around the world.

New high speed spinal CT technologies with .6 mm slices and a reduction in imaging time to only a few minutes offers new possibilities in lung cancer screening. This technology, coupled with strategies for scheduling tests during low-use hours such as evenings and weekends, can make CT screening extremely efficient, reducing the cost to only a few dollars, i.e., range \$25-\$50, for thru-put clinics. Such an approach is being planned for the entire state of Nebraska, involving 28 major cooperating hospitals of this state of 1.3 million individuals.

Mulshine emphasized that now is the time for society to reap the benefits from the pioneering work of Claudia Henschke and associates. Her work is rapidly becoming convincing that lung cancer can be identified in early stages, treated, and cured, with a minimization of basic surgical procedures for benign techniques.



**Dr. James Mulshine,  
Provost for  
Research, Rush  
University,  
Chicago**

## SIZE MATTERS IN ELCAP SCREENING

*Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size* (Arch Intern Med 2006;166:321-325)  
(No authors listed)

**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

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**Exciting Times  
Ahead!**

**Dr. James Mulshine, a leader in lung cancer biology, diagnosis, and treatment hails CT as a new public health measure for the identification and treatment, i.e., control of lung cancer. The widespread use of low dose radiation helical CT scanning by thru-put scheduling strategies can make CT widely available to all patients at risk. Dr. Claudia Henschke's work shows that small tumors, i.e., 4 mm or less, are rarely metastatic and can most often be cured. Articles in this issue suggest that molecular markers in sputum will soon become practical. Thus, we may be entering a new era in the comprehensive diagnosis of early stage lung cancer, the first step in treatment.**



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.

**Lymph node status has a strong relationship to tumor diameter for non-small cell and small cell cancers.**

**If screening is being considered, doctors and patients should discuss the pros and cons of screening before going ahead with x-ray, CT scan, or sputum cytologic examination to screen for lung cancer.**

**... congress declaring lung cancer a major national public health priority and calling for a 50% reduction in mortality.**

**Editorial Comment (TLP): This is the latest report from ELCAP, initiated by Claudia Henschke in her landmark article in the Lancet in 1999. These results are important because they provide direct evidence of the importance of size and the likelihood of lung cancer metastasis. Small tumors identified by CT (< 4mm) are rarely metastatic and a high cure rate can be expected from resection of these early cancers.**

**IS THIS PROGRESS?**

*United States Prevention Service Task Force stated, 2006,* “The USPSTF recommends neither for nor against using chest x-ray, computed tomography (CT scan), or sputum cytologic examination to look for lung cancer in people who have no symptoms to suggest the disease. If screening is being considered, doctors and patients should discuss the pros and cons of screening before going ahead with x-ray, CT scan, or sputum cytologic examination to screen for lung cancer. Patients should be aware that there are no studies showing that screening helps people live longer. They should also know that false-positive test results are common and can lead to unnecessary worry, testing, and surgery.

**Editorial Comment: This new policy is a departure from the previous positions**

**that lung cancer screening is not appropriate, even for persons at high risk. The excuse is that the Task Force is awaiting the results of a large, nationwide comparison on the results of screening by standard chest x-ray (improved with CT screening). This study began in 2002 and enrolled about 50,000 patients. But in the annual follow-up, patients where x-rays are suspicious of change receive CT for further definition of new shadows. Thus this trial is in reality a comparison of delayed CT screening with initial CT screening. Since the study will not be concluded for several years, widespread screening in patients at high risk may still be delayed. They are being denied a chance of cure! Contrast this recommendation with the ELCAP studies cited above and the citations that follow.**

***FLASH – NEWS  
RELEASE:***

***THIS IS PROGRESS!***

**LUNG CANCER  
ALLIANCE  
LEGISLATIVE  
MILESTONE**

**(Washington, DC – March 29, 2006) –** A milestone was reached last night as the first ever bicameral bipartisan legislation was introduced in Congress declaring lung cancer a major national public health priority and calling for a 50% reduction in mortality within nine years.

Unveiled during the Lung Cancer Alliance Advocacy Conference, Senator Chuck Hagen (R-NE) and Senator Hillary Clinton (D-NY) introduced S.Res. 408 for Senate consideration. Congressman Clay Shaw (R-FL) introduced H.Res. 739, a similar resolution, in the House of Representatives. Laurie Fenton, President of the Lung Cancer Alliance, praised the legislation as historic.

**The bipartisan resolution requests the President to declare lung cancer a national public health priority and calls for a 50% reduction in lung cancer's high mortality rate by 2015.**

**Senator Clinton noted that lung cancer is now killing nearly twice as many women as breast cancer, with a disturbing increase of lung cancer in non-smoking women.**

**Our hypothesis is that the use of a two-step strategy, using a sputum biomarker, may increase the detection rate of lung cancer . . .**

“This is tremendous,” she said. “It is the first time we have the House and Senate recognizing that lung cancer is not a political issue, rather, it’s a major public health epidemic affecting smokers and non-smokers. This must be addressed as a disease – not a punishment.”

The bipartisan resolution requests the President to declare lung cancer a national public health priority and calls for a 50% reduction in lung cancer’s high mortality rate by 2015. It lays out a multi-agency action blueprint emphasizing the need for a carefully coordinated approach among the federal agencies, including the Department of Health and Human Services as well as the Department of Defense.

Currently, lung cancer is under-funded and under-researched. Only \$1,829 is spent per lung cancer death, the least amount of cancer research dollars per death for the nation’s leading cancer killer. By comparison, breast cancer research receives \$23,474 per estimated death, and prostate cancer receives \$14,369.

“Lung cancer is the most lethal form of cancer in the United States,” said Senator Hagel, whose state will be the first in the nation to initiate a state-wide screening program for lung cancer. “Over 900 Nebraskans will die from lung cancer in 2006. We have made great advances in breast and prostate cancer survival rates. We must commit ourselves to making the same progress in lung cancer.”

Senator Clinton noted that lung cancer is now killing nearly twice as many women as breast cancer, with a disturbing increase of lung cancer in non-smoking women.

“Despite the gains we have made in cancer treatment and research, we have made far too little progress in addressing lung cancer, the leading cause of cancer deaths in our nation. As part of our overall battle against cancer, we must improve our research, treatment and detection efforts in order to increase the five-year survival rate beyond 15%,” Senator Clinton said.

Congressman Shaw, himself a lung cancer survivor, has been the leading spokesman for lung cancer in the House of Representatives. Recently he sent a letter signed by 73 members of both parties of the house asking the National Cancer Institute about their oft-quoted 2015 target for “ending the pain and death from all cancer.”

“That cannot be done,” said Shaw, “if we continue to under-fund research and early diagnosis in the biggest cancer killer.”

Fenton concluded, “Our tipping point has begun and we look forward to continuing our work with these and other legislators to expand support for this legislation.”

The Lung Cancer Alliance ([www.lungcanceralliance.org](http://www.lungcanceralliance.org)) is the only national non-profit organization solely dedicated to patient support and advocacy for people living with lung cancer and those at risk for the disease. In January 2006, LCA issued the first-ever Report Card on Lung Cancer, an assessment of progress being made in the battle against this lethal disease. The majority of grades received were failing.

#### **Citations from the Peer-Reviewed Literature**

The following pages of *Lung Cancer Frontiers* carry the very latest in the transitional research that ultimately will lead to the control of lung cancer as this decade ends.

#### **No. 1**

#### ***Lung Cancer Screening Using Multi-Slice Thin-Section Computed Tomograph and Autofluorescence Bronchoscopy***

J Thorac Oncol 2006;1:61-68

Annette M. McWilliams, M.D., John R. May, M.D., Myeong Im Ahn, M.D., Sharyn L. S. MacDonald, M.D., and Stephen C. Lam, M.D.

Background: Thoracic computed tomography (CT) for lung cancer screening is sensitive for the detection of early peripheral lung cancer but is not sensitive for detecting central preinvasive and microinvasive cancer. Our hypothesis is that the use of a two-step strategy, using a sputum biomarker, may increase the detection rate of lung cancer by identifying

individuals at highest risk.  
Methods: We completed a pilot study of 561 volunteer current or former smokers 50 years of age or older, with a smoking history of more than or equal to 30 pack years. All subjects received induced sputum examination and low-dose thoracic CT scan and were offered autofluorescence bronchoscopy.

Results: CT detected 2408 pulmonary nodules, 80% of which were less than or equal to 4 mm in diameter. During 2-year follow-up, 95% of these nodules were stable or resolved, with only 4% showing growth at any time. A total of 28 cancers were detected in 22 subjects: 21 by CT scan and seven by autofluorescence bronchoscopy. Overall, 0.9% nodules were malignant, but growth on more than or equal to two CT scans increased the malignancy rate to 75%. The mean diameter of malignant nodules on detection was 12.8 mm (range, 3 to 36.4 mm). However, 18% of malignant nodules were less than or equal to 4 mm in diameter when first seen.

Conclusions: Multi-detector row CT scanners found multiple small 2-year follow-up. Persistent interval growth increases the probability of malignancy from less than 1% to 75%. One quarter of detected cancers were CT occult and only seen with autofluorescence bronchoscopy. Prescreening using a sputum biomarker improved the detection rate of lung cancer from 3 to 5%.

**Editorial Comment (TLP): This article and the one that follows makes the important point that CT screening can miss early central lesions. Thus dual screening, when possible, is preferred.**

No. 2  
*Screening for lung cancer using low dose CT scanning: results of 2 year follow up*

Thorax 2006;61:54-56

MacRedmond R, McVey G, Lee M, Costello RW, Kenny D, Foley C, Logan PM

Department of Medicine, Royal College of Surgeons in Dublin, Ireland

BACKGROUND: Screening with low dose chest computed tomographic scanning (LDCCT) may improve survival by identifying early asymptomatic lung cancer. METHODS: Four hundred and forty nine

high risk subjects were screened with serial LDCCT scanning over 2 years. Fine needle aspiration biopsy was recommended for non-calcified nodules (NCNs) of >10 mm diameter or demonstrating interval growth. RESULTS: NCNs were identified in 111 subjects (24.7%), three of which were lung cancer. The overall prevalence (0.4%) and incidence (1.3%) rates of lung cancer detection were low. Three of the six lung cancers detected in the study were stage 1 non-small cell lung cancer; the remainder were unresectable central tumours. By contrast, eight subjects developed extrathoracic malignancy during the study period and other incidental pathology was noted in 221 subjects (49.2%). Smoking cessation rates at 19% were higher than in the general population, but 60.8% of subjects continued to smoke. CONCLUSION: LDCCT scanning is useful in detecting early peripheral non-small cell lung cancers but its usefulness as a screening tool is limited by low specificity and by poor sensitivity for central tumours.

**Editorial Comment (TLP): This study also makes the point that cancer CT screening is not adequately sensitive for central lesions and again underscores the importance of dual screening. (see Citation No. 1)**

### Diagnostic Reports

No. 3

*Emphysema detected by lung cancer screening with low-dose spiral CT: Prevalence and correlation with smoking habits and pulmonary function in Japanese male subjects.*

Respirology 2006;11:205-210

Omori H, Nakashima R, Otsuka N, Mishima Y, Tomiguchi S, Marimatsu A, Nonami Y, Mihara S, Koyama W, Marubayashi T, Morimoto Y

Japanese Red Cross Kumamoto Health Care Center, Nagamineminami, Japan

Objective: Screening with low-dose spiral CT is a promising new tool for early lung cancer detection. A study was undertaken to assess the prevalence of

**CT detected 2408 pulmonary nodules, 85% of which were less than or equal to 4 mm in diameter.**

**A total of 28 cancers were detected in 22 subjects.**

**One quarter of detected cancers were CT occult and only seen with autofluorescence bronchoscopy.**

**Emphysema was detected in 30.5% of current smokers, 14.1% of former smokers and 3.0% of non-smokers.**

**The acquired OCT images closely match histologically defined patterns in terms of structural profiles.**

emphysema detected by CT screening, and to assess the correlation between the extent of emphysema and the severity defined according to the recently published Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Methods: After informed consent, CT screening and pulmonary function tests were performed on 615 men between the ages of 40 and 69. Severity of emphysema was assessed visually. Only the pulmonary function data for male subjects were analysed because there were too few female subjects with emphysema. Results: Emphysema was detected in 30.5% of current smokers, 14.1% of former smokers and 3.0% of non-smokers. In male current smokers, airflow obstruction ( $FEV(1)/FVC < 0.7$ ) was seen in 18.1% of subjects with mild emphysema, and in 33.3% of subjects with moderate emphysema. FEV(1) values were less than 80% of the predicted normal in 8.5% of subjects with mild emphysema, and 28.6% of subjects with moderate emphysema. The percentage of male subjects with emphysema equivalent to GOLD stage 0 was 90.0% for subjects in their 40s, 82.5% for those in their 50s, and 68.2% for those in their 60s. Conclusion: A considerable percentage of the subjects with emphysema as detected by CT screening had GOLD stage 0. CT screening assists in detecting early-stage emphysema.

**Editorial Comment (TLP): The results of this study are not surprising since COPD and lung cancer are so closely related. In fact, 80% of lung cancers are in the upper half of lung fields, which is exactly the location of central lobular emphysema. A short time ago the editor presented some musings on the association between COPD and lung cancer (Are COPD and lung cancer two manifestations of the same disease? Chest 2005;128:1895-1897).**

No. 4

*Optical coherence tomography: real-time imaging of bronchial airways microstructure and detection of inflammatory/neoplastic morphologic changes.*

Clin Cancer Res 2006;12:813-818

[Whiteman SC](#), [Yang Y](#), [Gey van Pittius D](#), [Stephens M](#), [Parmer J](#), [Spiteri MA](#).

Institute of Science and Technology in Medicine, School of Postgraduate Medicine, Keele University, Stoke-on-Trent, United

Kingdom. [suzannewhiteman@yahoo.co.uk](mailto:suzannewhiteman@yahoo.co.uk)

**PURPOSE:** Current diagnostic imaging modalities for human bronchial airways do not possess sufficient resolution and tissue penetration depth to detect early morphologic changes and to differentiate in real-time neoplastic pathology from nonspecific aberrations. Optical coherence tomography (OCT) possesses the requisite high spatial resolution for reproducible delineation of endobronchial wall profiling. **EXPERIMENTAL DESIGN:** To establish whether OCT could differentiate between the composite microstructural layers of the human airways and simultaneously determine in situ morphologic changes, using a bench-top OCT system, we obtained cross-sectional images of bronchi from 15 patients undergoing lung resections for cancer. All scanned sections underwent subsequent detailed histologic analysis, allowing direct comparisons to be made. **RESULTS:** OCT imaging enables characterization of the multilayered microstructural anatomy of the airways, with a maximum penetration depth up to 2 to 3 mm and 10-microm spatial resolution. The epithelium, subepithelial components, and cartilage are individually defined. The acquired OCT images closely match histologically defined patterns in terms of structural profiles. Furthermore, OCT identifies in situ morphologic changes associated with inflammatory infiltrates, squamous metaplasia, and tumor presence. **CONCLUSIONS:** Our results confirm that OCT is a highly feasible optical tool for real-time near-histologic imaging of endobronchial pathology, with potential for lung cancer surveillance applications in diagnosis and treatment.

**Editorial Comment (TLP): The possibilities of an optical biopsy are intriguing. This technique has promise but is not quite ready for prime time.**

**The following articles deal with multiple gene markers in sputum.**

No. 5

*Promoter hypermethylation of multiple genes in sputum precedes lung cancer incidence in a high-risk cohort.*

[Belinsky SA](#), [Liechty KC](#), [Gentry FD](#), [Wolf HJ](#), [Rogers J](#), [Vu K](#), [Haney J](#), [Kennedy TC](#), [Hirsch FR](#), [Miller Y](#), [Franklin WA](#), [Herman JG](#), [Baylin SB](#), [Bunn PA](#), [Byers T](#).

[Cirincione R](#), [Lintas C](#), [Conte D](#), [Mariani L](#), [Roz L](#), [Vignola AM](#), [Pastorino U](#), [Sozzi G](#).  
Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, Italy.

Lovelace Respiratory Research Institute,  
Albuquerque, New Mexico.

We evaluated the aberrant promoter methylation profile of a panel of 3 genes in DNA from tumor and sputum samples, in view of a complementary approach to spiral computed tomography (CT) for early diagnosis of lung cancer. The aberrant promoter methylation of RARbeta2, p16(INK4A) and RASSF1A genes was evaluated by methylation-specific PCR in tumor samples of 29 CT-detected lung cancer patients, of which 18 had tumor-sputum pairs available for the analysis, and in the sputum samples from 112 cancer-free heavy smokers enrolled in a spiral CT trial. In tumor samples from 29 spiral CT-detected patients, promoter hypermethylation was identified in 19/29 (65.5%) cases for RARbeta2, 12/29 (41.4%) for p16(INK4A) and 15/29 (51.7%) for RASSF1A. Twenty-three of twenty-nine (79.3%) samples of the tumors exhibited methylation in at least 1 gene. In the sputum samples of 18 patients, methylation was detected in 8/18 (44.4%) for RARbeta2 and 1/18 (5%) for both RASSF1A and p16(INK4A). At least 1 gene was methylated in 9/18 (50%) sputum samples. Promoter hypermethylation in sputum from 112 cancer-free smokers was observed in 58/112 (51.7%) for RARbeta2 and 20/112 (17.8%) for p16, whereas methylation of the RASSF1A gene was found in only 1/112 (0.9%) sputum sample. Our study indicates that a high frequency of hypermethylation for RARbeta2, p16(INK4A) and RASSF1A promoters is present in spiral CT-detected tumors, whereas promoter hypermethylation of this panel of genes in uninduced sputum has a limited diagnostic value in early lung cancer detection. (c) 2005 Wiley-Liss, Inc.

No. 7

*Molecular profiling of computed tomography screen-detected lung nodules shows multiple malignant features.*

Cancer Epidemiol Biomarkers Prev 2006;15:373-380

[Pajares MJ](#), [Zudaire J](#), [Lozano MD](#), [Agorreta J](#), [Bastarrika G](#), [Torre W](#), [Remirez A](#), [Pio R](#), [Zulueta JJ](#), [Montuenga LM](#).

Oncology Division, Center for Applied Medical Research, Clinica Universitaria de Navarra, Pamplona, Spain.

**A sensitive screening approach for lung cancer could markedly reduce the high mortality rate for this disease.**

**Twenty-three of twenty-nine (79.3%) samples of the tumors exhibited methylation in at least 1 gene. In the sputum samples of 18 patients . . .**

**This is the first study to prospectively examine a large panel of genes for their ability to predict lung cancer . . .**

A sensitive screening approach for lung cancer could markedly reduce the high mortality rate for this disease. Previous studies have shown that methylation of gene promoters is present in exfoliated cells within sputum prior to lung cancer diagnosis. The purpose of the current study is to conduct a nested case-control study of incident lung cancer cases from an extremely high-risk cohort for evaluating promoter methylation of 14 genes in sputum. Controls (n = 92) were cohort members matched to cases (n = 98) by gender, age, and month of enrollment. The comparison of proximal sputum collected within 18 months to >18 months prior to diagnosis showed that the prevalence for methylation of gene promoters increased as the time to lung cancer diagnosis decreased. Six of 14 genes were associated with a >50% increased lung cancer risk. The concomitant methylation of three or more of these six genes was associated with a 6.5-fold increased risk and a sensitivity and specificity of 64%. This is the first study to prospectively examine a large panel of genes for their ability to predict lung cancer and shows the promise of gene promoter hypermethylation in sputum as a molecular marker for identifying people at high risk for cancer incidence. (Cancer Res 2006; 66(6): 3338-44).

**Editorial Comment (TLP): This article by Belinsky included a large number of cases obtained from sputa collected using mail-in containers and Saccomanno fixative by collaborating pulmonologists in Colorado and the surrounding seven-state region. This study establishes the possibility of involvement of pulmonologists in sputum studies everywhere!**

No. 6

*Methylation profile in tumor and sputum samples of lung cancer patients detected by spiral computed tomography: a nested case-control study.*

The objective of the current study was to analyze the phenotypic and genetic alterations in the small pulmonary malignancies.

. . . Screen-detected cancers are not overdiagnosed.

**RATIONALE AND PURPOSE:** Low-dose spiral computerized axial tomography (spiral CT) is effective for the detection of small early lung cancers. Although published data seem promising, there has been a significant degree of discussion concerning the potential of overdiagnosis in the context of spiral CT-based screening. The objective of the current study was to analyze the phenotypic and genetic alterations in the small pulmonary malignancies resected after detection in the University of Navarra/ International Early Lung Cancer Action Project spiral CT screening trial and to determine whether their malignant molecular features are similar to those of resected lung tumors diagnosed conventionally. **EXPERIMENTAL DESIGN:** We analyzed 17 biomarkers of lung epithelial malignancy in a series of 11 tumors resected at our institution during the last 4 years (1,004 high-risk individuals screened), using immunohistochemistry and fluorescence in situ hybridization (FISH). A parallel series of 11 gender-, stage-, and histology-matched lung cancers diagnosed by other means except screening was used as control. **RESULTS:** The molecular alterations and the frequency of phenotypic or genetic aberrations were very similar when screen-detected and nonscreen-detected lung cancers were compared. Furthermore, most of the alterations found in the screen-detected cancers from this study were concordant with what has been described previously for stage I-II lung cancer. **CONCLUSIONS:** Small early-stage lung cancers resected after detection in a spiral CT-based screening trial reveal malignant molecular features similar to those found in conventionally diagnosed lung cancers, suggesting that the screen-detected cancers are not overdiagnosed.

**Editorial Comment (TLP):** The above two articles are supportive of the concept that multiple gene will ultimately provide reliable screening markers.

#### New Treatment Studies

No. 8

*Does lobectomy for lung cancer in patients with chronic obstructive pulmonary disease affect lung function? A multicenter national study.*

J Thorac Cardiovasc Surg 2005;130:1616-1622

[Baldi S](#), [Ruffini E](#), [Harari S](#), [Roviaro GC](#),

[Nosotti M](#), [Bellaviti N](#), [Venuta F](#), [Diso D](#), [Rea F](#), [Schiraldi C](#), [Durigato A](#), [Pavanello M](#), [Carretta A](#), [Zannini P](#).

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**OBJECTIVE:** The purpose of this study was to evaluate the effect of lobectomy on pulmonary function in patients with chronic obstructive pulmonary disease. **METHODS:** One hundred thirty-seven patients were analyzed; 49 had normal pulmonary function tests, and 88 had chronic obstructive pulmonary disease. Different functional parameter groups were identified: obstructive (forced expiratory volume in 1 second [FEV1], forced expiratory volume in 1 second/forced vital capacity [FEV1/FVC], and chronic obstructive pulmonary disease index), hyperinflation (residual volume and functional residual capacity), and diffusion (transfer factor of the lung for carbon monoxide). Also, the ratio between observed and predicted postoperative FEV(1) was calculated. **RESULTS:** In patients with preoperative FEV1 greater than 80% of predicted, postoperative FEV1/FVC slightly but not significantly decreased, and postoperative FEV1 significantly decreased. In patients with preoperative FEV1 less than 65%, postoperative FEV1 and FEV1/FVC significantly increased. In patients with preoperative FEV1/FVC greater than 70%, postoperative FEV1 and FEV1/FVC significantly decreased. In patients with preoperative FEV1/FVC less than 70%, postoperative FEV1/FVC increased, and FEV1 remained unchanged. In patients with a chronic obstructive pulmonary disease index greater than 1.5, postoperative FEV1 and FEV1/FVC significantly decreased, whereas in patients with a chronic obstructive pulmonary disease index less than 1.5, postoperative FEV1/FVC significantly increased and FEV1 remained unchanged. In patients with residual volume and functional residual capacity greater than 115% and transfer factor of the lung for carbon monoxide less than 80% of predicted, postoperative FEV1 diminished less (not significant) compared with patients who had residual

**Patients with mild to severe chronic obstructive pulmonary disease could have a better late preservation of pulmonary function after lobectomy than healthy patients.**

volume and functional residual capacity less than 115% (P = .0001). Observed postoperative/predicted postoperative FEV1 was higher if FEV1/FVC was less than 55% (1.46), if FEV1 was less than 80% of predicted (1.21), or if the chronic obstructive pulmonary disease index was less than 1.5 (1.17). **CONCLUSIONS:** Patients with mild to severe chronic obstructive pulmonary disease could have a better late preservation of pulmonary function after lobectomy than healthy patients.

**Editorial Comment (TLP): This is a somewhat surprising outcome based on conventional thinking. However, the likelihood of improving or at least maintaining lung function by lobectomy through improving elastic recoil as a result of lung volume reduction surgery is the reason why lung function may be maintained in spite of a major resection in patients with significant COPD.**

No. 9

*Percutaneous computed tomography-guided radiofrequency thermal ablation of small unresectable lung tumours.*

Eur Respir J 2006;27:556-563

Percutaneous computed tomography-guided radiofrequency thermal ablation of small unresectable lung tumours.

[Rossi S](#), [Dore R](#), [Cascina A](#), [Vespro V](#), [Garbagnati F](#), [Rosa L](#), [Ravetta V](#), [Azzaretti A](#), [Di Tolla P](#), [Orlandoni G](#), [Pozzi E](#).

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The aim of the current study was to evaluate the safety and the efficacy of radiofrequency thermal ablation (RFTA) for the treatment of nonsmall cell lung cancer (NSCLC) and isolated pulmonary metastases (METs) from colorectal cancer (CRC). A total of 31 patients (15 with NSCLCs and 16 with CRC lung METs), with 36 lung tumour nodules (mean+/-sd diameter: 22+/-8 mm, range: 10-35 mm) underwent computed tomography (CT)-guided RFTA using expandable electrodes. Contrast-enhanced CT was performed

before and after (immediately and 30+/-5 days) each RFTA session to assess immediate results and complications and repeated 3 and 6 months post-RFTA, as well as every 6 months thereafter, to evaluate long-term results. Complete radiological necrosis was defined as a nonenhancing area at the tumour site that was equal to or larger than the treated tumour; persistence of enhancement at the tumour site indicated incomplete treatment. Local recurrence was defined as an increase in tumour size and/or enhancing tissue at the tumour site. Complete radiological necrosis of the 36 tumours was achieved with 39 RFTA sessions and 42 electrode insertions. No major complications or deaths were observed. Six patients experienced mild-to-moderate pain during the procedure. There were five cases of pneumothorax, none requiring drainage and four cases of pneumonia, which were successfully treated with antibiotics. After a mean follow-up of 11.4+/-7.7 months (range of 3-36 months), the overall local recurrence rate was 13.9% (20 and 9.5% for NSCLC and CRC-METs patients, respectively). Nineteen of the 31 (61.3%) patients were alive (15 apparently disease free) and 12 (38.7%) had died (three from causes unrelated to their cancer). Radiofrequency thermal ablation seems to be a safe, effective method for producing complete ablation of small nonsmall cell lung cancers and pulmonary colorectal cancer metastases.

**Editorial Comment (TLP): The possibility of localized ablation of lung cancer via a variety of different energies is intriguing.**

**Smoking Cessation Remains Top Priority**

No. 10

*Effect of smoking reduction on lung cancer risk*

JAMA 2005;294:1505-1510

[Godtfredsen NS](#), [Prescott E](#), [Osler M](#).

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**CONTEXT:** Many smokers are unable or unwilling to completely quit smoking. A proposed means of harm reduction is to reduce the number of cigarettes smoked per day. However, it is not clear whether this strategy

**Radiofrequency thermal ablation seems to be a safe, effective method for producing complete ablation of small nonsmall cell lung cancers and pulmonary colorectal cancer metastases.**

**Brief clinician intervention and telephone counseling are both effective aids for smoking cessation.**

**Among individuals who smoke 15 or more cigarettes per day, smoking reduction by 50% significantly reduces the risk of lung cancer.**

**Telephone care increases the use of behavioral and pharmacologic assistance and leads to higher smoking cessation . . .**

decreases the risk for tobacco-related diseases. OBJECTIVE: To assess the effects of smoking reduction on lung cancer incidence. DESIGN, SETTING, AND PARTICIPANTS: Observational population-based cohort study with up to 31 years of follow-up from the Copenhagen Centre for Prospective Population Studies, which administrates data from 3 longitudinal studies conducted in Copenhagen and suburbs, the Copenhagen City Heart Study, the Copenhagen Male Study, and the Glostrup Population Studies, Denmark. Participants were 11,151 men and 8563 women (N = 19,714) aged 20 to 93 years, who attended 2 consecutive examinations with a 5- to 10-year interval between 1964 and 1988. Participants underwent a physical examination and completed self-filled questionnaires about lifestyle habits. The study population was divided into 6 groups according to smoking habits: continued heavy smokers (> or =15 cigarettes/d), reducers (reduced from > or =15 cigarettes/d by minimum of 50% without quitting), continued light smokers (1-14 cigarettes/d), quitters (stopped between first and second examination), stable ex-smokers, and never smokers. MAIN OUTCOME MEASURE: Incident primary lung cancer cases assessed by record linkage with the National Cancer Registry until December 31, 2003. RESULTS: There were 864 incident lung cancers during follow-up. Using Cox regression, the adjusted hazard ratio (HR) for lung cancer in reducers was 0.73 (95% confidence interval [CI], 0.54-0.98) compared with persistent heavy smokers. The HR for light smokers was 0.44 (95% CI, 0.35-0.56); for quitters, HR 0.50 (95% CI, 0.36-0.69), for stable ex-smokers, HR 0.17 (95% CI, 0.13-0.23), and for never smokers, HR 0.09 (95% CI, 0.06-0.13). CONCLUSION: Among individuals who smoke 15 or more cigarettes per day, smoking reduction by 50% significantly reduces the risk of lung cancer.

**Editorial Comment (TLP): Although complete smoking cessation is the goal, we should not overlook the possibilities of a benefit from less than a complete abstinence.**

No. 11

*Benefits of telephone care over primary care for smoking cessation: a randomized trial.*

Arch Intern Med 2006;166:536-542

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BACKGROUND: Brief clinician intervention and telephone counseling are both effective aids for smoking cessation. However, the potential benefit of telephone care above and beyond routine clinician intervention has not been examined previously. The objective of this study is to determine if telephone care increases smoking cessation compared with brief clinician intervention as part of routine health care. METHODS: This 2-group, prospective, randomized controlled trial enrolled 837 daily smokers from 5 Veterans Affairs medical centers in the upper Midwest. The telephone care group (n = 417) received behavioral counseling with mailing of smoking cessation medications as clinically indicated. The standard care group (n = 420) received intervention as part of routine health care. The primary outcome was self-reported 6-month duration of abstinence 12 months after enrollment. Secondary outcomes were 7-day point prevalence abstinence at 3 and 12 months, participation in counseling programs, and use of smoking cessation medications. RESULTS: Using intention-to-treat procedures, we found that the rate of 6-month abstinence at the 12-month follow-up was 13.0% in the telephone care group and 4.1% in the standard care group (odds ratio [OR], 3.50; 95% confidence interval [CI], 1.99-6.15). The rate of 7-day point prevalence abstinence at 3 months was 39.6% in the telephone care group and 10.1% in the standard care group (OR, 5.84; 95% CI, 4.02-8.50). Telephone care compared with standard care increased the rates of participation in counseling programs (97.1% vs 24.0%; OR, 96.22; 95% CI, 52.57-176.11) and use of smoking cessation medications (89.6% vs 52.3%; OR, 7.85; 95% CI, 5.34-11.53). CONCLUSION: Telephone care increases the use of behavioral and pharmacologic assistance and leads to higher smoking cessation rates compared with routine health care provider intervention.

**Editorial Comment (TLP): We**

**continue to look for practical ways of improving smoking cessation. Perhaps telephone methods or even computer-assisted methods might be the answer.**

No. 12

*Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer.*

Am J Respir Crit Care Med

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**RATIONALE:** Chronic inflammation has been implicated in the development of airway dysplasia and lung cancer. It is unclear whether circulating biomarkers of inflammation could be used to predict progression of airway dysplasia.

**OBJECTIVE:** We determined whether circulating levels of C-reactive protein (CRP) or other inflammatory biomarkers could predict progression of bronchial dysplasia in smokers over 6 mo.

**METHODS:** The plasma levels of CRP, interleukins 6 and 8, and monocyte chemoattractant protein 1 were measured at baseline in 65 ex- and current smokers who had at least one site of bronchial dysplasia > 1.2 mm in size. Additional bronchial biopsies were taken after 6 mo from the same sites where dysplastic lesions were discovered at baseline. Progressive dysplastic lesions were defined as worsening of the dysplastic lesion by at least two grades or development of new dysplastic lesions. **RESULTS:** Half of the participants developed progressive dysplastic lesions after 6 mo. The baseline CRP levels in these participants were 64% higher than those without progressive disease ( $p = 0.027$ ). Only one of eight (13%) participants with  $CRP \leq 0.5$  mg/L developed progressive disease, whereas 31 of 57 (54%) participants with  $CRP > 0.5$  mg/L developed progressive disease ( $p = 0.011$ ). The odds of developing progressive disease were 9.6-fold higher in the latter than in the former group. **CONCLUSION:** Plasma CRP, in concert with lung function and pack-years of smoking, appears to have excellent predictive powers in identifying participants with bronchial dysplastic

lesions whose lesions progress to more advanced stages of dysplasia.

**Editorial Comment (TLP): CRP is a marker of inflammation in relation to pack years of smoking, not surprisingly, is related to progressive stages of dysplasia. Perhaps molecular markers of lung cancer can be identified in such patients in the future.**

**Lung Cancer in Ethnic Groups:**

No. 13

*Ethnic and racial differences in the smoking-related risk of lung cancer.*

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**BACKGROUND:** There is remarkable variation in the incidence of lung cancer among ethnic and racial groups in the United States. **METHODS:** We investigated differences in the risk of lung cancer associated with cigarette smoking among 183,813 African-American, Japanese-American, Latino, Native Hawaiian, and white men and women in the Multiethnic Cohort Study. Our analysis included 1979 cases of incident lung cancer identified prospectively over an eight-year period, between baseline (1993 through 1996) and 2001. **RESULTS:** The risk of lung cancer among ethnic and racial groups was modified by the number of cigarettes smoked per day. Among participants who smoked no more than 30 cigarettes per day, African Americans and Native Hawaiians had significantly greater risks of lung cancer than did the other groups. Among those who smoked no more than 10 and those who smoked 11 to 20 cigarettes per day, relative risks ranged from 0.21 to 0.39 ( $P < 0.001$ ) among Japanese Americans and Latinos and from 0.45 to 0.57 ( $P < 0.001$ ) among whites, as compared with African

**Chronic inflammation has been implicated in the development of airway dysplasia and lung cancer.**

**Half of the participants developed progressive dysplastic lesions after 6 mo.**

**The risk of lung cancer among ethnic and racial groups was modified by the number of cigarettes smoked per day.**

Americans. However, at levels exceeding 30 cigarettes per day, these differences were not significant. Differences in risk associated with smoking were observed among both men and women and for all histologic types of lung cancer. CONCLUSIONS: Among cigarette smokers, African Americans and Native Hawaiians are more susceptible to lung cancer than whites, Japanese Americans, and Latinos. Copyright 2006 Massachusetts Medical Society.

## **Editor's Perspective on This Issue**

**The drama of deaths of national figures, such as the late Peter Jennings and Dana Reeves, to focus attention on the tragedy of lung cancer. Although most lung cancer occurs in smokers or former smokers, there are other risk factors. Unfortunately, the American Cancer Society continues to drag its feet on screening, even in high risk groups. Amazingly, however, they have suddenly become neutral on this issue. Big deal!**

**What is most exciting is the movement in Congress to try to make lung cancer understood as the major tragedy that it is and to attempt to reduce its incidence by 50% in the immediate future. Now we are really talking!**

**This issue of *LCF* should be encouraging to all pulmonologists who practice comprehensive pulmonary medicine. It is the pulmonologist and the referring primary care physician who together hold the key to controlling lung cancer.**

**As has been shown in the Grand Junction Study, lung cancer is most common in heavy smokers with airflow obstruction and particularly those with a family history of occupational risk, as well, or even without smoking.**

**The increased ethnic risk in Blacks and Hispanics also requires attention. Thus, we now have the knowledge and tools to tackle lung cancer in a comprehensive way. Supplementing CT scanning, which is great for peripheral lesions but not so sensitive to small central lesions, is sputum cytology with molecular markers and autofluorescence bronchoscopy to find the cancer, and sometimes ablate it locally. We now have a powerful armamentarium to bring to bear and the knowledge that can control lung cancer. It only requires societal will and this, of course, takes the horsepower of our government and adequate funding.**

**Exciting times indeed, lie ahead!**