

July 2006

**LUNG  
CANCER****FRONTIERS****HIGHER LUNG CANCER  
RISK IN WOMEN!**

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**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).

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

International Early Lung Cancer Action Program Investigators  
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Dr. Claudia I. Henschke

**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

# The Forum for Early Diagnosis and Treatment of Lung Cancer

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## Zeroing in On High Risk

*The headline of this issue of Lung Cancer Frontiers, "Higher Lung Cancer Risk in Women," and many of the selected abstracts help to zero in on the highest risk patients who may fall victim to lung cancer.*

*Certainly our stratification of risk must go beyond standard smoking and environmental risks that are well established. It has been known for sometime that women afflicted with lung cancer have a lower degree, i.e., pack years, of smoking and at a younger age. It certainly is time to recognize that even non-smoking women may have lung cancer as was evidenced by the tragic death of the late Dana Reeves.*

*It is time to abandon conventional thinking and to be more aggressive in targeting the screening of patients with a high or multiple risks of lung cancer.*



(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.

Tanimoto M, Sobue T

Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan.

*Claudia Henschke's ELCAP Network continues to expand the horizons for early diagnosis and treatment of lung cancer.*

Editorial Comment (TLP): Claudia Henschke's ELCAP Network continues to expand the horizons for early diagnosis and treatment of lung cancer. In time, screening, at least in high risk groups, may become the standard of care! It must be clear by the work of Henschke, et al that early diagnosis of lung cancer is resulting in a very high cure rate approaching 90% in a growing series of smokers screened for lung cancer. Somehow we must break the logjam that has existed for so many years and finally recommend target screening in high risk patients, as I argued previously in an article in CHEST (Petty TL: It's time to pick the low-hanging fruit. Chest 2000;117:1-2).

To evaluate recent improvements in lung cancer screening, we compared the results of recently conducted lung cancer screening with those of a previous screening. This study compared the survival of lung cancer patients detected by lung cancer screening conducted between 1976 and 1984 (early period) with that conducted between 1989 and 1997 (late period). Two hundred seventy-six patients with lung cancer were detected in the early period and 541 patients with lung cancer were detected in the late period. The median survival time (late : 49.8 vs. early : 27.8 months) and the 5-year survival rate (late : 47.8 vs. early : 34.8%) of the patients with lung cancer detected in the late period were significantly better than those in the early period (p = 0.0054). Among patients undergoing resection, the proportion of pathological stage I patients in the late period was significantly higher than that in the early period (late : 60.8 vs. early : 54.9%, p = 0.005). Multivariate analysis showed that the screening time period was a significant prognostic factor (hazard ratio = 0.685, 95% confidence interval : 0.563-0.832, p = 0.0002). These results were consistent with the findings of case-control studies of lung cancer screening programs in

*Somehow we must break the logjam that has existed for so many years and finally recommend target screening in high risk patients . . . .*

**PEER REVIEWED LITERATURE CITATIONS**

Selected Abstracts

1. **Recent improvement in lung cancer screening: a comparison of the results carried out in two different time periods**  
Acta Med Okayama 2006;60:173-179

Kitajima T, Nishii K, Ueoka H, Shibayama T, Gemba K, Kodani T, Kiura K, Tabata M, Hotta K,

*Multivariate analysis showed that the screening time period was a significant prognostic factor . . .*

**Screening for lung cancer, including sputum cytology and CT scans, is the standard of care in Japan for all smokers over age 45.**

**The test result was positive in 102 of the 842 baseline screenings (12%) and in 45 of the 942 annual repeat screenings (5%) . . .**

**. . . . . 842 former and current smokers underwent baseline low-dose CT screening . . .**

the late period recently conducted in Japan, which also showed a greater efficacy for screening than for previous case-control studies in the early period.

Editorial Comment (TLP): Screening for lung cancer, including sputum cytology and CT scans, is the standard of care in Japan for all smokers over age 45. In recent years screening has been increased throughout the country. This study shows that contemporary screening is becoming more effective in diagnosing early stage lung cancer and that lung cancer survival is improving through screening.

2.

**Computed tomography screening for lung cancer: applicability of an international protocol in a single-institution environment**

Clin Lung Cancer 2006;7:262-267

Shaham D, Breuer R, Copel L, Agid R, Makori A, Kisselgoff D, Goitein O, Izhar U, Berkman N, Heching N, Sosna J, Bar-Ziv J, Libson E  
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BACKGROUND: The purpose of this study was to assess the applicability of an annual low-dose computed tomography (CT) screening program for lung cancer in a single institution in Israel, which has a relatively lower prevalence of lung cancer compared with other Western countries, and to examine stage distribution of detected lung cancers. PATIENTS AND METHODS: A cohort of 842 former and current smokers underwent baseline low-dose CT screening and a total of 942 annual repeat

screenings over a period of 68 months. The definition of positive results on baseline and repeat screening and their diagnostic workup were guided by the common International Early Lung Cancer Action Program protocol. Recommendations for biopsy of suspicious nodules were based on nodule size, nodule growth, non-resolution following antibiotic therapy, and positron emission tomography scan. RESULTS: The test result was positive in 102 of the 842 baseline screenings (12%) and in 45 of the 942 annual repeat screenings (5%), and biopsy was recommended in 12 baseline and 2 annual screenings. Twelve of the 14 cancers diagnosed (86%) were stage I tumors. CONCLUSION: Our study indicates that the adoption of a common international protocol is feasible, even in a very different clinical setting, yielding a high proportion of early-stage lung cancers.

Editorial Comment (TLP): This study suggests an international protocol for lung cancer screening and gives evidence that international protocols will find predominantly early stage lung cancer. This is the direction in which we should be moving.

3.

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

Cancer Epidemiol Biomarkers

***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.***

***Low-dose spiral computerized axial tomography (spiral CT) is effective for the detection of small early lung cancers.***

***We analyzed 17 biomarkers of lung epithelial malignancy in a series of 11 tumors resected at our institution during the last 4 years.***

Prev 2006;15:373-380

Pajares MJ, Zudaire I, Lozano MD, Agorreta J, Bastarrika G, Torre W, Ramirez A, Pio R, Zulueta JJ, Montuenga LM  
Oncology Division, Center for Applied Medical Research, Clinica Universitaria de Navarra, Pamplona, Spain.

**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):** This study presents a body of evidence that indicates that early stage screening-detected lung cancer has a biological behavior similar to those found in invasive cancers diagnosed by lung resection.

4.

**Early detection of bronchial lesions using newly developed videoendoscopy-based autofluorescence bronchoscopy**

Lung Cancer 2006;52:21-27

Ikeda N, Honda, Hayashi A, Usuda J, Kato Y, Tsuboi M, Ohira T, Hirano T, Kato H, Serizawa H, Aoki Y  
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The combination of white light and autofluorescence bronchoscopy has been reported to show better sensitivity in detecting dysplasia and cancer of

*... fiberoptic bronchoscopy has been replaced by videoendoscopy at most leading facilities for over a decade.*

*Data from the case-control study (256 incident cases and 314 population controls) were analysed to define a high-risk population.*

*This videoendoscopy-based autofluorescence system had significantly higher sensitivity for intraepithelial lesions than white light videoendoscopy.*

the bronchus than white light alone. However, fiberoptic bronchoscopy has been replaced by videoendoscopy at most leading facilities for over a decade. To avoid interruption of the videoendoscopy examination to perform fiberscopy-based autofluorescence examination as well as enhancing the sensitivity of intraepithelial lesions, autofluorescence diagnosis system integrated into a videoendoscope (SAFE 3000, Pentax, Tokyo) was created. A total of 154 consecutive patients were studied using this system, containing 83 known or suspected lung cancer cases, 46 of the cases with abnormal sputum cytology findings, 10 follow up cases following lung cancer operations, and 15 heavy smokers with respiratory symptoms. Abnormal findings were recognized by white light and/or SAFE 3000 at 166 sites and biopsies were taken to evaluate the relationship between endoscopic findings and pathology results. The sensitivity of the system for CIS+dysplasia was 65% in white light and 90% in SAFE. This videoendoscopy-based autofluorescence system had significantly higher sensitivity for intraepithelial lesions than white light videoendoscopy

Editorial Comment (TLP): New technology is adding to the sensitivity and specificity of diagnosing small epithelial lesions. These are the tiny intraepithelial lesions that may not be found by CT scanning.

5.

**Defining high-risk individuals in a population-based molecular-epidemiological study of lung cancer**

Int J Oncol 2006;28:1295-1301

Cassidy A, Myles JP, Liloglou T, Duffy SW, Field JK  
Roy Castle Lung Cancer Research Programme, University of Liverpool Cancer Research Centre, University of Liverpool, Liverpool L3 9TA, UK.

Within the framework of the Liverpool Lung Project (LLP), population-based case-control and prospective cohort studies are in progress to identify molecular and epidemiological risk factors and define populations and individuals most at risk of developing lung cancer. This report describes a strategy for selection of a high-risk population and further provides support for the inclusion of occupational and genetic risk factors in future models. Data from the case-control study (256 incident cases and 314 population controls) were analysed to define a high-risk population. Detailed lifestyle and occupational information were collected during structured interviews. Models were constructed using conditional logistic regression and included terms for age, tobacco consumption and previous respiratory disease. Smoking duration was chosen as the most important predictor of lung cancer risk [ $>50$  years (OR 15.65, 95% CI 6.10-40.15)]. However, such a model would preclude younger individuals. Several combinations of previous respiratory disease were also considered, of which a history of bronchitis, emphysema or pneumonia (BEP) was the most significant (OR 1.86, 95% CI 1.28-2.69). A high-risk subset (based on combinations of smoking duration and BEP) was identified, which

***Aims: To define the natural history of pre-invasive lesions and assess lung cancer risk in patients harbouring these lesions.***

***There is real potential for environmental and genetic factors to improve on risk prediction and targeting of susceptible individuals beyond the traditional models based only on smoking and age.***

***Although the risk of malignant progression of SD or CIS is relatively small, patients harbouring these lesions are at high lung cancer risk.***

have a 4.5-fold greater risk of developing lung cancer (OR 4.5, 95% CI 2.33-8.68). Future refinement of the risk model to include individuals occupationally exposed to asbestos and with the p21 genotypes is discussed. There is real potential for environmental and genetic factors to improve on risk prediction and targeting of susceptible individuals beyond the traditional models based only on smoking and age. The development of a molecular-epidemiological model will inform the development of effective surveillance, early detection and chemoprevention strategies.

Editorial Comment (TLP): This study helps to define high-risk populations. It is not surprising that very heavy smokers with pulmonary symptoms identify a population (as well as those exposed to asbestos) are identified as a population at extremely high risk. Certainly these extremely high risk populations should be the subject of screening.

6.

#### **Surveillance for the detection of early lung cancer in patients with bronchial dysplasia**

Thorax 2006;(ahead of print)

George PJ, Banerjee A, Read CA, O'Sullivan C, Falzon M, Pezzella F, Nicholson A, Shaw P, Laurent G, Robbitts P  
UCL Hospitals NHS Foundation Trust, United Kingdom.

Background: The natural history of bronchial pre- invasive lesions and the risk of developing lung cancer in patients harbouring these lesions are not clear. Previous studies have treated severe dysplasia (SD) and

carcinoma-in-situ (CIS) on the assumption that the majority will progress to invasive carcinoma. Aims: To define the natural history of pre-invasive lesions and assess lung cancer risk in patients harbouring these lesions. Hypotheses: The majority of pre-invasive lesions will not progress to invasive carcinoma but patients harbouring these lesions will be at high risk. Methods: A cohort of patients with pre-invasive lesions underwent fluorescence bronchoscopy every 4-12 months and chest CT annually. The main endpoint was the development of invasive carcinoma. Results: Twenty-two patients with 53 lesions were followed for 12-85 months. Eleven cancers were diagnosed in 9 patients. Six progressed from high-grade lesions (SD and CIS), while 5 developed at remote sites in patients harbouring high-grade lesions. All cancers were NOM0 and curative treatment was given to 8/9 patients. The cumulative risk of a high-grade lesion progressing to invasive carcinoma was 10% at 1 year and 21% at 2 years, while the cumulative risk of developing lung cancer in a patient harbouring a high-grade lesion was 33% and 54% at 1 and 2 years respectively. Conclusions: Although the risk of malignant progression of SD or CIS is relatively small, patients harbouring these lesions are at high lung cancer risk. Surveillance facilitated early detection and treatment with curative intent in the majority of patients.

Editorial Comment (TLP): This early release abstract has additional information on the natural history of pre-invasive lesions. Although many of these lesions will not progress, surveillance is still required because the potential for progression remains in these patients.

7.

#### **Lack of Association between Sputum Atypia and Chronic Obstructive Pulmonary Disease Mortality**

*... sputum cytology is not a predictor of death from the most common disease associated with lung cancer and COPD.*

*The authors hypothesized that sputum atypia would reflect the processes leading to progressive airflow obstruction and might be a novel biomarker of more rapidly progressive COPD.*

*Patients with nonsmall cell lung cancer (NSCLC) have been shown to have a higher prevalence of comorbidity associated with age and tobacco consumption.*

J Thorac Oncol 2006;1:302-307  
Miller, YE, Vu KO, Kennedy TC, Hirsch FR, Petty TL, Bunn PA, Keith RL, Franklin WA, Wolf, HJ, Prindiville S, Byers T

Hypothesis: Chronic obstructive pulmonary disease (COPD) and lung cancer are thought to share common elements in pathogenesis. The authors hypothesized that sputum atypia would reflect the processes leading to progressive airflow obstruction and might be a novel biomarker of more rapidly progressive COPD. Methods: The authors analyzed the association between COPD death and sputum cytologic atypia in an ongoing cohort of 2013 smokers with varying degrees of airflow obstruction during the period between January 1, 1993, and July 1, 2001. Results: There were 326 deaths attributed to COPD over 4495 person-years, giving a COPD death rate of 7.25 deaths per 100 person-years, which is highly elevated compared with fewer than 0.2 COPD deaths per 100 person-years for the United States population aged between 65 and 74 years. Sputum atypia was not associated with either the degree of airflow obstruction or death from COPD. COPD death was associated with age and degree of airflow obstruction, as expected. Conclusion: Sputum cytologic atypia is not predictive of death from COPD. As sputum cytologic grades of moderate or worse atypia are associated with a significant increase in the risk for lung cancer and do not denote a group with increased competing death rates from COPD, patients with sputum atypia are a good high risk group in whom chemoprevention and early detection studies can be conducted.

Editorial Comment (TLP): This study is important because it gives evidence that

sputum cytology is not a predictor of death from the most common disease associated with lung cancer and COPD. Even in patients with advanced COPD, chemoprevention studies for lung cancer would be reasonable.

8.  
**Comorbidities and Charlson score in resected stage I nonsmall cell lung cancer**

Eur Respir J 2005;26:480-486  
[Moro-Sibilot D](#), [Aubert A](#), [Diab S](#), [Lantuejoul S](#), [Fourneret P](#), [Brambilla E](#), [Brambilla C](#), [Brichon PY](#).

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Patients with nonsmall cell lung cancer (NSCLC) have been shown to have a higher prevalence of comorbidity associated with age and tobacco consumption. The objective of the present study was to determine the impact of comorbidity on survival after surgery of stage I NSCLC. In total, 588 consecutive patients operated on for a pathological stage I NSCLC between January 1, 1979 and December 31, 2003 were studied. Comorbidities were analysed individually. Overall comorbidity was assessed using the Charlson index of comorbidity (CCI). Survival data were collected for each patient from the date of operation, with a median duration of follow-up of 104 months. Survival analyses and Cox proportional hazards model analyses were used. The mean age

of patients was 62.7 yrs, and 529 (89%) patients were male. The distribution of overall comorbidity severity was as follows. CCI grade 0: 47.1%; grade 1-2: 43.7%; grade 3-4: 8.3%; and grade  $\geq$  5: 0.8%. The 2, 3 and 5 yrs survival were 69, 62 and 50%, respectively. Multivariable analysis showed that T stage, age, a concomitant history of moderate-to-severe liver disease, a past history of cured cancer, cerebrovascular disease and CCI were independent predictors of survival (Hazard Ratio for CCI grade  $\geq$  2: 1.81; 95% confidence interval 1.25-2.63). In conclusion, comorbidity has a significant impact on survival after surgical resection of patients with stage I nonsmall cell lung cancer. The use of a validated index of comorbidity in prognostic analyses of resected nonsmall cell lung cancer is recommended.

Editorial Comment (TLP): A comorbidities score is offered, which will help in prognostic estimates for candidates for resectional surgery. Coronary disease, congestive, heart failure, and chronic pulmonary disease head the list.

9.

### **The Role of Pulmonary Resection in Small Cell Lung Cancer**

Mayo Clin Proc 2006;81:619-624  
Chandra V, Allen MS, Nichols III FC, Deschamps C, Cassivi SD, Pairolero PC  
Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN 55905, USA.

**OBJECTIVE:** To analyze the outcome of surgical resection for patients with small cell lung cancer

(SCLC). **PATIENTS AND METHODS:** We identified all patients who underwent thoracotomy for SCLC at our institution from January 1985 to July 2002. All patients were staged using the American Joint Committee on Cancer TNM system. **RESULTS:** The median age of the 77 patients (44 men and 33 women) was 65 years (range, 35-85 years). Operations performed included thoracotomy with biopsy of hilar mass in 10 patients, wedge excision in 30 (6 with talc pleurodesis), segmentectomy in 4, lobectomy in 28, bilobectomy in 3, and pneumonectomy in 2. Mediastinal lymphadenectomy was performed in 50 patients and lymph node sampling in 19. Postoperative therapy Included chemotherapy alone in 20 patients, radiation therapy in 3, and combined chemotherapy and radiation therapy in 40. Median tumor diameter was 4 cm (range, 1.0-10.0 cm). Postsurgical tumor stage was IA in 7 patients, IB in 11, IIA in 8, IIB in 7, IIIA in 30, IIIB in 10, and IV in 4. A total of 19 patients (25%) had complications: atrial arrhythmia in 7 patients, pneumonia in 6, prolonged air leak in 3, and myocardial infarction, postoperative bleeding, and cerebrovascular accident in 1 each. Operative mortality was 3% (2/77). Follow-up ranged from 4 days to 170 months (median, 19 months). At last follow-up, 20 patients were alive. The estimated overall 5-year survival was 27% when excluding the 10 patients who underwent a biopsy without additional surgery. Five-year survival for stage I and II combined (n=33) was 38% compared with only 16% for stage III and IV combined (n=34) (P=.02). Overall median survival was 24 months; median survival for patients who underwent curative surgery was 25 months compared with 16 months for those who had a palliative procedure (P=.34). **CONCLUSION:** Pulmonary resection in patients with stage I or stage II SCLC is

*The use of a validated index of comorbidity in prognostic analyses of resected nonsmall cell lung cancer is recommended.*

*The estimated overall 5-year survival was 27% . . . . .*

safe with low mortality and morbidity. Curative resection is associated with long-term survival in early stage SCLC in some patients and should be considered in selected patients.

Editorial Comment (TLP): We ordinarily think of small cell lung cancer as a nonsurgical disease, but the cited study shows that cures as possible, based upon TNM staging. Although most small cell cancers are central about 10% are peripheral including solitary nodules where the cure rate can be high.

10. **Smokers with Airway Obstruction are more Likely to Quit Smoking** [Thorax](#). 2006 Jun 29; [Epub ahead of print]

[Bednarek M](#), [Gorecka D](#), [Wielgomas J](#), [Czajkowska-Malinowska M](#), [Regula J](#), [Mieszko-Filipczyk G](#), [Jasionowicz M](#), [Bijata-Bronisz R](#), [Lempicka-Jastrzebska M](#), [Czajkowski M](#), [Przybylski G](#), [Zielinski J](#).

National Research Institute of Tuberculosis and Lung Diseases, Poland.

Background and aim: COPD, usually caused by tobacco smoking, is one of the leading causes of morbidity and mortality. Smoking cessation at an early stage of the disease usually stops further progression of the disease. Our aim was to determine if diagnosis of airway obstruction (AO) was associated with subsequent success in smoking cessation, as advised by a physician. Methods: 4494 current smokers (57.4% males) with a history of at least 10 pack-years of smoking were recruited from 110,000 subjects screened by spirometry for signs of AO. At the time of screening, all received simple anti-smoking advice.

1,177 (26.2%) subjects had AO and were told that they had COPD and that smoking cessation would halt rapid progression of their lung disease. No pharmacological treatment was proposed. After one year, all subjects were invited for a follow-up visit. Smoking status was assessed by history and validated by exhaled carbon monoxide level. Results: Nearly 70% attended a follow-up visit (n=3,077): 61% were men, mean age was 52+/-10 years, mean tobacco exposure was 30+/-17 pack-years, and 33.3% had AO during the baseline exam. The validated quit rate in those with AO was 16.3%, compared to 12.0% in those with normal spirometry (p=0.0003). After correction for age, gender, nicotine dependence, number of cigarettes smoked daily and lung function success in quitting smoking was predicted by lower lung function, lower nicotine dependence, and lower tobacco exposure. Conclusions: Simple anti-smoking advice combined with spirometry test resulted in good one-year cessation rates, especially in subjects with AO.

Editorial Comment (TLP): This new study by leaders in Poland has shown convincingly that knowledge of spirometric abnormalities can encourage smokers with all stages of COPD to quit smoking. It is encouraging that even smokers who had normal pulmonary function had a significant movement away from smoking, which has been observed in other population studies. It has become increasingly clear that the spirometer can be a powerful tool in the encouragement of smoking

**Simple anti-smoking advice combined with spirometry test resulted in good one-year cessation rates, especially in subjects with AO.**

**Smoking cessation at an early stage of the disease usually stops further progression of the disease.**

*The position expounded by the American Agency for Health Research Quality (AAHRQ) is untenable in light of these new studies .*

.....

*The obvious solution for lung cancer is a reduction or curtailment in smoking, but this is far in the future.*

*For weeks 9 through 12, the 4-week continuous abstinence rates were 44.0% for varenicline vs 17.7% for placebo . . . .*

cessation. The position expounded by the American Agency for Health Research Quality (AAHRQ) in untenable is light of these new studies, as well as others (Enright editorial, CHEST 200;129:833-835) and should be reversed, as I have argued recently in CHEST (“Harm From Spirometry?” CHEST in press). Together knowledge of airflow obstruction combined with drugs to aid in smoking cessation, such as Varenicline, as summarized in the next three articles, along with other nicotine replacement products, provide a powerful armamentarium in our continued battle to reduce and eliminate smoking as a risk for lung cancer in our population. This idea, of course, is far in the future, but we are making progress.

#### **NEW HELP HOPE FOR ADDICTED SMOKERS**

The following two articles are controlled clinical trials that establish a new agent in the control of smoking. The obvious solution for lung cancer is a reduction or curtailment in smoking, but this is far in the future.

11.  
**Varenicline, an  $\alpha 4\beta 2$  Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release and Bupropion and Placebo for Smoking Cessation**  
**A Randomized Controlled Trial**  
JAMA 2006;296:47-55

[Gonzales D](#), [Rennard SI](#), [Nides M](#), [Oncken C](#), [Azoulay S](#), [Billing CB](#), [Watsky EJ](#), [Gong J](#), [Williams KE](#), [Reeves KR](#); [Varenicline Phase 3 Study Group](#).

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**CONTEXT:** The  $\alpha 4\beta 2$  nicotinic acetylcholine receptors (nAChRs) are linked to the reinforcing effects of nicotine and maintaining smoking behavior. Varenicline, a novel  $\alpha 4\beta 2$  nAChR partial agonist, may be beneficial for smoking cessation. **OBJECTIVE:** To assess efficacy and safety of varenicline for smoking cessation compared with sustained-release bupropion (bupropion SR) and placebo. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind, parallel-group, placebo- and active-treatment-controlled, phase 3 clinical trial conducted at 19 US centers from June 19, 2003, to April 22, 2005. Participants were 1025 generally healthy smokers ( $>$  or  $=$ 10 cigarettes/d) with fewer than 3 months of smoking abstinence in the past year, 18 to 75 years old, recruited via advertising. **INTERVENTION:** Participants were randomly assigned in a 1:1:1 ratio to receive brief counseling and varenicline titrated to 1 mg twice per day (n = 352), bupropion SR titrated to 150 mg twice per day (n = 329), or placebo (n = 344) orally for 12 weeks, with 40 weeks of nondrug follow-up. **MAIN OUTCOME MEASURES:** Primary outcome was the exhaled carbon monoxide-confirmed 4-week rate of continuous abstinence from smoking for weeks 9 through 12. A secondary outcome was the continuous abstinence rate for weeks 9 through 24 and weeks 9 through 52. **RESULTS:** For weeks 9 through 12, the 4-week continuous abstinence rates were 44.0% for varenicline vs 17.7%

***Varenicline, a partial agonist at the alpha4beta2 nicotinic acetylcholine receptor, has the potential to aid smoking cessation by relieving nicotine withdrawal symptoms . . .***

***Varenicline reduced craving and withdrawal and, for those who smoked while receiving study drug, smoking satisfaction.***

for placebo (odds ratio [OR], 3.85; 95% confidence interval [CI], 2.70-5.50; P<.001) and vs 29.5% for bupropion SR (OR, 1.93; 95% CI, 1.40-2.68; P<.001). Bupropion SR was also significantly more efficacious than placebo (OR, 2.00; 95% CI, 1.38-2.89; P<.001). For weeks 9 through 52, the continuous abstinence rates were 21.9% for varenicline vs 8.4% for placebo (OR, 3.09; 95% CI, 1.95-4.91; P<.001) and vs 16.1% for bupropion SR (OR, 1.46; 95% CI, 0.99-2.17; P = .057). Varenicline reduced craving and withdrawal and, for those who smoked while receiving study drug, smoking satisfaction. No sex differences in efficacy for varenicline were observed. Varenicline was safe and generally well tolerated, with study drug discontinuation rates similar to those for placebo. The most common adverse events for participants receiving active-drug treatment were nausea (98 participants receiving varenicline [28.1%]) and insomnia (72 receiving bupropion SR [21.9%]). CONCLUSION: Varenicline was significantly more efficacious than placebo for smoking cessation at all time points and significantly more efficacious than bupropion SR at the end of 12 weeks of drug treatment and at 24 weeks. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00141206.

12.

**Efficacy of Varenicline, an  $\alpha 4\beta 2$  Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation**

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[Jorenby DE](#), [Hays JT](#), [Rigotti NA](#), [Azoulay S](#), [Watsky EJ](#), [Williams KE](#),

[Billing CB](#), [Gong J](#), [Reeves KR](#); [Varenicline Phase 3 Study Group](#).

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CONTEXT: Varenicline, a partial agonist at the alpha4beta2 nicotinic acetylcholine receptor, has the potential to aid smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine. OBJECTIVE: To determine the efficacy and safety of varenicline for smoking cessation compared with placebo or sustained-release bupropion (bupropion SR). DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled trial conducted between June 2003 and March 2005 at 14 research centers with a 12-week treatment period and follow-up of smoking status to week 52. Of 1413 adult smokers who volunteered for the study, 1027 were enrolled; 65% of randomized participants completed the study. INTERVENTION: Varenicline titrated to 1 mg twice daily (n = 344) or bupropion SR titrated to 150 mg twice daily (n = 342) or placebo (n = 341) for 12 weeks, plus weekly brief smoking cessation counseling. MAIN OUTCOME MEASURES: Continuous abstinence from smoking during the last 4 weeks of treatment (weeks 9-12; primary end point) and through the follow-up period (weeks 9-24 and

**For weeks 9 through 24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; P <.001) and 20.2% in the bupropion group (OR, 1.69; 95% CI, 1.19-2.42; P = .003).**

**... there is no “silver bullet,” to smoking cessation that will work in all patients.**

9-52). RESULTS: During the last 4 weeks of treatment (weeks 9-12), 43.9% of participants in the varenicline group were continuously abstinent from smoking compared with 17.6% in the placebo group (odds ratio [OR], 3.85; 95% confidence interval [CI], 2.69-5.50; P<.001) and 29.8% in the bupropion SR group (OR, 1.90; 95% CI, 1.38-2.62; P<.001). For weeks 9 through 24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; P<.001) and 20.2% in the bupropion group (OR, 1.69; 95% CI, 1.19-2.42; P = .003). For weeks 9 through 52, 23% of participants in the varenicline group were continuously abstinent compared with 10.3% in the placebo group (OR, 2.66; 95% CI, 1.72-4.11; P<.001) and 14.6% in the bupropion SR group (OR, 1.77; 95% CI, 1.19-2.63; P = .004). Treatment was discontinued due to adverse events by 10.5% of participants in the varenicline group, 12.6% in the bupropion SR group, and 7.3% in the placebo group. The most common adverse event with varenicline was nausea, which occurred in 101 participants (29.4%).

CONCLUSIONS: Varenicline is an efficacious, safe, and well-tolerated smoking cessation pharmacotherapy. Varenicline's short-term and long-term efficacy exceeded that of both placebo and bupropion SR. TRIAL REGISTRATION: [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00143364.

Editorial Comment (TLP): These two studies have convincing evidence that a new pharmacologic agent, Varenicline, aids in smoking cessation. Smoking abstinence and behavioral modification remains unsuccessful in many patients. This

continues to show that there is no “silver bullet,” to smoking cessation that will work in all patients. Nonetheless we have still another product that appears to increase the probability of smoking cessation. The possibility of using Varenicline in combination therapy should be explored.