

April 2005

**LUNG
CANCER****FRONTIERS**

Comments may be submitted to:

**Lung Cancer
Frontiers**

899 Logan, Suite 203
Denver, CO 80203
or by email to:
tlpdoc@aol.com

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.

AVASTIN EFFECTIVE IN ADVANCED LUNG CANCER

Everyone who works in the field of lung cancer was delighted with the news reports that an antiangiogenesis drug is effective in non small lung cancer was reported in the press March 15. More information will be available in May at the annual meeting of the American Society of Clinical Oncology. AVASTIN (bevacizumab) has already been licensed for the treatment of colon cancer. It has yet to receive FDA approval for general use. In studies of non small lung cancer, some cases of serious or fatal hemorrhage from squamous cancers occurred. The drug was therefore limited to a trial in non squamous non small lung cancers, which are mostly peripheral adenocarcinomas.

Although it is great news that survival, even in advanced cases, now exceeds one year with AVASTIN in combination with chemotherapy agents (paclitaxel and carboplatin), this is obviously not the solution to the massive problem of identifying early and asymptomatic lung cancers, due to lack of support for screening, even in high risk patients. LCF has hammered on this theme since its inception in 1996. But great progress is beginning, as cited in the work that

is ongoing in Grand Junction, Colorado, where a practical and economic approach to case finding in the primary care setting has been done (publication soon to appear in *Chest*).

MULTIDISCIPLINARY LUNG CANCER DIAGNOSTIC TREATMENT CENTER OPENS IN DENVER COLORADO

Swedish Hospital, which began as a sanitarium for tuberculosis in 1905, now celebrates its centennial with the launch of a new program to deal with the nation's most rapidly growing fatal cancer. Lung cancer killed more people in 2004 than heart disease, an astonishing figure. It is a fact that lung cancer is the most common fatal cancer in both men and women throughout the world. Since most lung cancer is caused by smoking, high risk patients can be identified readily, a huge need for multidisciplinary diagnostic and treatment centers exists throughout North America and elsewhere in the world. Such a clinic has been launched in Denver, Colorado beginning this

FEEDBACK NEEDED

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

Yes No

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The Forum for Early Diagnosis and Treatment of Lung Cancer

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*Comments may be
submitted to: Lung
Cancer Frontiers, 899
Logan St., Suite 203,
Denver, CO 80203
or by email at:
tlpdoc@aol.com*

**THE TIME TO DIAGNOSE
LUNG CANCER IS NOW!**

For more than a decade I have been presenting the case for the diagnosis of asymptomatic, and hopefully, early stages of lung cancer in patients at high risk. High risk is defined as heavy smoking, family history of lung cancer, and occupational risk, and airflow obstruction measured by simple spirometry. In several issues we have described the success of this approach by a primary care practice in Grand Junction, Colorado. The questionnaire which was used to identify a total of 12 cases in 430 questionnaires representing high risk patients has now been validated. Our methodology and early outcome, soon to be published in the peer reviewed journal CHEST. The questionnaire proved to be so successful that it is reproduced on the last page of this issue. Local insurance programs can be substituted and the questionnaire modified for local needs.

We now have the knowledge and technology to diagnose asymptomatic and early stage lung cancer, and should be doing it as the standard of care.

year.

On March 5, 2005, a conference was held to feature the new program. Featured speakers were David P. Carbone, M.D., Ph.D., Professor of Medicine and Medical Oncologist at Vanderbilt University; Claudia I. Henschke, Ph.D., M.D., a radiologist who initiated the early lung cancer action program for CT imaging for lung cancer from Cornell University; and Stephen Lam, M.D., Professor of Medicine at the University of British Columbia, one of the developers of the fluorescent LIFE bronchoscope.

Carbone emphasized the “molecular signatures” of cancers in individual patients. Although no clinically useful molecular marker yet exists, there are many clues in tissue, sputum and blood. New knowledge about an EGFR receptor mutation explains why some patients respond to new inhibitors of this receptor, i. e., Iressa® and Tarseva®, but others do not. But the response is not related solely to the mutation. Advances in proteomics will soon identify new therapeutic targets. Technologies ranging from immunohistochemistry to mass spectroscopy will help target drug distribution, metabolites and effectiveness. The possibility of making resistant cells sensitive again is possible through molecular manipulations.

Henschke emphasized that her approach using one mm CT cut scanning continues to be effective in finding very early cancers. Associated with CT scanning is a 25% quit rate from smoking. Annual repeat screenings should be done on any nodule 5 mm or more. All nodules 1 cm or more need immediate investigation. Solid and partly solid nodules have different significance. Margin spiculation is not just due to cancer; it may be due to inflammatory disorders.

It is likely that lung cancer evolves over a five year or more period, following the establishment of malignant mutant cells. When diagnosed early, you can expect to add five more years to life, thus extending quality of life by ten years is well worth the cost and effort. Annual screening is recommended for all smokers, even if they have quit more than 20 years before.

Stephen Lam dazzled the audience with the new technologies emerging, including tiny probes that can be targeted with a global position system type of approach to be able to find tiny nodules in the 6th or 7th order of bronchi. Guided needle biopsy is commonly successful. Making an optical tissue diagnosis may soon become a reality. Using endobronchial ultrasound to evaluate the extent of tumors in the major bronchi will help identify lesions that can be locally treated, thus sparing precious functional lung tissue.

Doctors York Miller and Robert Keith of Denver discussed principles of chemoprevention aimed to

stem the progress from early stages of metaplasia into progressive grades of dysplasia. Drugs such as COX-2 inhibitors and Iloprost are under trial as new prevention strategies.

The Swedish Hospital one-stop lung cancer weekly clinic is geared to deal with all stages of lung cancer, requiring any of the emerging modalities of therapy including local ablation, resectional surgery, chemotherapy, radiation therapy, and combinations. New and novel therapies are evolving. This one-day conference may be the model for other centers and may be effective in changing our approach to the diagnosis and treatment of lung cancer.

The following is a proposed stepwise approach (written for patients) for the diagnosis of asymptomatic and hopefully early stage lung cancer that can be employed by any hospital or clinic today, based on evidence from the Grand Junction Colorado study. (TLP Editor)

The following is a proposed stepwise approach (written for patients) for the diagnosis of asymptomatic and, hopefully, early state lung cancer that can be employed by an hospital or clinic today, based on evidence from the Grand Junction, Colorado study (TLP Editor):

IF YOU SMOKE AND HAVE LUNG CANCER, WE CAN FIND IT NOW!

(MOST EARLY CANCERS ARE CURED!)

Today lung cancer, mostly related to smoking, is the most common cause of death in adults, exceeding heart diseases. Lung cancer affects one in nine smokers. This year 177,000 new cases will be diagnosed on the basis of symptoms, or by chance when x-rays are done for some other reason. Chest x-rays are not very sensitive in diagnosing early stage lung cancers. Only about 15% of these tumors can be cured because they are diagnosed in late stages. We can cure most of them if found in early stages.

Also one in five smokers will get COPD (emphysema and chronic bronchitis). COPD and lung cancer are closely related diseases. Stopping smoking can help stop the development of both these diseases and prolong life

New knowledge about an EGFR receptor mutation explains why some patients respond to new inhibitors of this receptor, i. e., Iressa®

Associated with CT scanning is a 25% quit rate from smoking. Annual repeat screenings should be done by any nodule 5 mm or more.

Annual screening is recommended for all smokers, even if they have quit more than 20 years before.

Making an optical tissue diagnosis may soon become a reality.

and life quality. Some medicines improve the lungs in patients with COPD.

Most people who develop lung cancer do so over about five years before it is found. But today we know how to find it early by simple tests that can save your life. This new approach to lung cancer diagnosis is based on sound scientific tests and we can now offer this to you. Here are the steps:

A. Questionnaire. If you have smoked an equivalent of 30 pack years and are age 50, you are at risk. If you have a family history of lung, laryngeal, or esophageal cancer you are at risk. If you are exposed to asbestos, underground mining or, railroad work, there is increased risk. Add these together and your risk of lung cancer is about 1%,

B. Breathing test. If you have airflow obstruction and the above risk factors, your risk of having lung cancer is about 7%. Here is where we really need to look aggressively. A breathing test is easy to do. You do not need any preparation and do not get undressed. You just puff up and fill your chest and blow all the air into a device called a spirometer. This takes about five minutes to get good results.

C. Sputum test. Early cancer can be found in the mucus you cough from your lungs each day. You brush your teeth, take a hot shower for 15 minutes, then cough into a special cup container that collects and preserves the normal and early cancer cells that are found by the microscope. Special hospital trained pathologists determine if early or advanced cancer cells are in your sputum.

D. Bronchoscopy. A thin scope is inserted into your air passages to find the cancer. If it is in the large air passage it can usually be seen and often treated locally without major surgery.

E. Imaging by CT using low dose radiation (about the same as a mammogram) find tiny spots on your lungs, that cannot be seen by regular chest x-rays., or reached by the bronchoscope. If these are suspicious, they can be biopsied by a needle or simply removed by a small operation. Very small nodules are checked once a year to look for changes or growth. Since early cancers may grow slowly, there is time for a cure.

With this simple approach, about 90-95% of lung cancer patients are cured. You better find it early. If you don't, your cancer will find

you later and will not be able to be cured easily.

Our new program at -----clinic/hospital is designed to find, treat and cure lung cancer. We are here to serve you!

Citations From the Peer Reviewed Literature

1.
Lung Cancer 2005;47:9-15

Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer.

Gohagan JK, Marcus PM, Fagerstrom RM, Pinsky PF, Kramer BS, Prorok PC, Ascher S, Bailey W, Brewer B, Church T, Engelhard D, Ford M, Fouad M, Freedman M, Gelmann E, Gierada D, Hocking W, Inampudi S, Irons B, Johnson CC, Jones A, Kucera G, Kvale P, Lappe K, Manor W, Moore A, Nath H, Neff S, Oken M, Plunkett M, Price H, Reding D, Riley T, Schwartz M, Spizarny D, Yoffie R, Zylak C; THE LUNG SCREENING STUDY RESEARCH GROUP.

Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., EPN 3064, Bethesda, MD 20892, USA.

The Lung Screening Study (LSS) was a pilot study designed to assess the feasibility of conducting a large scale randomized controlled trial (RCT) of low radiation dose spiral computed tomography (LDCT) versus chest X-ray (CXR) for lung cancer screening. Baseline results of LSS have been previously reported. Here, we report on the findings at the year one screen and on the final results of the LSS study. A total of 1660 subjects were randomized to the LDCT arm and 1658 to the CXR arm. Compliance with screening declined from 96% at baseline to 86% at year one in the LDCT arm and declined from 93% at baseline to 80% at year one in the CXR arm. Positivity rates for the year one screen were 25.8% for LDCT and 8.7% for CXR. Cancer yield was significantly less at year one for LDCT, 0.57%, than at baseline, 1.9%; cancer yield for CXR increased from 0.45% at baseline to 0.68% at year one. Forty lung cancers in the LDCT arm and 20 in the CXR arm were diagnosed over the study period. Stage I cancers comprised 48% of cases in the LDCT arm and 40% in the CXR arm. A total of 16 stage III-IV cancers were observed in the LDCT arm versus nine in the CXR arm. The LSS has established the feasibility of a RCT comparing annual spiral CT to chest X-ray for lung

With this simple approach, about 90-95% of lung cancer patients are cured.

Most people who develop lung cancer do so over about five years before it is found.

If you have airflow obstruction and the above risk factors, your risk of having lung cancer is about 7%.

You brush your teeth, take a hot shower for 15 minutes, then cough into a special cup container that collects and preserves the normal and early cancer cells that are found by the microscope.

Positivity rates for the year one screen were 25.8% for LDCT and 8.7% for CXR.

cancer screening.

Editorial Comment (TLP):

This “screening study” should probably have never been done because by the time the results are in, the technologies involved will be obsolete. Nonetheless a lot of money was expended on these comparisons and we will have to learn whether the results justified the effort.

2.

Cancer 2005;103:157-163

Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen.

Pinsky PF, Marcus PM, Kramer BS, Freedman M, Nath H, Kvale P, Reding D.

Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA. pp4f@nih.gov

BACKGROUND: Low-radiation dose spiral computed tomography (LDCT) currently is being evaluated as a screening modality for lung carcinoma in a randomized trial. Although several diagnostic algorithms for the workup of positive LDCT screens have been proposed, to the authors' knowledge there is no widely accepted standard to date and there are few nationwide data concerning how such diagnostic workups are actually being performed outside a research protocol setting.

METHODS: The Lung Screening Study (LSS) was a multicenter feasibility trial that randomized 1660 subjects to undergo LDCT and an equivalent number to undergo chest X-ray.

Subjects with positive screens were referred to their own health care providers for diagnostic follow-up; LSS did not specify a diagnostic algorithm. LSS collected and abstracted medical records regarding procedures employed in the diagnostic workup of positive screens.

RESULTS: Of the 522 subjects with a positive LDCT screen at baseline or at Year One, 12% underwent biopsy. Biopsy was less likely to be performed in subjects with 4-9-mm nodules (5%) than in subjects with nodules measuring 10+ mm (25%) or in subjects with no nodules but other suspicious findings (15%). Among 63% of the subjects who underwent chest CT on follow-up, the median time between screening and first follow-up chest CT was 82 days. Only a minority of subjects received diagnostic workups that were consistent with published algorithms. **CONCLUSIONS:** The data from the current study represent the ex-

perience of subjects followed by their health care providers in five different U.S. metropolitan areas and one rural area. As such, they provide some indication of practices in the U.S. with regard to the diagnostic workup of patients with positive spiral CT screens

Editorial Comment (TLP):

It is not surprising that proposed algorithms have not been followed after lesions are found by spiral CT scan. Several algorithms have been proposed, but not generally followed. Unfortunately lung cancer today is still not on the radar screen. Obviously CT scan finding must be put in context and pursued appropriately. Certainly, any new or growing non-calcified lesions greater than 10 mm diameter should be excised or biopsied. Those 4-9 mm in diameter need regular follow-up CTs at 3-6 and 12 months.

3.

Cancer 2005;00:000-000. 2005 American Cancer Society (in press)

Relation between Smoking Cessation and Receiving Results from Three Annual Spiral Chest Computed Tomograph Scans for Lung Carcinoma Screening

Abstract:

Background. The relation between undergoing a single computed tomography (CT) screening for lung carcinoma and the potential long-term impact on smoking status has been equivocal. Perhaps, recommendations from multiple cancer screenings may promote smoking abstinence among individuals at high risk for lung carcinoma.

Methods. The current longitudinal study comprised 926 current smokers and 594 former smokers who participated in 3 annual follow-up low-dose, fast spiral chest CT scan screenings for lung carcinoma. Baseline demographic, pulmonary function, smoking history variables, and previous abnormal findings were evaluated as predictors of self-reported point prevalence smoking abstinence.

Results. Among current smokers at baseline, abstinence from smoking during the 3-year follow-up was associated with older age, worse baseline pulmonary function, and abnormal CT finding the previous year requiring interim follow-up. Of participants who received abnormal screens each of the previous 3 years, 41.9% reported smoking abstinence compared with 28.0% with 2 abnormal screens, 24.2% with 1 abnormal screen, and 19.8% with no abnormal screens. Among former smokers, abstinence from smoking was associated with a longer duration of abstinence

Only a minority of subjects received diagnostic workups that were consistent with published algorithms.

... there is no widely accepted standard to date and there are few nationwide data concerning how such diagnostic workups are actually being performed outside a research protocol setting.

Perhaps, recommendations from multiple cancer screenings may promote smoking abstinence among individuals ...

The median age at diagnosis was 66 years for both men and women. However, women accounted for 40.9% of patients who were <50 years of age and for 35.4% of older patients.

Smokers with abnormal CT findings from multiple CT screens were more likely to be abstinent . . .

. . . Male gender was an independent negative prognostic factor ($p < 0.0001$).

Previous studies have attempted to investigate the impact of smoking cessation on lung cancer survival . . .

before the baseline visit. Conclusions. Smokers with abnormal CT findings from multiple CT screens were more likely to be abstinent from smoking at the 3-year follow-up. Multiple low-dose, fast spiral chest CT scan screenings for lung carcinoma may represent teachable moments and opportunities to enhance motivation for smoking abstinence. Further research is needed to continue to investigate how annual screening may enhance motivation for health behavior change.

Editorial Comment (TLP):

This is an interesting spin-off of CT screening studies. Finding an abnormality on CT may well be a “teachable moment” for smoking cessation. One may be concerned about the expense of CT, but available smoking cessation programs, often cost \$500 to \$1,000. Not diagnosing lung cancer becomes really expensive in terms of the costs of long term palliative care (\$50,000 or more in mid-1990s dollars)!

4.
Chest 2005;127:768-777

Lung cancer in women: analysis of the national surveillance, epidemiology, and end results database.

Fu JB, Kau TY, Severson RK, Kalemkerian GP.

Department of Medicine, University of Michigan, Ann Arbor, MI, USA.

OBJECTIVES: In order to further characterize the effect of gender on the clinicopathologic features and survival of patients with lung cancer, and to determine gender-associated differences in temporal trends, we analyzed data that had been entered into a population-based cancer database. **PATIENTS AND METHODS:** Data on demographics, stage at diagnosis, histology, initial therapy, and survival were obtained on all patients with primary bronchogenic carcinoma registered in the national Surveillance, Epidemiology, and End Results database from 1975 to 1999. **RESULTS:** Of the 228,572 eligible patients, 35.8% were female. The median age at diagnosis was 66 years for both men and women. However, women accounted for 40.9% of patients who were < 50 years of age and for 35.4% of older patients. The incidence of lung cancer in men peaked at 72.5 per 100,000 person-years in 1984 and then declined to 47 per 100,000 person-years by 1999. In women,

the incidence continued to rise to a peak of 33.1 per 100,000 person-years in 1991 before reaching a plateau at 30.2 to 32.3 per 100,000 person-years from 1992 to 1999. These changes have resulted in a marked narrowing of the male/female incidence ratio from 3.56 in 1975 to 1.56 in 1999. As initial treatment, women with local disease underwent surgery more frequently than did men. Stage-specific survival rates were better for women at all stages of disease ($p < 0.0001$). In a multivariate analysis, male gender was an independent negative prognostic factor ($p < 0.0001$). **CONCLUSION:** The incidence rate of lung cancer in women in the United States has reached a plateau. However, women are relatively over represented among younger patients, raising the question of gender-specific differences in the susceptibility to lung carcinogens. At each stage of the disease, the relative survival of women is better than that of men, with the largest difference noted in patients with local disease.

Editorial Comment (TLP):

Lung cancer has long been suspected to be more common in women than in men at a given level of smoking exposure. Whether or not this is true remains debated but at least we know that lung cancer is more common in younger women than men. The relatively better survival in women than men is related to local disease. It would be best to find these lung cancers in early stages.

5.
Lung Cancer 2005;47:165-172

Duration of smoking abstinence as a predictor for non-small-cell lung cancer survival in women.

Ebbert JO, Williams BA, Sun Z, Aubry MC, Wampfler JA, Garces YI, Meyer RL, Yang P.

Division of Primary Care Internal Medicine, Department of Internal Medicine, Nicotine Research Program, Mayo Clinic College of Medicine, Rochester, MN 55905, USA.

Background: Previous studies have attempted to investigate the impact of smoking cessation on lung cancer survival but have been limited by small numbers of former smokers and incomplete data. **Methods:** Over a six-year period, 5229 patients with non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) were enrolled in a prospective cohort of whom 2052 were former smokers. Patient's characteristics were obtained from medical records and a baseline interview. Vital status was determined through multiple sources. Cox proportional hazards models were used to estimate the effect of smoking abstinence on post-diagnosis mortality. **Results:** For all patients with NSCLC, the median survival among never, former, and current smokers was 1.4 years, 1.3 years, and

Over seven years of follow up, 97 people had newly diagnosed lung cancer, 20 had upper respiratory cancers (pharynx, larynx), and 14 died from chronic obstructive pulmonary disease or emphysema.

No effect of smoking abstinence on mortality was observed for women with SCLC or for men with either histologic group.

Odd ratios were consistently higher in former smokers than in those who had never smoked.

Frequent exposure to environmental tobacco smoke during childhood was associated with lung cancer in adulthood . . .

1.1 years, respectively ($P < 0.01$). Female NSCLC patients had a significantly lower risk of mortality with a longer duration of smoking abstinence (RR per 10 years of smoking abstinence = 0.85; 95% CI: 0.75, 0.97). No effect of smoking abstinence on mortality was observed for women with SCLC or for men with either histologic group. Conclusions: The identification of smoking history as a prognostic factor in lung cancer survival supports previous research suggesting a direct biologic effect of smoking on survival. However, this effect may vary by sex and type of lung cancer.

Editorial Comment (TLP):

Alas, smoking abstinence has not been shown to eliminate the excess rate of smoking related to lung cancer if sufficient exposure has already taken place. Today more lung cancer is diagnosed in former smokers than in current smokers.

6.

BMJ 2005;330:277

Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study.

Vineis P, Airoidi L, Veglia P, Olgiati L, Pastorelli R, Autrup H, Dunning A, Garte S, Gormally E, Hainaut P, Malaveille C, Matullo G, Peluso M, Overvad K, Tjonneland A, Clavel-Chapelon F, Boeing H, Krogh V, Palli D, Panico S, Tumino R, Bueno-De-Mesquita B, Peeters P, Berglund G, Hallmans G, Saracci R, Riboli E.

Imperial College, London W2 1PG. p.
vineis@imperial.ac.uk

OBJECTIVES: To investigate the association between environmental tobacco smoke, plasma cotinine concentration, and respiratory cancer or death. **DESIGN:** Nested case-control study within the European prospective investigation into cancer and nutrition (EPIC). **PARTICIPANTS:** 303,020 people from the EPIC cohort (total 500,000) who had never smoked or who had stopped smoking for at least 10 years, 123,479 of whom provided information on exposure to environmental tobacco smoke. Cases were people who developed respiratory cancers or died from respiratory conditions. Controls were matched for sex, age (plus or minus 5 years), smoking status, country of recruitment, and time elapsed since recruitment. **MAIN OUTCOME MEASURES:** Newly diagnosed cancer of lung, pharynx, and larynx; deaths from chronic obstructive pulmonary disease or emphysema. Plasma cotinine concentration was measured in 1574 people. **RESULTS:** Over seven years of follow up, 97 people had newly diagnosed lung cancer, 20 had upper

respiratory cancers (pharynx, larynx), and 14 died from chronic obstructive pulmonary disease or emphysema. In the whole cohort exposure to environmental tobacco smoke was associated with increased risks (hazard ratio 1.30, 95% confidence interval 0.87 to 1.95, for all respiratory diseases; 1.34, 0.85 to 2.13, for lung cancer alone). Higher results were found in the nested case-control study (odds ratio 1.70, 1.02 to 2.82, for respiratory diseases; 1.76, 0.96 to 3.23, for lung cancer alone). Odds ratios were consistently higher in former smokers than in those who had never smoked; the association was limited to exposure related to work. Cotinine concentration was clearly associated with self reported exposure (3.30, 2.07 to 5.23, for detectable/non-detectable cotinine), but it was not associated with the risk of respiratory diseases or lung cancer. Frequent exposure to environmental tobacco smoke during childhood was associated with lung cancer in adulthood (hazard ratio 3.63, 1.19 to 11.11, for daily exposure for many hours). **CONCLUSIONS:** This large prospective study, in which the smoking status was supported by cotinine measurements, confirms that environmental tobacco smoke is a risk factor for lung cancer and other respiratory diseases, particularly in ex-smokers.

Editorial Comment (TLP):

No reasonable person can doubt the relationship between secondary tobacco smoke to the risk of lung cancer if all of the literature is reviewed. This is another excellent study based upon cotinine levels which is quite convincing.

7.

Elsevier

Mech Aging Dev 2004;125:581-590

Age-promoted creation of a pro-cancer micro-environment by inflammation: pathogenesis of dyscoordinated feedback control.

Schwartzburd PM.

Institute of Theoretical and Experimental Biophysics, Russian Academy of Science, Pushchino, Moscow Region. schwartzburd@iteb.ru

Aging and local chronic inflammation are established risk factors for epithelial tumorigenesis. These risk factors can act individually and/or synergistically to increase the incidence of age-related carcinomas. The basis for this co-stimulatory response has not yet been defined, nor have the feedback mechanisms that are responsible for this synergism. This review provides insight into the age-stimulated dysregulation of coordination of feedbacks in oxygen-, heme-, and proteolysis-

The cancer-induced environment has certain features in common with chronic inflammatory-induced PCM.

A marked improvement of survival was found since the introduction of the third-generation agents . . .

. . . age-related metabolic changes create opportunities for chronic (not acute) inflammatory response, which supports the PCM-condition with the non-healing wound state that often occurs around carcinomas.

A significant improvement of survival in patients with NSCLC was observed in the last decade.

dependent metabolic pathways caused by acute and chronic inflammation, and its role as a possible pathological basis for the creation of a pro-cancer microenvironment (PCM). The PCM facilitates the selective survival and growth of transformed cells (in a manner similar to a cancer-supportive microenvironment (CM)). The cancer-induced environment has certain features in common with chronic inflammatory-induced PCM. Namely, there are: enhanced oxidative cell resistance against apoptosis, increased production of matrix-degrading enzymes, switching to glycolytic metabolism, angiogenesis and vasorelaxation thus providing nutrient delivery, but restriction of the immune cell mobilization and/or its activation. The hypothetical model of PCM-genesis is presented as a result of enzymatic dysregulation of feedback control including oxygen-, heme-, prostaglandin E(2)-, metalloproteinase-9-, and NO/CO-dependent pathways. PCM-genesis takes place between the growth-inhibiting (cytotoxic) and growth promoting (regenerative) stages of inflammatory response. According to this model, age-related metabolic changes create opportunities for chronic (not acute) inflammatory response, which supports the PCM-condition with the non-healing wound state that often occurs around carcinomas.

Editorial Comment (TLP):

This abstract was selected because it focuses on the important concept of age-related metabolic changes which create the environment for the induction of lung cancer.

8.
Chest 2005;127:738-747

Significant progress in palliative treatment of non-small cell lung cancer in the past decade.

Waechter F, Passweg J, Tamm M, Brutsche M, Herrmann R, Pless M.

Department of Medical Oncology, University Hospital of Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

STUDY OBJECTIVES: Prospective randomized trials (PRTs) have suggested that third-generation agents (eg, gemcitabine, the taxanes, and vinorelbine) improve the survival time of patients with non-small cell lung cancer (NSCLC). However, < 30% of unselected NSCLC patients fulfill the eligibility criteria of such trials. We analyzed the outcomes of all consecutive and unselected patients with inop-

erable NSCLC in a single institution to determine whether there was an improvement in survival over time, and if so, to identify the factors that were associated with improved survival. **METHODS:** A total of 230 documented patients with NSCLC at the Basel University Hospital treated after 1990 were analyzed retrospectively. Break points by year of treatment were determined using sequential Cox proportional hazards regression models and the Kaplan-Meier estimator. Multivariate analysis was used to determine which factors were associated with improved survival over time. **RESULTS:** A marked improvement of survival was found since the introduction of the third-generation agents in 1997. The 1-year (40% vs 19%, respectively) and 2-year survival rates (23% vs 5%, respectively, $p < 0.0001$) of patients in whom NSCLC had been diagnosed since 1997 were significantly better than those prior to 1997. The two cohorts did not differ significantly in sex, stage, performance status, weight loss, and lactate dehydrogenase levels. The improvement since 1997 was due to better best supportive care ($p < 0.025$), better first-line chemotherapy (median overall survival [OS] time (9.2 vs 6.9 months, respectively; $p < 0.0016$), and better second-line chemotherapy ($p < 0.0001$). Finally, patients who received therapy with platinum plus a third-generation drug had significantly better outcomes than those who received an older therapy regimen (median OS time, 9.3 vs 6.7 months, respectively; $p < 0.027$). **CONCLUSIONS:** A significant improvement of survival in patients with NSCLC was observed in the last decade. The results of PRTs for palliative treatment of NSCLC seem to be applicable to an unselected group of patients with NSCLC, and therapeutic nihilism in the palliative setting seems not to be justified.

9..
Lung Cancer 2005;47:85-91

Long-term survivors in stage IV non-small cell lung cancer.

Okamoto T, Maruyama R, Shoji F, Asoh H, Ikeda J, Miyamoto T, Nakamura T, Miyake T, Ichinose Y.

Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka 811-1395, Japan.

Background and Objectives: To determine the prognostic factors for long-term survivors (LTS) with stage IV non-small cell lung cancer (NSCLC) who had undergone various treatments. **Patients and methods:** From 1990 to 1999, 222

NSCLC patients with stage IV disease, who had been treated in our department, were reviewed. As the initial treatment, 135 patients (48%) were treated with chemotherapy alone, 52 patients with a combination of chemotherapy and radiotherapy, 19 patients underwent an operation with or without any other therapeutic modalities and 16 were received radiotherapy alone. Results: Seventeen (7.7%) patients survived for more than 2 years, and all but one had adenocarcinoma. Among these LTS, eight patients received surgery as the initial therapy, and 16 (94.1%) received some type of local-control therapy, including surgery or radiotherapy, during the course of their disease. Regarding the clinical characteristics between LTS and others (non-LTS), an early N status, a single metastatic site, a good performance status, and surgery for initial therapy were all found to be significantly important factors for LTS. A multivariate analysis using a logistic regression model also showed an early N status and surgical treatment to be significantly associated with LTS. Conclusions: Selected patients with an early N status may be appropriate candidates for aggressive multimodality treatment including surgery, in order to provide a long-term survival for stage IV NSCLC.

Radiofrequency ablation has been used for patients with primary lung cancer and limited pulmonary metastases.

Seventeen (7.7%) patients survived for more than 2 years, and all but one had adenocarcinoma.

Editorial Comments (TLP):

It is wonderful that such progress is made in the palliation and treatment of lung cancer in the past decade. This should reduce or eliminate the nihilistic attitude that remains in the minds of many, including pulmonologists and patients in particular. Certainly the availability of Avastin as cited in the headlines story is an additional advantage.

10.
Clin Lung Cancer 2004;6:149-153

Radiofrequency ablation: identification of the ideal patient.

Fernando HC, Hoyos AD, Litle V, Belani CP, Luketich JD.

Department of Cardiothoracic Surgery, Boston Medical Center, MA 02118, USA. hiran.fernando@bmc.org

Radiofrequency (RF) ablation (RFA) is a relatively new modality that is being used for lung tumors with increasing frequency. Radiofrequency energy consists of an alternating current that moves from an active electrode that is placed within the tumor to dispersive electrodes that are placed on the patient. As the RF energy is applied, frictional heating of tissues results, with cell death occurring at temperatures > 60 degrees C. This article discusses preclinical and early clinical experience with RFA for lung

tumors. Radiofrequency ablation has been used for patients with primary lung cancer and limited pulmonary metastases. Current data suggest that RFA is most suitable for tumors < or = 4 cm in size and is better for peripheral rather than centrally based nodules. Additionally, studies of RFA followed by resection have demonstrated a learning-curve effect with improved tumor kill in the later cases performed in these series. Surgical resection should continue to be the primary modality offered to patients with early-stage non-small-cell lung cancer and limited metastatic disease to the lungs (when the primary tumor is controlled). Radiofrequency ablation is a good option for those patients who are believed to be at increased risk for resection or who refuse resection, when operation would otherwise be appropriate therapy. Additionally, RFA may be used for local control of peripheral tumors in patients with more advanced cancers in combination with other therapies.

Editorial Comment (TLP):

This appears to be a reasonable option for patients who are not candidates for surgical resection. This represents additional progress in our ability to treat selected patients with lung cancer.

11.
Journal of the national Cancer Institute 2004;96:1769-1780

Death receptor regulation and celecoxib-induced apoptosis in human lung cancer cells.

Liu X, Yue P, Zhou Z, Khuri FR, Sun SY.

Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA.

BACKGROUND: Celecoxib, a cyclooxygenase 2 inhibitor, has chemopreventive and therapeutic activities toward lung cancer and other epithelial malignancies. Celecoxib can induce apoptosis in various cancer cell lines through a mechanism that is independent of its cyclooxygenase 2 inhibitory activity but is otherwise largely uncharacterized. We investigated the mechanism of celecoxib-induced apoptosis further. **METHODS:** All experiments were conducted in human non-small-cell lung carcinoma (NSCLC) cell lines; results in celecoxib-treated and untreated cells were compared. Cell survival was assessed with a sulforhodamine B assay. Apoptosis was assessed by DNA fragmentation with an enzyme-linked immunosorbent assay, by terminal deoxynucleotidyl-transferase-mediated dUTP nick-end-labeling (TUNEL) assay, and by western blot analysis of caspase activation. Death receptor gene and pro-

Radiofrequency ablation is a good option for those patients who are believed to be at increased risk for resection or who refuse resection, when operation would otherwise be appropriate therapy.

Celecoxib can induce apoptosis in various cancer cell lines through a mechanism that is independent of its cyclooxygenase 2 inhibitory activity.

Those who resisted victim blaming maintained that the real culprits were tobacco companies with unscrupulous policies.

. . . . decreased cell survival, activated caspase cascades, and increased DNA fragmentation. . .

A few patients were worried that diagnosis, access to care, and research into lung cancer might be adversely affected by the stigma attached to the disease and those who smoke.

tein expression was detected by northern and western blot analysis, respectively. Gene silencing was achieved with small interfering RNA (siRNA) technology. **RESULTS:** Celecoxib treatment decreased cell survival, activated caspase cascades, and increased DNA fragmentation, all of which were abrogated when caspase 8 expression was silenced with caspase 8 siRNA. Celecoxib treatment induced the expression of death receptors, particularly that of DR5. Overexpression of a dominant negative Fas-associated death domain mutant, but not of BCL2, reduced the level of celecoxib-induced apoptosis, and silencing of DR5 expression by DR5 siRNA suppressed celecoxib-induced caspase 8 activation and apoptosis. Combination treatment with celecoxib and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced additional apoptosis. For example, survival of A549 cells was decreased with 50 μ M celecoxib alone by 38.7% (95% confidence interval [CI] = 35.2% to 42.2%), with TRAIL alone by 29.3% (95% CI = 25.1% to 33.6%), but with their combination by 77.5% (95% CI = 74.5% to 79.5%), a greater than additive effect. **CONCLUSION:** Celecoxib appears to induce apoptosis in human NSCLC through the extrinsic death receptor pathway.

Editorial Comment (TLP):

Chemoprevention is a great challenge in lung cancer. Perhaps the celecoxib drugs will find a role here, recognizing the increased cardiovascular risks.

12.
BMJ 2004;328:1470

Stigma, shame, and blame experienced by patients with lung cancer: qualitative study.

Chapple A, Ziebland S, McPherson A.

DIPEX Research Group, Department of Primary Health Care, University of Oxford, Oxford OX3 7LF. alison.chapple@dphpc.ox.ac.uk

OBJECTIVES: To draw on narrative interviews with patients with lung cancer and to explore their perceptions and experience of stigma. **DESIGN:** Qualitative study. **SETTING:** United Kingdom. **PARTICIPANTS:** 45 patients with lung cancer recruited through several sources. **RESULTS:** Participants experienced stigma commonly felt by patients with other types of cancer, but, whether they smoked or not, they felt particularly stigmatised because the disease is so strongly associated with smoking. Interaction with family, friends, and doctors was often affected as a result, and many patients, particularly those who had stopped smoking years ago or had never smoked, felt unjustly blamed for their illness. Those who resisted victim blaming maintained that the real culprits were tobacco com-

panies with unscrupulous policies. Some patients concealed their illness, which sometimes had adverse financial consequences or made it hard for them to gain support from other people. Some indicated that newspaper and television reports may have added to the stigma: television advertisements aim to put young people off tobacco, but they usually portray a dreadful death, which may exacerbate fear and anxiety. A few patients were worried that diagnosis, access to care, and research into lung cancer might be adversely affected by the stigma attached to the disease and those who smoke. **CONCLUSION:** Patients with lung cancer report stigmatisation with far reaching consequences. Efforts to help people to quit smoking are important, but clinical and educational interventions should be presented with care so as not to add to the stigma experienced by patients with lung cancer and other smoking related diseases.

Editorial Comment (TLP):

Patients who suffer from lung cancer associated with smoking developed this dread disease by use of a legal product that was vigorously and effectively promoted by the tobacco industry, even with the denial of risk. There is no place for stigmatisation of lung cancer, COPD or any other human ailment.

TELEVISION NEWS ANCHORMEN WITH LUNG CANCER

We were saddened by news of the diagnosis of lung cancer in Peter Jennings, age 66 and a smoker, of ABC News. He is currently undergoing chemotherapy. In 1965 Edward R. Murrow, anchor of CBS News, died of lung cancer at age 57. he was never seen on television without a cigarette.

In 1974 Chet Huntley, anchor of NBC News, died of lung cancer at age 62. He was often seen smoking his pipe on TV.

Maybe it is time for the mainstream me-

dia to start promoting the early diagnosis and treatment of lung cancer. We know who to test, how to test, and how to find a cure in early stages of disease!

TOBACCO TIDBITS

- Each pack of cigarettes sold in the United States costs the nation \$7 in medical care and lost productivity.
- The nation's total cost of smoking at \$3,391 a year for every smoker, or \$157.7 billion. Health experts had previously estimated \$96 billion.
- Americans buy about 22 billion packs of cigarettes annually.
- The nation's smoking-related medical costs are estimated to be \$3.45 per pack. Job productivity lost because of premature death from smoking amounted to \$3.73 per pack, for a total of \$7.18.
- The average cost of a pack of cigarettes in the USA in 2005 is \$3.25.
- Smoking results in about 440,000 deaths a year in the United States, up from the government's previous figure of 430,000 established in the early 1990s. Smoking causes an average man to lose more than 13 years of life, and an average woman to lose 14.5 years.

Grand Junction Questionnaire

Did you know that in 1999 it is estimated that 171,600 new lung cancer cases were diagnosed in the United States? Lung cancer is the most common cause of cancer deaths for both men and women in the United States. Dr. Joel Bechtel, Dr. Thomas Petty, The Saccomanno Research Institute at St. Mary's Hospital and Medical Center, and Primary Care Partners, P.C. hope to learn more about the lung cancer risks in our community. We have undertaken a community screening project with the purpose of investigating methods for detecting lung cancer at an earlier, more treatable stage. Patients choosing to take part in the project will be evaluated using spirometry (a test of lung function done by blowing into a measurement device), sputum cytology (cells coughed up from deep in the lungs are looked at through a microscope), a chest x-ray and a chest CT scan. We would appreciate your help in this important project by completing this brief questionnaire.

1) Name: _____ Date: _____ Age: _____

Telephone Number: _____

2) Type of Insurance coverage: Rocky Mt HMO Other No insurance

3)

Please circle the answer that best describes your smoking habits: I have never smoked I currently smoke* I smoked in the past, but no longer smoke* Packs per day: _____ Year or age started _____ Year or age stopped: _____

Please circle the answers that apply to you: I currently work or have previously worked in one or more of these occupations: Under Ground Mining Construction Railroad

I have had significant industrial and/or occupational exposure to the following substances: Asbestos Silica Dust Coal Dust

4) Please circle the answer that best describes who in your family has been diagnosed with cancer of the lung and/or larynx: No One Self Parent Brother or Sister Children

I would like to get more information about this important project: No Yes*

Thank you. Please stop here. Your doctor will complete the remainder of the information.