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NUMBER The Forum for Early Diagnosis and Treatment of Lung Cancer

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LUNG CANCER FRONTIERS

Comments may be submitted to:
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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 .

SPIROMETRY NOW HIGH PRIORITY

On July 7, The National Committee for Quality Assurance (NCQA) released specifications for the 2006 edition of its Health Plan Employer Data and Information Set (HEDIS), adding five new measures to the tool that defines how health care quality is measured in certain key areas of patient care. Top on the list was the use of spirometry in the diagnosis and assessment of Chronic Obstructive Pulmonary Disease, the fourth leading cause of death in the USA. This really puts spirometry on the front burner, and almost demands that clinicians use this most valuable tool in their practices. *LCF* has reported many times on the use of spirometry in the stratification of risk of lung cancer, which can be a powerful tool in case finding in asymptomatic lung cancer (Bechtel, et al: Chest 2005;127:1140-1145).

LAWSUIT LOST BECAUSE SPIROMETRY NOT DONE

Your editor recently was involved in the defense of a board certified pulmonologist who had failed to use spirometry in the monitoring of numerous high doses of corticosteroids for exacerbations of asthma, in a severe and life long asthmatic who had had needs for emergency room care and hospitalizations in the past. As a heavy smoker in his 40s and because of his life long asthma, he also

FEEDBACK NEEDED

THIS JULY ISSUE OF LCF IS THE THIRD OF FOUR QUARTERLY ISSUES PLANNED FOR 2005. WE NEED TO HEAR FROM YOU ABOUT YOUR SATISFACTION WITH OUR ELECTRONIC VERSION OF LCF.

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SIR RICHARD DOLL 1912—2005

Sir Richard Doll died this month at age 92. Sentinel work on the epidemiology that led to the seminal 1950 study, which he wrote with Sir Austin Bradford Hill, identified smoking as the major cause of lung cancer.[1-3] *In his original research, he interviewed over 700 lung cancer patients and identified the common thread that clearly linked lung cancer to the smoking habit. It was during this study that he gave up smoking. Doll remained active throughout his entire productive life and published a follow-up of his findings as recently as 2004.*[4] *Richard Doll is credited with preventing the premature deaths of millions of people worldwide, as a direct result of his research. He also is credited for being the godfather for the health movement against tobacco and its effects. Pioneers such as Sir Richard Doll are never forgotten.*

Doll R, Hill AB: A study of the etiology of carcinoma of the lung. Er Med J 1952;2:1271.

Doll R, Peto R: Mortality in relation to smoking 20 years: observations on average smokers. Er Med J 1976;2:1525.

Doll R: Hemispheric pollution and lung cancer. Environ Health Prospective 1978;22:23.

Doll R, Peto R, Boreham J, et al: Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519.

Continued from Page 1

After he developed aseptic necrosis of both femoral heads requiring hip replacement, he sued, for the inappropriate use of steroids . . .

. . . he never once did spirometry in 25 office visits over several years!

had a major degree of fixed airways disease, yet he still showed significant response to both steroids and bronchodilators. After he developed aseptic necrosis of both femoral heads requiring hip replacement, he sued, for the inappropriate use of steroids in his COPD. Asthma was the correct diagnosis, but his lawyer was clever and convincing in court that the doctor had practiced substandard care, because he never once did spirometry in 25 office visits over several years! The case was lost on the failure to do what all physicians should do in their practices, i.e., offer state of the art care. The National Lung Health Education Program published a consensus statement about the use of spirometry for health assessment in adults, recommending spirometry in all current and former smokers age 45 or older, and in anyone with chronic cough, dyspnea on exertion, mucus hypersecretion, or wheeze (Ferguson, et al: Chest 2000; 45: 1146-1161). Had the doctor followed this advice or just used common sense, he would not have lost a large lawsuit.

MISCELLANEOUS ABSTRACTS:

1.

Relationship between pulmonary function and lung cancer surgical outcome

T. Win, A. Jackson, L. Sharples, et al. Eur Respir J 2005;25:594-599

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. . . the relationship between pulmonary function test results and surgical outcome were studied prospectively in a large cohort of lung cancer patients.

Lung function values expressed as a percentage of the predicted value are more useful predictors of post operative outcome than absolute values.

The British Thoracic Society and American College of Chest Physician guidelines outline criteria for investigating patients for lung cancer surgery. However, the guidelines are based on relatively old studies. Therefore, the relationship between pulmonary function test results and surgical outcome were studied prospectively in a large cohort of lung cancer patients. From January 2001 to December 2003, 110 patients underwent surgery for lung cancer. All underwent full lung function testing in order to predict post-operative lung function. The hospital mortality rate was 3% and major complication rate 22%. There was poor overall outcome in 13%. Mean pre-operative lung function values were: forced expiratory volume in one second (FEV1) 2.0 L (79.4% of the predicted value), and carbon monoxide diffusing capacity of the lung (D(L,CO)) 73.6% pred. The mean post-operative lung function values were: FEV1 1.4 L (55.6% pred), and D(L,CO) 51.3% pred. All lung function values were better predictors of poor surgical outcome when expressed as a percentage of the predicted value. Using a threshold of pre-operative FEV1 of 47% pred resulted in the most useful positive and negative predictive probabilities, 0.90 and 0.67, respectively. Lung function values expressed as a percentage of the predicted value are more useful predictors of post-operative outcome than absolute values. The threshold of predicted forced expiratory volume in one second for surgical intervention could be lower (45-50% pred) than is currently accepted without increased mortality.

Editorial Comment (TLP):
It amazes me that simple lung function tests such as spirometry are only recently catching on. See lead story. Surgeons have long known that poor ability to walk two flights of stairs are related to poor outcome. In fact, many in the past recom-

mended pre-operative spirometry assessment. Only in recent years have we "rediscovered the wheel" in establishing the need for spirometry and other pulmonary function tests in the pre-operative workup of patients who are surgical candidates for lung cancer resection.

2.
Early lung cancer detection using spiral computed tomography and positron emission tomography.
Bastarrika G, Carcia-Velloso MJ, Lozano MD, et al. Am J Respir Crit Care Med 2005;171:1378-1383.

Rationale: Lung cancer screening using computed tomography (CT) is effective in detecting lung cancer in early stages.

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The sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for the diagnosis of malignancy were 69, 91, 90 and 71%.

Rationale: Lung cancer screening using computed tomography (CT) is effective in detecting lung cancer in early stages. Concerns regarding false-positive rates and unnecessary invasive procedures have been raised. Objective: To study the efficiency of a lung cancer protocol using spiral CT and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET). Methods: High-risk individuals underwent screening with annual spiral CTs. Follow-up CTs were done for noncalcified nodules of 5 mm or greater, and FDG-PET was done for nodules 10 mm or larger or smaller (> 7 mm), growing nodules. Results: A total of 911 individuals completed a baseline CT study and 424 had at least one annual follow-up study. Of the former, 14% had noncalcified nodules of 5 mm or larger, and 3.6% had nodules of 10 mm or larger. Eleven non-small cell lung cancers (NSCLC) and one small cell lung cancer (SCLC) were diagnosed in the baseline study (prevalence rate, 1.32%), and two NSCLCs in the annual study (incidence rate, 0.47%). All NSCLCs (92% of prevalence cancers) were diagnosed in stage I (12 stage IA, 1 stage IB). FDG-PET was helpful for the correct diagnosis in 19 of 25 indeterminate nodules. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for the diagnosis of malignancy were 69, 91, 90, and 71%, respectively. However, the sensitivity and negative predictive value of the screening algorithm, which included a 3-month follow-up CT for nodules with a negative FDG-PET, was 100%. Conclusion: A protocol for early lung cancer detection using spiral CT and FDG-PET is useful and may minimize unnecessary invasive procedures for benign lesions.

Editorial Comment (TLP):
The evolution of technology through the wedding of CT and FDT-PET scanning is now helping to assess the indeterminate nodules and correctly identify those that are benign.

3.
CT scanning for lung cancer: five-year prospective experience
Swenson SJ, Jett JR, Hartman TE, et al. Radiology 2005;235:259-265.

Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. swensen.stephen@mayo.edu

PURPOSE: To report results of a 5-year prospective low-dose helical chest computed tomographic (CT) study of a cohort at high risk for lung

cancer. MATERIALS AND METHODS: After informed written consent was obtained, 1520 individuals were enrolled. Protocol was approved by institutional review board and National Cancer Institute and was compliant with Health Insurance Portability and Accountability Act, or HIPAA. Participants were aged 50 years and older and had smoked for more than 20 pack-years. Participants underwent five annual (one initial and four subsequent) CT examinations. A significant downward shift was evaluated in non-small cell lung cancers detected initially from advanced stage down to stage I by using a one-sided binomial test of proportions. Poisson regression and Fisher exact tests were used for comparisons with Mayo Lung Project. RESULTS: In 788 (52%) men and 732 (48%) women, 61% (927 of 1520) were current smokers, and 39% were former smokers. After five annual CT examinations, 3356 uncalcified lung nodules were identified in 1118 (74%) participants. Sixty-eight lung cancers were diagnosed (31 initial, 34 subsequent, three interval cancers) in 66 participants. Twenty-eight subsequent cases of non-small cell cancers were detected, of which 17 (61%; 95% confidence interval: 41%, 79%) were stage I tumors. Diameter of cancers detected subsequently was 5-50 mm (mean, 14.4 mm; median, 10.0 mm). Analysis for a more than 50% shift in proportion of stage I non-small cell cancer detection did not show statistical significance. Forty-eight participants died of various causes since enrollment. Lung cancer mortality rate for incidence portion of trial was 1.6 per 1000 person-years. There was no significant difference in lung cancer mortality rates of cancers detected in subsequent examinations between this trial and Mayo Lung Project after separation of participants into subsets (2.8 vs 2.0 per 1000 person-years, P = .43). CONCLUSION: CT allows detection of early-stage lung cancers. Benign nodule detection rate is high. Results suggest no stage shift. (c) RSNA, 2005.

Participants were aged 50 years and older and had smoked for more than 20 pack-years.

Sixty-eight lung cancers were diagnosed (31 initial, 34 subsequent, three interval cancers) in 66 participants.

Forty-eight participants died of various causes since enrollment.

Editorial Comment (TLP):
It is surprising that there appear to be no stage shift in the early diagnosis of lung cancer in this study. This is what we are striving for in finding in our early detection efforts. Of course, there will be lots of benign nodules in the Midwest where this study was done. Strategies of followup and the use of PET scanning may help eliminate unnecessary surgery for these patients.

4.
Risk of lung cancer among white and black relatives of individuals with early-onset lung cancer
Cote ML, Kardia SL, Wenzlaff AS, et al. JAMA 2005;293;3036-3042

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CONTEXT: Evidence exists that lung cancer aggregates in families and recent findings of a chromosomal region linked to lung cancer susceptibility support a genetic component to risk. Family studies of early-onset lung cancer patients offer a unique opportunity to evaluate lifetime risk of lung cancer in relatives. OBJECTIVE: To measure lung cancer aggregation and

Family studies of early-onset lung cancer patients offer a unique opportunity to evaluate lifetime risk of lung cancer in relatives.

estimate lifetime risk among relatives of early-onset cases and population-based controls. DESIGN AND SETTING: Familial aggregation and cumulative risk estimates from interview data of incident cases and concurrently ascertained controls between 1990 and 2003 in metropolitan Detroit, Mich. PARTICIPANTS: The study included 7576 biological mothers, fathers, and siblings of 692 early-onset cases and 773 frequency-matched controls. One third of the population was black. MAIN OUTCOME MEASURES: Cumulative lifetime risk of lung cancer, stratified by race and smoking behavior in relatives of early-onset cases and controls. RESULTS: Smokers with a family history of early-onset lung cancer in a first-degree relative had a higher risk of developing lung cancer with increasing age than smokers without a family history. An increase in risk occurs after age 60 years in these individuals, with 17.1% (SE 2.4%) of white case relatives and 25.1% (SE 5.8%) of black case relatives diagnosed with lung cancer by age 70 years. Relatives of black cases were at statistically significant increased risk of lung cancer compared with relatives of white cases (odds ratio, 2.07, 95% confidence interval, 1.29-3.32) after adjusting for age, sex, pack-years, pneumonia, and chronic obstructive lung disease. CONCLUSIONS: First-degree relatives of black individuals with early-onset lung cancer have greater risk of lung cancer than their white counterparts, and these risks are further amplified by cigarette smoking. These data provide estimates of lung cancer risk that can be used to offer counseling to family members of patients with early-onset lung cancer.

Smokers with a family history of early-onset lung cancer in a first-degree relative had a higher risk of developing lung cancer with increasing age than smokers without a family history.

A study was undertaken to explore the pathway to diagnosis among a group of patients recently diagnosed with lung cancer.

Editorial Comment (TLP):
The familial risk for lung cancer has been established by many authors who have previously commented in earlier items in *Lung Cancer Frontiers*. This adds one more factor in the estimation of risk.

5.

Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis.

Corner J, Hopkinson J, Fitzsimmons D, et al. **Thorax 2005;60:268-269**

School of Nursing and Midwifery, University of Southampton, Highfield, Southampton SO17 1BJ, UK. jlc@soton.ac.uk

BACKGROUND: A study was undertaken to explore the pathway to diagnosis among a group of patients recently diagnosed with lung cancer. METHODS: A directed interview study triangulating patients' accounts with hospital and GP records was performed with 22 men and women recently diagnosed with lung cancer at two cancer centres in the south and north of England. The main outcome measures were the symptoms leading up to a diagnosis of lung cancer and patient and GP responses before diagnosis. RESULTS: Patients recalled having new symptoms for many months, typically over the year before their diagnosis, irrespective of their disease stage once diagnosed. Chest symptoms (cough, breathing changes, and pain in the chest) were common, as were systemic symptoms (fatigue/lethargy, weight loss and eating changes). Although symptoms were reported as being marked changes in health, these were not in the main (with the exception of haemoptysis) interpreted as serious by patients at the time and not acted on. Once the

trigger for action occurred (the event that took patients to their GP or elsewhere in the healthcare system), events were relatively speedy and were faster for patients who presented via their GP than via other routes. Patients' beliefs about health changes that may indicate lung cancer appeared to have played a part in delay in diagnosis. CONCLUSION: Further investigation of the factors influencing the timing of diagnosis in lung cancer is warranted since it appears that patients did not readily attend GP surgeries with symptoms. Insight into patients' perspectives on their experience before diagnosis may help medical carers to recognise patients with lung cancer more easily so that they can refer them for diagnosis and treatment. Encouragement to present early with signs of lung cancer should be considered alongside other efforts to speed up diagnosis and treatment.

Patients' beliefs about health changes that may indicate lung cancer appeared to have played a part in delay in diagnosis.

Editorial Comment (TLP):
When we wait until symptoms lead to the diagnosis of lung cancer, we will make little progress for obvious reasons. Most symptomatic lung cancers are in advanced stages of disease and not operable for cure. Stratification of risk should include smoking history, family history, occupational risk history, as well as the presence of airflow obstruction as previously commented upon at length in *Lung Cancer Frontiers*' previous issues.

Encouragement to present early with signs of lung cancer should be considered alongside other efforts to speed up diagnosis and treatment.

6.
Effective detection of bronchial preinvasive lesions by a new autofluorescence imaging broncho videoscope system.
Chiyo M, Shibuya K, Hoshino H, et al. Lung Cancer 2005;48:307-313

A new autofluorescence imaging bronchovideoscope system (AFI) comprises three signals . . . ."

Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan.

Autofluorescence bronchoscopy is an important tool for the early detection of preinvasive bronchial lesions. However, autofluorescence bronchoscopy has difficulty distinguishing between preinvasive lesions and other benign epithelial changes. A new autofluorescence imaging bronchovideoscope system (AFI) comprises three signals, including an autofluorescence (460-690 nm) on excitation blue light (395-445 nm) and two different bands of reflected light: G' (550 nm) and R' (610 nm). We hypothesized that color analyses of these three wave lengths would improve our ability to differentiate between inflammation and preinvasive lesions. In order to prove this hypothesis and to evaluate the efficacy of AFI for detecting preinvasive lesions, we conducted a prospective study. A total of 32 patients with suspected or known lung cancer were entered into this study. Conventional white light bronchovideoscopy (WLB) and light induced fluorescence endoscopy (LIFE) were performed prior to using AFI. WLB and LIFE detected 62 lesions, including lung cancers (n=2), squamous dysplasias (n=30), and bronchitis (n=30). By utilizing AFI, 24 dysplasias and 2 cancer lesions were magenta in color, while 25 bronchitis lesions were blue. The sensitivities of detecting dysplasia by LIFE and AFI were 96.7% and 80%, respectively. The specificity of AFI (83.3%) was significantly higher than that of LIFE (36.6%) (p=0.0005). We conclude that AFI appears to represent a significant advance in distinguishing preinvasive and malignant lesions from bronchitis or hyperplasia under circumstances where LIFE would identify these all as abnormal lesions.

The specificity of AFI (83.3%) was significantly higher than that of LIFE (36.6%) (p=0.0005).

Editorial Comment (TLP): Autofluorescence bronchoscopy is emerging as an important tool in the diagnosis and evaluation of early and preinvasive intrabronchial lesions of the major airways. This new technology using a bronchovideoscope system and three wave lengths rather than two, appears to be an improvement in distinguishing preinvasive lesions. Therapies for preinvasive lesions might well offer tissue sparing oblation therapy, using a variety of technologies including photodynamic therapy, thermal oblation and brachytherapy.

To our knowledge, the consequences of such self-directed supplementation have not been examined previously in non-small cell lung cancer (NSCLC) patients.

7.
Is voluntary vitamin and mineral supplementation associated with better outcome in non-small cell lung cancer patients? Results from the Mayo Clinic lung cancer cohort.
Jatoi A, Williams B, Nichols F, et al.
Department of Oncology, Mayo Clinic, Rochester, MN 55905, USA.

Seven hundred and fourteen were vitamin/mineral users of either multivitamins or other specific vitamin/mineral supplements, and the rest non-users.

BACKGROUND: Some previous studies report that 80% of cancer patients take multivitamin and/or mineral supplements. To our knowledge, the consequences of such self-directed supplementation have not been examined previously in non-small cell lung cancer (NSCLC) patients. The goal of this study was to determine whether vitamin/mineral supplementation is associated with improved survival and quality of life in a cohort of NSCLC patients. METHODS: NSCLC patients or their proxies who responded to a questionnaire on vitamin/mineral use were assessed for survival and quality of life. RESULTS: A total of 1129 patients or their proxies responded to a vitamin/mineral questionnaire. Seven hundred and fourteen were vitamin/mineral users of either multivitamins or other specific vitamin/mineral supplements, and the rest non-users. Median survival was 4.3 years versus 2.0 years for vitamin/mineral users and non-users, respectively. A Cox proportional hazards model showed a relative risk of death of 0.74 (95% confidence interval (CI): 0.44, 0.65) ($p < 0.01$) in favor of vitamin/mineral use after adjustment for multiple prognostic factors, including tumor stage. The Lung Cancer Symptom Scale (LCSS) showed better quality of life among vitamin/mineral users (mean difference in score of 3 (95% CI: 0.8, 5.1) ($p < 0.01$); and after adjusting for related variables, there remained a trend in favor of vitamin/mineral use mean difference 1.8 (95% CI: 0.2, 3.9) ($p = 0.08$). CONCLUSIONS: Vitamin/mineral supplementation is associated with better survival and quality of life in this cohort of NSCLC patients. Future prospective clinical trials should focus on the role of such supplements in patients with NSCLC.

Editorial Comment (TLP): Although this is a study based upon questionnaires, a large number of patients were enrolled. Even though the beta-carotene and alpha-tocopherol, studies showed an increase in the prevalence of lung cancer (N Engl J Med 1994;330:1029-1035) use of multiple vitamin and mineral supplements might still be valuable.

8.
Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer

justify prophylactic cranial irradiation or early detection?
Carolan H, Sun AY, Bezjak A, et al. Lung Cancer 2005;49:109-115.
Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, University of Toronto, Toronto, Canada M5G 2M9.

OBJECTIVE: The radical treatment of locally advanced non-small cell lung cancer (LA-NSCLC) currently involves combined modality therapy (CMT) with the use of chemotherapy in addition to radiation therapy and/or surgery. Chemotherapy has been shown to improve survival, but does not alter brain relapse. We reviewed the outcomes of Stage IIIA and IIIB LA-NSCLC patients treated with CMT at our institution. We assessed the incidence of brain metastases and the management and outcome of these patients. METHODS: Using our radiation-planning database (RSTS), we identified 230 consecutive patients from the years 1999 and 2000 who received radical radiation therapy to the lung. Extracting data from the chart, we identified 83 patients who were treated radically with chemotherapy, radiation and possibly surgery. These patients form the basis of this study. RESULTS: At 2 years, the actuarial rates for any brain failure, first failure in the brain and sole failure in the brain were 34.2%, 24.6% and 11.0%, respectively. Age was the only factor among sex, histology, stage, weight loss and the timing of chemotherapy and radiation that predicted for an increased risk of first failure in the brain. Patients less than age 60 had a risk of 25.6% versus 11.4% for those greater than 60 (p = 0.022). Among the patients who failed first in the brain, those who had aggressive management of their brain metastases with surgical resection in addition to whole brain radiotherapy had a median survival of 26.3 months compared with 3.3 months for those treated with palliative whole brain radiotherapy alone. CONCLUSION: Brain metastases are common in patients with LA-NSCLC treated with CMT. These patients may benefit from either prophylactic cranial irradiation or early detection and aggressive treatment of brain metastases.

The radical treatment of locally advanced non-small cell lung cancer (LA-NSCLC) currently involves combined modality therapy (CMT).

Patients less than age 60 had a risk of 25.6% versus 11.4% for those greater than 60 (p=0.022).

Editorial Comment (TLP):
This controversial subject is argued at many of the lung cancer conferences that I attend. Although this is not a randomized clinical trial, it suggests benefits from either prophylactic or aggressive therapeutic radiation.

Forthcoming Workshop
Woodstock, Vermont
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