

June 2004

**LUNG  
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**LCF GOES ALL  
ELECTRONIC**

**Lung Cancer Frontiers** is funded by The Snowdrift Pulmonary Conference and a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the unrestricted grant to expand and report our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado, will provide new and exciting material for *Lung Cancer Frontiers*.

"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).**

The Editorial Board of *Lung Cancer Frontiers* is pleased to announce that LCF will now be published approximately quarterly in an all-electronic format. This gives us many advantages of flexibility and cost savings. We plan to keep abreast of the exciting and emerging literature on the early identification and intervention in lung cancer, our nation's and the world's most common fatal malignancy. Former issues, beginning in 1996, are all available on [www.lungcancerfrontiers.org](http://www.lungcancerfrontiers.org). They can be downloaded into a print format. We hope that this important new step for *Lung Cancer Frontiers* will continue to expand its readership and stimulate more pulmonologists and other practitioners to take a keen interest in lung cancer from all aspects, emphasizing early diagnosis.

**CHANGES IN THE  
EDITORIAL BOARD**

The Editorial Board proudly announces the appointment of York E. Miller, M.D. of the Veterans Administration Hospital and a present member of the Editorial Board to the post of deputy editor. Robert L. Keith, M.D., also of Denver will become a deputy editor. This will strengthen the editorial office in Denver. Both are actively involved in both basic and clinical studies in lung cancer.

We are also delighted to announce the appointment of Elizabeth Brambilla, Cedex, France, as a new member of the

Editorial Board. She will help guide us in selecting important articles from the European continent and covering conferences that may take place there. We thank our longtime friend and contributor, Stephen Lam, who has served as deputy editor since 2000. He will remain active on the Editorial Board. We also thank John A. Nakhosteen, M.D. of Bochum, Germany, an original board member of LCF for his major contribution over the years. He is now in semi-retirement. Finally, we thank the remaining members of the Editorial Board for their past contributions to our efforts and continued contributions to LCF. Thomas L. Petty, M.D., Editor

**A US PREVENTIVE  
SERVICES CHEST  
TASK FORCE CONTINUES TO  
RECOMMEND AGAINST SCREENING**

In spite of advances in the technologies used in early stage lung cancer resulting in improved survival in subset groups, it is a disappointing fact that the USPS Task Force continues to recommend against screening (Ann Intern Med 2004;140:740-753). The authors, it is fair to say, are not recognizable clinical experts in lung cancer. Yet they do continue to comment on the 171,900 new cases which occurred in the United States in 2003, resulting in 157,200 deaths. But on the same page as this article, they repeat a fact which we all know, that "survival is directly related to the stage of lung cancer at the time of diagnosis, ranging from 70% at Stage I to less than 5% for Stage IV." Even heavy smokers who are at high risk are not recommended for screening, though we know that this is where cancer is found, particularly in patients with airflow

# The Forum for Early Diagnosis and Treatment of Lung Cancer

## Lung Cancer Frontiers Editorial Board

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**Robert L. Keith MD**  
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**“Even heavy smokers who are at high risk are not recommended for screening though we know that this is where cancer is found, particularly in patients with airflow obstruction.”**

**“Today lung cancer screening is the standard of care in Japan.”**

**“The combination of sputum cytology and CT scanning for individuals in high risk groups should emerge as the standard of care in North America and elsewhere in the world, and hopefully in the United States.”**

**“The development of pragmatic programs for the early diagnosis and treatment of asymptomatic lung cancer is long overdue.”**

obstruction. Therefore, I remain bewildered by this reactionary position.

The Task Force emphasizes the emotional trauma caused by screening that identifies false positives. But they ignore the anguish of patients who suffer after failure of cure of the majority of patients with late stage lung cancer, which is the stage at which most lung cancers is diagnosed in the USA.

Today lung cancer screening is the standard of care in Japan. It is interesting that only two references to the Japanese literature are included, amongst the 125 references cited in the abstract (Yoshino I, et al: *Surgery* 2002;131:242-8 and Sobue: *Cancer* 1992;69:685-92).

As we have stated many times on these pages, we have the knowledge and technology to change the outcome of lung cancer. What we must do is find lung cancer amongst those at highest risk, treat it, and cure it. In so doing, we will change the outcome of lung cancer, not only in the United States but ultimately elsewhere in the world. The combination of sputum cytology and CT scanning for individuals in high risk groups should emerge as the standard of care in North America and elsewhere in the world, and hopefully in the United States. Waiting for the results of a just-begun controlled clinical trial which will compare chest x-rays and CT scanning for individuals at high risk in my opinion. Results will not be available for some 8-10 years and these technologies may be obsolete by then.

Some day common sense may replace the reactionary position of those who “worship at the altar of evidence”, particularly when the evidence they will accept is only from old and inadequate, randomized prospective controlled clinical trials and not modern cohort studies which are closer to an immediate answer.

#### **Arch Bronconeumol 2004;40:268-274**

**Overall long-term survival in lung cancer analyzed in 610 unselected patients. Sanchez De Cos Escuin J, Disdier Vicente C, Corral Penafiel J, Riesco Miranda JA, Sojo Gonzalez MA, Masa Jimenez JF.**

Introduction and objectives: Many studies of lung cancer survival are carried out in patients selected for certain features that usually influence prognosis favorably. The objective of this study was to assess the overall survival of unselected patients with a diagnosis of lung cancer in our practice. Patients and methods: We studied 610 patients for whom survival information was

available, a population comprising 88% of the 694 with lung cancer diagnosed in our hospital from 1991 through 1998. The variables analyzed for their correlation with survival were age, sex, histology, tumor-node-metastasis (TNM) stage, treatment, and time of diagnosis (with patients grouped by 2-year periods). Results: The cases of 596 men and 14 women with a mean age of approximately 67 years were studied. Small cell tumors were found in 141, non-small cell tumors in 447, and other tissue types in 22. Surgical excision was carried out on 118 (19.3%), and treatment was confined to control of symptoms for 6.4% of the patients with small cell tumors and 40.5% of those with non-small cell cancer. Symptomatic treatment alone was more common for patients older than 70 years (52.5%) and less common during the last 2 years of the study period (1997-1998: 19%). Overall 5-year survival was 7.9% (2.8% in small cell cancer and 9.4% in non-small cell cancer). Survival rates were lower in patients over 70 years of age. Significant differences in survival were seen for successive TNM stages, with the exception of IIIA and IIIB. The 1997-1998 period saw better survival rates, at 40.8% after 1 year and 11.2% after 5 years. Conclusions: The survival rates in lung cancer patients in our hospital practice are low because the rate of surgical resections is low owing to the high percentage of cases found in advanced stages. Our observations are similar to those reported from other European countries.

**Editorial Comment (TLP):** Once more we have well documented evidence of the dismal outcome of lung cancer that is usually diagnosed on the basis of local symptoms or metastatic spread. The development of pragmatic programs for the early diagnosis and treatment of asymptomatic lung cancer is long overdue. Note the Report of the US Preventive Services Chest Task Force that continues to recommend against screening for early diagnosis!

#### **NEJM 2004;350**

**Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib.**

**Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA.**

**Background** Most patients with non-small-cell lung cancer have no response to the tyrosine kinase inhibitor gefitinib, which targets the epidermal growth factor receptor (EGFR). However, about 10 percent of patients have a rapid and often dramatic clinical response. The molecular mechanisms underlying sensitivity to gefitinib are unknown. **Methods** We searched for mutations in the EGFR gene in primary tumors from patients with non-small-cell lung cancer who had a response to gefitinib, those who did not have a response, and those who had not been exposed to gefitinib. The functional consequences of identified mutations were evaluated after the mutant proteins were expressed in cultured cells. **Results** Somatic mutations were identified in the tyrosine kinase domain of the EGFR gene in eight of nine patients with gefitinib-responsive lung cancer, as compared with none of the seven patients with no response (P0.001). Mutations were either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain. Similar mutations were detected in tumors from 2 of 25 patients with primary non-small-cell lung cancer who had not been exposed to gefitinib (8 percent). All mutations were heterozygous, and identical mutations were observed in multiple patients, suggesting an additive specific gain of function. In vitro, EGFR mutants demonstrated enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to inhibition by gefitinib. **Conclusions** A subgroup of patients with non-small-cell lung cancer have specific mutations in the EGFR gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib. **Notice:** To coincide with the online release of similar findings by Science, this article was published at [www.nejm.org](http://www.nejm.org) on April 29, 2004. It will appear in the May 20 issue of the Journal.

**Editorial Comment (TLP):** This is an extremely important discovery that there may be a genetic basis for response to HER-1/EGFR receptor inhibitors, which include Iressa, now marketed, and soon to-be-marketed Tarceva. But there was one patient without this mutation who also responded for some reason. More research, of course, will help explain the various receptors that determine the effectiveness of these important cancer-inhibiting agents.

**Lung Cancer 2004;43:317-322**

**Gefitinib as first-line, compassionate use therapy in patients with advanced non-small-cell lung cancer.**  
**Argiris A, Mittal N.**

Division of Hematology-Oncology, The Feinberg School of Medicine, Northwestern University

**PURPOSE:** To evaluate the efficacy of single-agent gefitinib (Iressa, ZD1839), an oral, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, as first-line compassionate use therapy for advanced non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** Twenty-five patients who were unfit or refused chemotherapy received oral gefitinib 250mg daily as first-line therapy for the treatment of recurrent or metastatic NSCLC in a compassionate use program at a single institution. **RESULTS:** Four of 22 evaluable patients (18%), two with adenocarcinomas and two with bronchioloalveolar carcinomas, had an objective response and five patients (23%) had stable disease. Duration of response or stable disease was 3.5-22+ months. Median time to progression was 2.2 months, median survival was 12.6 months and 1-year survival 52%. The partial response plus stable disease rate by Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 4/5 for PS 0 patients; 3/6 for PS 1-2 patients; and 2/14 for PS 3-4 patients. The two patients with PS > 2 who derived benefit from gefitinib had PS 3 due to co-morbidities. Two patients discontinued therapy due to severe toxicities: one patient had severe liver dysfunction and hemorrhagic cystitis, and another patient developed diarrhea with hypotension. A correlation between rash and antitumor activity was noted. Of seven patients who received chemotherapy subsequent to gefitinib, one had a partial response, three had stable disease, two progressed, and one was non-evaluable for response. **CONCLUSION:** We report encouraging response and survival results with gefitinib as first-line treatment in

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**“A subgroup of patients with non small-cell lung cancer have specific mutations in the EGFR gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib.”**

unselected patients with advanced NSCLC. Gefitinib monotherapy should undergo further evaluation as first-line therapy in advanced NSCLC.

**Editorial Comment (TLP):** It is probably good that gefitinib is now considered as first line therapy for patients with advanced, non-small cell carcinoma, even before failure of chemotherapy as is currently advised. This may well be appropriate strategy in selected patients because of the simplicity of the oral dosing. Of course, finding the patient with a genetic predisposition to response as indicated in the previous abstract would be most important.

“... finding the patient with a genetic predisposition to response as indicated in the previous abstract would be most important.”

**Clin Cancer Res 2004;10:3237-3248**

**Gene expression profiling in non-small cell lung cancer: from molecular mechanisms to clinical application.**

**Petty RD, Nicolson MC, Kerr KM, Collier-Duguid E, Murray GI.**

Department of Oncology, Aberdeen and Oncology Research Group, Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, United Kingdom. r.d.petty@abdn.ac.uk

Non-small cell lung cancer (NSCLC) is the most common cause of premature death from malignant disease in western countries. A better understanding of the molecular mechanisms underlying NSCLC etiology, pathogenesis, and therapeutics will lead to improved clinical outcomes. Recent technological advances in gene expression profiling (in particular, with cDNA and oligonucleotide microarrays) allow the simultaneous analysis of the expression of thousands of genes. In this review, the technology of global gene expression profiling is discussed, and the progress made thus far with it in NSCLC is reviewed. A new molecular classification of NSCLC has been developed, which has provided important insights into etiology and pathogenesis. Other studies have found potential biomarkers for NSCLC that may be of use in diagnosis, screening, and assessing the effectiveness of therapy. Finally, advances have been made in the understanding of the molecular mechanisms of NSCLC progres-

“A new molecular classification of NSCLC has been developed, which has provided important insights into etiology and pathogenesis.”

sion and the molecular mechanisms of action of currently used cytotoxic drugs. This may facilitate the improvement of current therapeutics and the identification of novel targets. Taken together, these advances hold the promise of an improved understanding of the molecular biology of NSCLC and its treatment, which in turn will lead to improved outcomes for this deadly disease.

**Editorial Comment (TLP):** As we learn more about the various molecular and associated biological responses involved in the pathogenesis, growth and dissemination of non small cell lung cancer, we will develop new therapeutic strategies for treatment.

**Cancer Epidemiol Biomarkers Prev. 2003;12(10):987-93**

**Sputum cytological atypia as a predictor of incident lung cancer in a cohort of heavy smokers with airflow obstruction.**

**Prindiville SA, Byers T, Hirsch FR, Franklin WA, Miller YE, Vu KO, Wolf HJ, Baron AE, Shroyer KR, Zeng C, Kennedy TC, Bunn PA.**

Department of Medicine, School of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.

Individuals with cytological atypia in sputum may be at increased risk for lung cancer. We conducted a longitudinal analysis of the association between lung cancer incidence and cytological atypia in sputum samples collected prospectively from an ongoing cohort of adults at high risk for lung cancer. Cohort members had a smoking history of > or = 30 pack-years and chronic obstructive pulmonary disease documented by pulmonary airflow testing. Sputum samples collected at baseline and periodically thereafter were examined by standard cytological methods. From the cohort of 2,006 people, there were 83 incident lung cancers over 4,469 person-years of observation. At baseline, the association between personal and behavioral characteristics, and sputum cytological atypia was assessed by multiple logistic regression. The association between sputum cytological atypia and incident lung cancer was then as-

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“Incident lung cancer was increased among those with moderate or worse cytological atypia (adjusted hazards ratio, 2.8, 95% confidence interval, 1.4-5.5).”

essed by hazard ratios using proportional hazards regression analysis, adjusting for potential confounding factors. Cytological atypia graded as moderate or worse was associated with continuing cigarette smoking (adjusted odds ratio, 2.5; 95% confidence interval, 1.5-4.1), and with lower levels of intake of fruits and vegetables (P for trend = 0.04). Atypia was not associated with several other factors, including the degree of airflow obstruction, the use of vitamin supplements, nonsteroidal anti-inflammatory drugs, or metered-dose steroid inhalers. Incident lung cancer was increased among those with moderate or worse cytological atypia (adjusted hazards ratio, 2.8; 95% confidence interval, 1.4-5.5). This association was not confounded by other risk factors. We conclude that in this high-risk cohort, cytological atypia is associated with continuing smoking and low intake of fruits and vegetables, but that independent of these and other factors, the risk of incident lung cancer is increased among those with moderate or worse grades of cytological atypia in their sputum.

**Editorial Comment (TLP):** This is a very well done study on high risk patients with heavy smoking and airflow obstruction, which is where lung cancer is most commonly found. In fact, atypia is an indicator of the presence of lung cancer in patients with airflow obstruction that is not related to the degree of airflow obstruction. This is extremely important. Thus any degree of airflow obstruction raises the issue of excessive risk in lung cancer.

“... any degree of airflow obstruction raises the issue of excessive risk in lung cancer.”

**Thorax 2004 Mar;59(3):237-41**  
**Screening for lung cancer using low dose CT scanning.**  
**MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW.**

Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland.  
rmacredmond@rcsi.ie

**BACKGROUND:** Lung cancer is the most common cause of cancer related death in Ireland. The majority of lung cancers are inoperable at the time of diagnosis and consequently the overall 5 year survival is less than 10%. The objective of the ProActive Lung Cancer Detection (PALCAD) study was to evaluate whether low dose chest computed tomo-

graphic scanning (LDCCT) can detect early stage asymptomatic lung cancer in a high risk urban population. **METHODS:** Four hundred and forty nine subjects of median age 55 years (range 50-74) with a median pack year smoking history of 45 years (range 10-160), with no previous cancer history and medically fit to undergo thoracic surgery were recruited. After informed consent, LDCCT was performed on all subjects. Non-calcified nodules (NCNs) of  $\geq 10$  mm in diameter were referred for biopsy. Follow up with interval LDCCT at 6, 12 and 24 months to exclude growth was recommended for NCNs  $< 10$  mm in diameter. **RESULTS:** Six (1.3%) NCNs of  $\geq 10$  mm were detected of which one (0.23%) had non-small cell lung cancer stage 1; 145 NCNs of  $< 10$  mm were detected in 87 (19.4%) subjects. Mediastinal masses were detected in three subjects (0.7%)-one small cell lung cancer and two benign duplication cysts. Incidental pathology was noted in 276 patients (61.5%), most commonly emphysema and coronary artery calcification. **CONCLUSION:** The prevalence of resectable lung cancer detected by LDCCT at baseline screening was low at 0.23%, but there was a high rate of significant incidental pathology.

**Editorial Comment (TLP):** CT scanning will continue to emerge as the way to find tiny peripheral lesions, which are commonly adenocarcinomas. The resection of these early cancers results in a very good outcome. (See Kato abstract later in this issue.)

#### Lung Cancer 2004;44:61-68

**Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection.**

**Nakamura H, Saji H, Ogata A, Saijo T, Okada S, Kato H.**

Department of Surgery, Tokyo Medical University Hospital, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Small lung cancers frequently have been detected in mass screening by computed tomography (CT) in recent years. Suitability of limited resection for these small lung cancers remains controversial. One hundred patients who underwent sublobular limited resection (wedge resection or segmentectomy) for lung cancer in our hospital from 1981 to 2002 were analyzed retrospectively. From CT findings, tumors were classified into two groups; pure ground-glass opacity (PGGO) and non-PGGO. Patients included 44 women and 56

“The objective of the ProActive Lung Cancer Detection (PALCAD) study was to evaluate whether low dose chest computed tomographic scanning (LDCCT) can detect early stage asymptomatic lung cancer in a high risk urban population.”

**“Overall and lung cancer specific 5-year survival rates in all patients were 58.0 and 64.8% respectively.”**

men, and ages ranged from 40 to 92 years (mean, 71.0). Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. Clinical stages included 83 stage IA and 17 stage IB. By high-resolution CT, 27 tumors (27%) showed PGGO; at postoperative histopathologic examination, all of these were localized bronchioloalveolar carcinomas. Diameter of tumors showing PGGO was 9.3+/-mm (mean +/- S.D.); that of non-PGGO tumors was 21.2+/-13.7 mm. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0 and 64.8%, respectively. Overall 5-year survival rate with small adenocarcinomas (<or=20mm) was 93.7%, significantly better than 24.8% with larger adenocarcinomas ( P<0.0001 ). No intrathoracic recurrence or distant metastasis has been observed in PGGO tumors. For peripheral localized bronchioloalveolar carcinoma showing PGGO, wedge resection appears to be the best operation. Definitive study of more patients with longer follow-up is needed.

**Editorial Comment (TLP):** A number of patients with ground-glass opacities identified by CT are localized alveolar cell carcinoma. Apparently wedge resection is gaining popularity, at least in Japan for this early lesion which might, in fact, be considered a curative operation.

**Lung Cancer 2004;44:175-181**

**FDG-PET in staging lung cancer; How does it change the algorithm?**

**Verhagen AF, Bootsma GP, Tjan-Heijnen VC, Van Der Wilt GJ, Cox AL, Brouwer MH, Corstens FH, Oyen WJ.**

Department of Cardio-thoracic surgery (414), University Medical Center Nijmegen, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands.

Background: In patients with lung cancer, positron emission tomography (PET) using fluor-18-fluorodesoxyglucose (FDG) may be used both to detect extrathoracic metastases (ETM) and for mediastinal lymph node staging (MLS), potentially reducing the need for mediastinoscopy. We assessed the added value of FDG-PET in detecting ETM and focused on the reliability of FDG-PET and mediastinoscopy for MLS. Patients and methods: In 72 consecutive

**“We assessed the added value of FDG-PET in detecting ETM and focused on the reliability of FDG-PET and mediastinoscopy . . .”**

patients with non-small cell lung cancer, the impact of adding FDG-PET to full conventional clinical staging was prospectively analyzed. The predictive value of FDG-PET findings and tumor location for pathologic mediastinal lymph node status were assessed in a logistic regression analysis. Results: Unexpected extrathoracic metastases were detected by FDG-PET in 15% of patients. In MLS overall negative and positive predictive values were 71 and 83% for FDG-PET, and 92 and 100% for mediastinoscopy. However, the negative predictive value of FDG-PET was only 17% in case of FDG-PET positive N1 nodes and/or a centrally located primary tumor, whereas it was 96% in case of FDG-PET negative N1 nodes and a non-centrally located primary tumor. Conclusion: By incorporating FDG-PET in clinical staging, 15% of patients with lung cancer are upstaged due to unexpected extrathoracic metastases. In case of a negative mediastinal FDG-PET, mediastinoscopy can only be omitted in the presence of a non-centrally located primary tumor and without FDG-PET positive N1 nodes.

**Editorial Comment (TLP):** This is a study in a large number of consecutive patients with dual imaging of FDG-PET scanning. Major findings are unexpected extrathoracic metastasis detected by this technique. But the negative predictive value was small and scanning resulted in the considerable upstaging of lung cancer, but did not omit mediastinoscopy. Histology is still needed in cases where there is doubt, in spite of the results of imaging.

**BJM. 2004 Jan 10;328(7431):72**

**Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982-8.**

**Harris JE, Thun MJ, Mondul AM, Calle EE.**

Department of Economics, Massachusetts Institute of Technology, Cambridge, MA 02139

OBJECTIVE: To assess the risk of lung cancer in smokers of medium tar filter cigarettes compared with smokers of low tar and very low tar filter cigarettes. DESIGN: Analysis of the association between the tar rating of the brand of cigarette smoked in 1982 and mortality from lung cancer over

**“We report the patterns of ETS exposure history in a clinical cohort of women with newly diagnosed lung cancer.”**

**“Irrespective of the tar level of their current brand, all current smokers had a far greater risk of lung cancer than people who had stopped smoking or had never smoked.”**

**“Over 95% of women with lung cancer in our study were exposed to tobacco smoke through a personal smoking History or ETS.”**

the next six years. Multivariate proportional hazards analyses used to assess hazard ratios, with adjustment for age at enrollment, race, educational level, marital status, blue collar employment, occupational exposure to asbestos, intake of vegetables, citrus fruits, and vitamins, and, in analyses of current and former smokers, for age when they started to smoke and number of cigarettes smoked per day. SETTING: Cancer prevention study II (CPS-II). PARTICIPANTS: 364 239 men and 576 535 women, aged > or = 30 years, who had either never smoked, were former smokers, or were currently smoking a specific brand of cigarette when they were enrolled in the cancer prevention study. MAIN OUTCOME MEASURE: Death from primary cancer of the lung among participants who had never smoked, former smokers, smokers of very low tar (< or = 7 mg tar/cigarette) filter, low tar (8-14 mg) filter, high tar (> or = 22 mg) non-filter brands and medium tar conventional filter brands (15-21 mg). RESULTS: Irrespective of the tar level of their current brand, all current smokers had a far greater risk of lung cancer than people who had stopped smoking or had never smoked. Compared with smokers of medium tar (15-21 mg) filter cigarettes, risk was higher among men and women who smoked high tar (> or = 22 mg) non-filter brands (hazard ratio 1.44, 95% confidence interval 1.20 to 1.73, and 1.64, 1.26 to 2.15, respectively). There was no difference in risk among men who smoked brands rated as very low tar (1.17, 0.95 to 1.45) or low tar (1.02, 0.90 to 1.16) compared with those who smoked medium tar brands. The same was seen for women (0.98, 0.80 to 1.21, and 0.95, 0.82 to 1.11, respectively). CONCLUSION: The increase in lung cancer risk is similar in people who smoke medium tar cigarettes (15-21 mg), low tar cigarettes (8-14 mg), or very low tar cigarettes (< or = 7 mg). Men and women who smoke non-filtered cigarettes with tar ratings > or = 22 mg have an even higher risk of lung cancer.

**Editorial Comment (TLP):** It has been well known for a long time that there is no safe cigarette. Cigarettes with low tar and nicotine are not safe. However, the highest tar-containing cigarettes that are not filtered are the most damaging and create a greater risk of lung cancer and COPD, amongst the other smoking-related diseases.

**Lung Cancer 2004 Feb;43(2):127-34**  
**Environmental tobacco smoke exposure in women with lung cancer.**

**de Andrade M, Ebbert JO, Wampfler JA, Miller DL, Marks RS, Croghan GA, Jatoi A,**

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**BACKGROUND:** Investigations on environmental tobacco smoke (ETS) exposure that include source intensity, childhood exposure, and association with histologic subtypes among never smoking lung cancer cases are limited. We report the patterns of ETS exposure history in a clinical cohort of women with newly diagnosed lung cancer. **METHODS:** From 1997 to 2001, 810 women with lung cancer were interviewed to obtain data including the source, intensity, and duration of ETS exposure. In this descriptive study, relationships between smoking history, ETS exposure, and lung cancer histologic subtypes were analyzed. **RESULTS:** Among the 810 patients, 773 (95.4%) reported personal smoking or ETS exposure including 170 of 207 (82%) never smokers. Among the never smokers with a history of ETS exposure, the mean years of exposure were 27 from a smoking spouse, 19 from parents, and 15 from co-workers. For each major subtype of lung cancer (adenocarcinoma, squamous cell, unclassified non-small cell lung cancer, small cell, or carcinoids) among never smokers, 75-100% of patients had ETS exposure. Trends for adenocarcinoma, squamous, and small cell carcinoma are statistically significant using the Cochran-Armitage Test for Trend ( $P < 0.001$ ) among never smokers without ETS exposure, never smokers with ETS exposure, former smokers, and current smokers. **CONCLUSIONS:** Over 95% of women with lung cancer in our study were exposed to tobacco smoke through a personal smoking history or ETS. The cumulative amount of tobacco smoke exposure may be significantly underestimated if only personal smoking history is considered. Our results add to the public health implications of exposure to tobacco smoke and highlight the importance of eliminating tobacco smoking in public and private settings.

**Tob Control 2004 Mar;13 Suppl 1:148-56**

**Carcinogen derived biomarkers: applications in studies of human exposure to secondhand tobacco smoke.**  
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“These biomarkers are specifically related to known carcinogens in tobacco smoke and include urinary metabolites, DNA adducts, and blood protein adducts.”

**OBJECTIVE:** To review the literature on carcinogen derived biomarkers of exposure to secondhand tobacco smoke (SHS). These biomarkers are specifically related to known carcinogens in tobacco smoke and include urinary metabolites, DNA adducts, and blood protein adducts. **METHOD:** Published reviews and the current literature were searched for relevant articles. **RESULTS:** The most consistently elevated biomarker in people exposed to SHS was 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (NNAL-Gluc), urinary metabolites of the tobacco specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The tobacco specificity of this biomarker as well as its clear relation to an established lung carcinogen are particularly appropriate for its application in studies of SHS exposure. **CONCLUSION:** The results of the available carcinogen derived biomarker studies provide biochemical data which support the conclusion, based on epidemiologic investigations, that SHS causes lung cancer in non-smokers.

**Editorial Comment (TLP):** The above two abstracts provide additional evidence about the epidemiology and biochemical factors that are risks for lung cancer in nonsmokers who inhale environmental tobacco smoke. Thus a continued large body of evidence implicating secondhand smoking is emerging. Fortunately, reason and political will are gradually leading to an elimination of smoking in public arenas in most of the United States. This needs to become standardized throughout our 50 states and elsewhere in the world.

**Thorax 2003 Dec;58(12):1071-6**

**Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. Nafstad P, Haheim LL, Oftedal B, Gram F, Holme I, Hjermann I, Leren P.**

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**BACKGROUND:** The well documented urban/rural difference in lung cancer incidence and the detection of known carcinogens in the atmosphere have produced the hypothesis that long term air pollution may have an effect on lung cancer. The association between incidence of lung cancer and long term air pollution exposure was investigated in a cohort of Oslo men fol-

lowed from 1972/73 to 1998. **METHODS:** Data from a follow up study on cardiovascular risk factors among 16 209 40 to 49 year old Oslo men in 1972/73 were linked to data from the Norwegian cancer register, the Norwegian death register, and estimates of average yearly air pollution levels at the participants' home address in 1974 to 1998. Survival analyses, including Cox proportional hazards regression, were used to estimate associations between exposure and the incidence of lung cancer. **RESULTS:** During the follow up period, 418 men developed lung cancer. Controlling for age, smoking habits, and length of education, the adjusted risk ratio for developing lung cancer was 1.08 (95% confidence interval, 1.02 to 1.15) for a 10 micro g/m(3) increase in average home address nitrogen oxide (NO(x)) exposure between 1974 and 1978. Corresponding figures for a 10 micro g/m(3) increase in sulphur dioxide (SO(2)) were 1.01 (0.94 to 1.08). **CONCLUSIONS:** Urban air pollution may increase the risk of developing lung cancer.

**Editorial Comment (TLP):** Open air pollution has long been considered a risk factor in lung cancer. This present study adds additional evidence of the relationship. Thus inhaling clean air in both the personal and ambient environments is of great importance.

**NEJM 2004;350:1777-9**  
**A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung.**

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**BACKGROUND:** In a previous phase 3 trial of adjuvant chemotherapy after resection of non-small-cell lung cancer, a combination of uracil and tegafur (often referred to as UFT) taken orally was shown to prolong survival. A subgroup analysis disclosed that most patients who benefited had pathological stage I adenocarcinoma. **METHODS:** We randomly assigned patients with completely resected pathological stage I adenocarcinoma of the lung to receive either oral uracil-tegafur (250 mg of tegafur per square meter of body-surface area per day) for two years or no

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“We randomly assigned patients with completely resected pathological stage I adenocarcinoma of the lung to receive either oral uracil-tegafur (250 mg of tegafur per square meter of body-surface area per day) for two years or no treatment.”

“Adjuvant chemotherapy with uracil-tegafur improves survival among patients with completely resected pathological stage I adenocarcinoma of the lung.”

treatment. Randomization was performed with stratification according to the pathological tumor category (T1 vs. T2), sex, and age. The primary end point was overall survival. RESULTS: From January 1994 through March 1997, 999 patients were enrolled. Twenty patients were found to be ineligible and were excluded from the analysis after randomization; 491 patients were assigned to receive uracil-tegafur and 488 were assigned to observation. The median duration of follow-up for surviving patients was 73 months. The difference in overall survival between the two groups was statistically significant in favor of the uracil-tegafur group ( $P=0.04$  by a stratified log-rank test). Grade 3 toxic effects occurred in 10 of the 482 patients (2 percent) who actually received uracil-tegafur. CONCLUSIONS: Adjuvant chemotherapy with uracil-tegafur improves survival among patients with completely resected pathological stage I adenocarcinoma of the lung. Copyright 2004 Massachusetts Medical Society

**Editorial Comment (TLP):** This is an important study that shows that an oral preparation, uracil-tegafur can improve overall survival in Stage I adenocarcinoma of the lung that is resected. What is not explained in this study is the number and source of the patients that received resectional therapy and how they were diagnosed in early stages of disease. Presumably this was by CT scanning, which, along with sputum cytology, is the standard for care for all smokers over age 45 in Japan. This is the second study to appear this year on adjuvant chemotherapy in patients completely resected with non-small cell carcinoma. (See LCF 18, page 11, for: Arriagada R, Berman B, Dunant A, et al of the International Adjuvant Lung Cancer Trial Collaborative Group, Santiago, Chile: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-360) This earlier study, however, dealt largely with more advanced stages of disease (39.9 were Stage III). It is highly likely that use of adjuvant therapy in earlier stages of disease promises to be more successful, as concluded from this cited abstract.

**Thorax 2004;59:89-90**

**An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages.**

**de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P; European Community Respiratory Health Survey**

## Study Group.

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**BACKGROUND:** The recently published GOLD guidelines provide a new system for staging chronic obstructive pulmonary disease (COPD) from mild (stage I) to very severe (stage IV) and introduce a stage 0 (chronic cough and phlegm without airflow obstruction) that includes subjects "at risk" of developing the disease. **METHODS:** In order to assess the prevalence of GOLD stages of COPD in high income countries and to evaluate their association with the known risk factors for airflow obstruction, data from the European Community Respiratory Health Survey on more than 18,000 young adults (20-44 years) were analysed. **RESULTS:** The overall prevalence was 11.8% (95% CI 11.3 to 12.3) for stage 0, 2.5% (95% CI 2.2 to 2.7) for stage I, and 1.1% (95% CI 1.0 to 1.3) for stages II-III. Moderate to heavy smoking ( $\geq 15$  pack years) was significantly associated with both stage 0 (relative risk ratio (RRR)=4.15; 95% CI 3.55 to 4.84) and stages I+ (RRR=4.09; 95% CI 3.17 to 5.26), while subjects with stages I+ COPD had a higher likelihood of giving up smoking (RRR=1.39; 95% CI 1.04 to 1.86) than those with GOLD stage 0 (RRR=1.05; 95% CI 0.86 to 1.27). Environmental tobacco smoke had the same degree of positive association in both groups. Respiratory infections in childhood and low socioeconomic class were significantly and homogeneously associated with both groups, whereas occupational exposure was significantly associated only with stage 0. All the GOLD stages showed a significantly higher percentage of healthcare resource users than healthy subjects ( $p<0.001$ ), with no difference between stage 0 and COPD. **CONCLUSIONS:** A considerable percentage of young adults already suffered from COPD. GOLD stage 0 was characterised by the presence of the same risk factors as COPD and by the same high demand for medical assistance.

**Editorial Comment (TLP):** It is highly interesting that GOLD criteria identifies a significant number of young people with symptomatic stages of stage disease, but without any evidence of airflow obstruction. Here is where smoking cessation should be focused with greatest intensity. Providing symptomatic relief with long-acting bronchodilators may also be useful.

“The recently published GOLD guidelines provide a new system for staging chronic obstructive pulmonary disease (COPD) from mild (stage I) to very severe (stage IV) and introduce a stage 0 (chronic cough and phlegm without airflow construction) that includes subjects ‘at risk’ of developing the disease.”