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Highlights of The 2nd International Conference on Screening for Lung Cancer

CScreen represents the international collaboration of screening for lung cancer and is sponsored by Weill Medical College of Cornell University in New York City. It was held February 25th through 27th of this year. This second Conference, which brought together experts from the many fields involved in the study and treatment of early lung cancer, met for three days to consider the rapidly expanding frontier of early lung cancer diagnosis and treatment.

The roots of this major effort can reasonably be traced to the Varese, Italy Conference on the Prevention and Early Diagnosis of Lung Cancer, held on December 9th and 10th, 1998. Highlights of the Varese Conference were summarized in *Lung Cancer Frontiers*, (LCF), #5, March, 1999. At this Conference, Dr. Claudia I. Henschke, who co-chaired this most recent Conference along with Dr. James P. Smith, first described her Early Lung Cancer Action Project, (ELCAP), which began in 1993. ELCAP was designed to evaluate the usefulness of CT screening for lung cancer in a high risk population. The study was purposefully designed as a single cohort recruiting study, with no comparison arm.

The initial published report of the ELCAP baseline screening appeared in a landmark article (Henschke C.I. et al. ELCAP: Overall design and findings from baseline screening. *Lancet*, 1999;354:99-105). In brief, ELCAP enrolled, 1,000 symptom-free volunteers who were 60 years or older, who had smoked at least 10 pack-

years, and who had no previous evidence of cancer. Subjects were excluded if they were not, “medically fit to undergo thoracic surgery.” Low-dose helical CT scanning for non-calcified nodules revealed 233 nodules (23%), compared with only 68 (7%), that were identified by standard chest x-rays which were obtained in parallel with CT scanning. Follow-up of nodules of 5.0 mm or less for growth suggestive of malignancy was done at three months. Growing lesions were biopsied or removed. Nodules between 5.0 to 10.0 mm were evaluated on an individual basis. Those more than 10.0 mm were biopsied, staged, and treated, usually by lobectomy. In this study, malignant disease was found in 27 (2.7%), by CT, but only 7 of these (0.7%), were found by standard chest x-ray. Stage I disease was found in 23 of the 27 patients. Of these 27 patients, 26 were resectable in an attempt to cure. In this study, no subject had a lobectomy for a benign nodule. An important aspect of the CT scanning protocol was the follow-up of lesions for growth in three months. We now await the results of the annual repeat screening, as these are critical data for evaluation of screening efficacy. Initial results from the ELCAP and Japanese studies are very promising.

In the mission statement of the New York Conference, Dr. Henschke emphasized that the major aim was to develop a perspective of the patient at risk of lung cancer, and to learn how curable lung cancer is in its early stages. The overall aim was to find the most cost-effective approach to

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Dr. Claudia I. Henschke

diagnosis and treatment. At the time of this Conference, it was estimated that more than 20,000 individuals had been screened by helical CT scanning, and more than 9,000 by airway cell markers. What the ultimate outcome of these massive screening efforts will be, remains to be determined.

John K. Field, Ph.D. (Roy Castle International Center for Lung Cancer Research, London), reported on the European strategy in lung cancer screening. The approach was consistent with the recommendations of Doctors James L. Mulshine and Claudia I. Henschke cited later in this issue of *LCF* (Prospects for Lung Cancer Screening. *Lancet* 2000;355:592-593.) An approach to molecular epidemiology and sputum markers (Field J.K. et al. Genetic alterations in bronchial lavage as a potential marker for individuals with a high risk of developing lung cancer. *Cancer Res* 1999;59:2690-2695) used PCR-based screening. The goals of identifying a large number of candidate biomarkers, looking for "cancer-specific genetic instability," and establishing a strategy of periodic re-screening of high-risk cohorts were discussed

In general discussion, many of the participants concluded that it is time to reevaluate lung cancer screening. In fact, it is time to think positively about it. However, as pointed out by James P. Smith, lung cancer

“How to track the course of new technologies on early diagnosis, pooling data from multiple sites, and developing a large single-arm cohort registry to learn outcomes will most likely answer key questions about early diagnosis and interventions, even better than randomized clinical trials.”

“Using new automated image analysis and quantitative DNA stain instead of conventional Pap stain, the sensitivity is increased to 80% with a specificity of 90% for Stage 0/I. Even peripheral adenocarcinomas can be detected with a similar sensitivity and specificity.”

screening per se, does not have intrinsic value. It is determining the effect on mortality in defined populations that is required. Seeking a consensus on the ELCAP recommendations in the hope that we can reach consensus on interventions for small cancers was the goal set for the Conference, and the charge to the working groups that met on the second and third days. In the end, issues of changing public health policy will develop.

How to track the course of new technologies on early diagnosis, pooling data from multiple sites, and developing a large single-arm cohort registry to learn outcomes will most likely answer key questions about early diagnosis and interventions, even better than randomized clinical trials. Evolving technologies which are clearly going to happen in the near future will make randomized, controlled trials unwieldy, vulnerable to contamination, and unlikely to succeed.

Dr. Deborah Marshall (Bayer Diagnostics, Emeryville, California), presented estimates on cost-effectiveness of one-time prevalence screening with spiral CT. Using the data from the ELCAP study to estimate the lung cancer prevalence, detection rate, false-positive rate, and the probability of using other diagnostic tests for follow-up investigation, the cost per life year gained could be as low as \$6,000. If the lung cancer prevalence were 0.7% instead of 2.7%, the cost per life year gained would be \$23,000. A similar cost-effectiveness analysis by Robert Clark (H. Lee Moffitt Cancer Center, Tampa, Florida), showed a cost of \$28,000 to \$49,000 per life year gained for five years of screening and five years of follow-up. This is still within the usual benchmark of \$50,000 for a screening test. The cost of screening will be lower with a fully operational dedicated screening CT unit because of improved screening efficiency. The approximate cost per spiral CT would go down from the current \$200 to \$100.

Dr. Stefan Diederich (Muenster, Germany) reported 37,000 lung cancer deaths per year in Germany. His studies revealed a prevalence of lung cancer of

3.6% in patients over the age of 60 who were heavy smokers, 2.0% in patients over age 50, and 1.2% in persons over age 40.

Considerable discussion surrounded the description of the National Cancer Institute-proposed randomized, controlled trial. It may compare the outcome of patients screened for lung cancer by standard x-rays compared with helical CT. The number in each treatment arm necessary to find a 20% reduction in mortality was projected to be 44,000 in each treatment arm, and was predicated on an 85% compliance to assignment prediction. Virtually everyone in the audience felt that compliance to a screening study that employed conventional (and obsolete) standard chest x-rays was destined to failure, and at a huge cost. Many gave strong opinions against such studies, including Dr. Nathaniel Berlin (Miami, Florida), and Olli Miettinen, Ph.D. (Montreal, Canada). The concern was how one can ethically obtain an informed consent to enroll people into clinical trials with the knowledge that a test such as spiral CT is four times more sensitive than chest x-ray, and that early lung cancer is highly curable by current therapies. With ready access to spiral CT in the private sector, contamination of the “control” arm and selection bias due to inclusion of a disproportional number of people in lower socioeconomic status into the study that have a different risk profile and adherence to follow-up procedures would make the data from a randomized clinical trial uninterpretable.

Doctors Stephen Lam and Branko Palcic (Vancouver, Canada), reported upon automated image analysis of exfoliated sputum cells. Although conventional sputum cytology in experienced hands had been determined to be 98% specific, it is only 10% to 20% sensitive, and most applicable to central carcinomas. Using new automated image analysis and quantitative DNA stain instead of conventional Pap stain, the sensitivity is increased to 80% with a specificity of 90% for Stage 0/I. Even peripheral adenocarcinomas can be detected with a similar sensitivity and specificity. The hypothesis to test the use of quantitative

microscopy of sputum cells to improve the specificity of spiral CT was proposed.

The use of CT scanning in staging received considerable discussion. It has an approximate 65% accuracy in lymph node staging. Mediastinoscopy today, remains the gold standard. Whether or not positron emission tomography, (PET), can add significantly to CT scanning and replace mediastinoscopy is an interesting, but unanswered question.

Valerie Rusch (Memorial Sloan-Kettering Cancer Center), discussed the role of sentinel lymph nodes sampling. Whether or not this will be adequate for staging and planning of extended resection, remains an unanswered question.

Dr. Robert Ginsberg (Memorial Sloan-Kettering Cancer Center), discussed lung volume reduction surgery for palliation of emphysema. This surgery has resulted in an interesting shift in our concepts about what degree of respiratory insufficiency is an absolute limitation to resectional surgery. Some patients have improved pulmonary function following lobectomy for an apical solitary nodule in regions of central lobular emphysema. Conventional opinion concerning the extent of resection for lung cancer is that lobectomy is the surgery of choice. Segmentectomy represents some compromise in terms of recurrence. Wedge resection results in more compromise.

Others discussed the use of thoracoscopic surgery for peripheral nodules. Dr. Junji Yoshita (National Cancer Center East Hospital, Kishiwa, Japan), discussed the Japanese experience in limited resection in *in situ* or IA lesions. In 146 patients with tumors < 2.0 cm, the projected five-year survival is 97.8%. Whether limited surgery has a role in very small tumors detected by screening spiral CT needs to be evaluated in randomized clinical trials.

Chemoprevention using Cox-II drugs may be an appropriate subject in future chemoprevention studies. Such studies are currently ongoing in treatment of familial adenomatous polyposis for prevention of colon cancer.

Dr. Paul Bunn Jr. (University of Colorado Cancer Center, Denver, Colorado), reported

on the role of chemotherapy in early stage disease. Evolving therapeutic agents, such as carboplatinum and taxol are well tolerated by most patients. Preoperative compliance to chemotherapy is about 95% and results in a lower tumor burden, the down-staging of cancer, and sometimes easier resectional surgery. Whether or not better survival will be achieved through adjuvant preoperative chemotherapy in early stages of lung cancer remains to be determined by controlled clinical trials. Such studies are in progress.

At least two new acronyms received serious and sometimes lighthearted discussion. Atypical adenomatous hyperplasia, AAH, may be precursors of bronchoalveolar cell carcinoma. It makes a big difference in terms of survival, whether the cancer is purely superficial or invades the stroma. Indeterminate thoracic opacities, ITO, might be an appropriate term for the small, approximately 3.0 mm lesions that are commonly found by CT screening. If the ground glass density persists after a course of antibiotics, AAH or bronchoalveolar carcinoma should be considered. Diagnosis of these lesions require proper processing of the resected specimen and interpretation by experienced pathologists.

The ongoing PLCO study, which was started in 1993, aimed at the early identification of prostate, lung, colon, and ovarian cancer has now enrolled approximately 140,000 subjects. For lung cancer, its purpose was to determine whether screening chest radiography provided a mortality benefit. It is estimated that this study will be completed around 2015.

The workshop sections focused on the pooling of data, to develop an expanded data base to answer key questions about identification, course, prognosis, and treatment outcomes. Evaluation of evolving diagnostic screening research was a second workshop. Evaluation of interventions in screening research, quality assurance of imaging in screening research, and quality assurance of pathology in screening research completed the break-away workshop assignments. These resulted in consensus statement recommendations, which will appear in forthcoming publications of

“Chemoprevention using Cox-II drugs may be an appropriate subject in future chemoprevention studies.”

ELCAP and ICScreen, which certainly will gain momentum, even as this year unfolds.

Our take-away messages from this extremely informative and exciting Conference, are summarized as follows:

We must promote an approach aimed at early identification and intervention in lung cancer. We believe that we now have the tools and technology to change lung cancer outcomes, if applied in a systematic and efficient manner. The question is no longer, can we find lung cancer at an early stage, but rather is a quantitative one, "How frequently and how much of an influence will early lung cancer diagnosis and treatment have on cure?" A corollary to this question is, "What technology is most useful, and in what sequence?." Finally, "What are the costs?." Before embarking on an early detection program, expertise in the following areas must be available in order not to put the patient at risk: chest imaging, interventional radiology or pulmonology, cytopathology, histopathology, and thoracic surgery. A panel of experts should review atypical lesions.

Who Should We Screen?

Dr. Thomas L. Petty (Denver, Colorado), proposed major and minor criteria, somewhat akin to the Jones criteria for the diagnosis of rheumatic fever, which were popularized in the past among other rheumatologic criteria for disease designation.

Major criteria proposed would be:

- Age 45 or older
- Smoke 30 or more pack-years
- Any degree of airflow obstruction, identified by simple spirometry

The scientific foundation for these recommendations is the Lung Health Study, which enrolled patients between the ages of 35 and 60 who had any degree of airflow obstruction. At the end of five years, 1% of these patients had died of lung cancer, even though no attempts were made in identification, such as standard chest x-rays. In the late follow-up, of the total number of 5,887 patients in the original Lung Health Study, 227 (3.9%), have developed lung

cancer in this relatively young population (John E. Connett, personal communication, 1999). Patients who developed lung cancer had an average tobacco consumption of over 30 pack-years.

Many other studies have linked heavy smoking and airflow obstruction to a several-fold increased risk of lung cancer, compared to patients at equal risks, (i.e., age, smoking, and occupational risks) when airflow was normal (Skillrud D.M. et al. Higher risk of lung cancer in COPD. *Ann Intern Med* 1986;105:503-507; Tockman M.S. et al. Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987;106:512-518; Lange P. et al. Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. *Am Rev Respir Dis* 1990;141:613-617).

Minor criteria for diagnosis should be:

- Occupation (asbestos mining and dusty occupations)
- Symptoms of cough, dyspnea, expectoration, or wheeze
- Family history

Asbestos mining with smoking, is an immediate need for lung cancer screening. Other dusty occupations probably present a minor risk. Symptoms have been associated with risk, as has family history. Thus, we propose that men and women are candidates for screening if three major criteria are present. Two major criteria plus one minor criterion justifies screening, as does one major criterion with two minor criteria. Hopefully, this definition of risk and indications for screening will not eliminate any substantial population where lung cancer prevalence is significance.

It is clear that it is of key importance to involve pulmonologists in the rapidly expanding movement into lung cancer identification and treatment. The pulmonologist is already equipped with pulmonary function testing, bronchoscopy, and experience in managing complications of lung cancer in its advanced stages today. Also, through the National Lung Health

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Education Program, (NLHEP), pulmonologists are soon to promote early identification and intervention in incipient stages of COPD through networks with primary care physicians (Enright P.L. et al. Office Spirometry for Lung Health Assessment in Adults. A Consensus Statement from the NLHEP. *Chest*—in press). Thus, the NLHEP will begin to play an important role in the frontier of lung cancer identification, which is so closely intertwined with the evolution of all stages of COPD.

The above represents only a few selected highlights of this important Conference, which we believe will have the impact of heightening interest in early identification and intervention in lung cancer, immediately and in the future.

Prospects for Lung Cancer Screening

This is the title of an editorial, which recently appeared in the *Lancet* written by James L. Mulshine and Claudia I.

Henschke (*Lancet* 2000;355:592-593). These two leaders in lung cancer early identification who were heavily involved in the recent New York Conference, cite the emerging number of molecular biomarkers that were reported upon at a workshop at the Roy Castle Lung Cancer Foundation in October, 1999 in Liverpool, England. hnRNP A2/B1, K-ras, genomic instability, and abnormal methylation were offered as lung cancer biomarkers. The scientific basis for selection of these indicators was cited in the references included in this timely editorial. Developing a high through-put diagnostic platform for the analysis of biomarker expression in exfoliated bronchoepithelial cells could potentially use the same automated computer-driven processing system that has been widely applied to keep costs down in cervical cancer screening. Populations at high risk to be screened for lung cancer will inevitably include heavy smokers with other risk factors, such as airflow obstruction. The Mayo Clinic is screening such

patients with CT scan, which can identify the simultaneous presence of nodules, many of which are lung cancer, in association with emphysema. Certainly, a combination of airway cell markers and peripheral nodules identified by CT scanning is the direction that the field is taking.

Comment: One problem with the proposed restricted screening to high risk populations (Petty, T.L.) will likely occur when people who have a significant smoking history, such as 20 or more pack-years, but with no other risk such as airflow obstruction symptoms, family history, or occupational risk request screening for personal reasons. If these patients demand lung cancer screening, what should the response be? It seems reasonable to offer testing such as CT screening and identifying sputum cell markers to patients who are willing to pay for the procedures which statistically would have a relatively low yield. The results of such screening could result in value to the patient whether or not a lesion could be identified. In no case, however, should any lack of abnormality be construed as evidence of safety of continued smoking. Smoking cessation should be strongly advised for all smokers. Even when smoking cessation is successful, lung cancer risk does not diminish rapidly. In fact, there are more lung cancers diagnosed in former smokers today than in active smokers (Burns D.M. Primary prevention, smoking, smoking cessation - implications for future trends in lung cancer prevention.

Proceedings of the International Conference on Prevention and Early Diagnosis of Lung Cancer, Varese, Italy, 1998:164-170). This fact needs to be emphasized in our screening approaches.

Another problem which will inevitably face clinicians will be the consideration of which therapeutic strategy would be most appropriate for the earliest of lesions. Doing a lobectomy for a 3.0 mm intraepithelial lesion or peripheral lesion may be inappropriate. Since subsequent cancers may occur in 10% to 20% of patents treated for a primary lung cancer, further lobectomies might be prohibitive by sacri-

“Populations at high risk to be screened for lung cancer will inevitably include heavy smokers with other risk factors, such as airflow obstruction.”

ficing pulmonary function. *In situ* intraepithelial lesions, of course, are candidates for photodynamic therapy, or laser ablation. Brachytherapy may be appropriate for either central or peripheral tumors. Perhaps novel non-surgical approaches may emerge for tiny peripheral lesions. In any case, there is a great need to learn more about the biological evolution of early stage lung cancer and the factors that affect course and prognosis in order to be able to offer patients sufficient advice for informed decision making.

Early Hilar Lung Cancer

Terzi A., Pelosi G., Falezza G., et al. Early hilar lung cancer—clinical aspects and long term survival. Identification of a subgroup of stage IA patients with more favorable prognosis. *Lung Cancer* 2000;27:119-124.

Twenty-nine patients out of 2,018 operated on for a non-small-cell lung cancer between 1987 and 1998 met a proposed new Japanese definition for early hilar lung cancer, (EHLC). Twenty-six of these patients were symptomatic, and 20 had a radiologically visible lesion. More cancers were diagnosed by bronchoscopy, and all tumors were resected. All were squamous carcinomas. The second primary cancer occurred in 4 patients, (13.8 %), two of the same cell type, and two with other cell types. The survival rate, including deaths from any reason at three and five years was 85.6% and 65.6%, respectively. Three patients died of a second primary cancer, six, ten, and 24 months after the original operation. Four patients died from a cardiovascular death. EHLC was defined as “a cancer that is located in a segmental, lobar, or main bronchus with invasion limited to the bronchial wall, without nodal or distant metastases.” This is a small subset of T1 tumors, which carries a favorable prognosis. The authors questioned whether extensive resectional surgery is needed. However, alternatives including brachytherapy and photodynamic therapy are not

without risk. Careful follow-up of all EHLC cancers with sputum cytology and CT scanning was recommended.

Comment: No matter how you slice it, (sic) early stage cancer is easier to control/cure than late stage cancer. Surveillance in high risk populations is the key.

Bronchoscopy for Peripheral Lung Cancer

Adapted from: Tohda Y., Muraki M., Iwanaga T., Kubo H. et al. Applicability of uretero-pelvic fiberscopy in the diagnosis of peripheral lung cancer. *J of Bronchology* 1999;6:251-256.

Most endoscopists consider fiberoptic bronchoscopy to have a limited role in the diagnosis of peripheral solitary pulmonary nodules especially for nodules < 2 cm in diameter. In a study of 259 patients with peripheral primary lung cancer between 1989 and 1996, the diagnostic yield of bronchoscopy using adult sized bronchoscopes (outer diameter 5.3 mm to 6.3 mm) was compared with that using a fine uretero-pelvic fiberscope (Olympus URF, outer diameter 3.3 mm, biopsy channel 1.2 mm). Eighty-three percent of 18 tumors ≤ 2 cm were diagnosed using URF in the first bronchoscopic procedure compared to 58% of 12 tumors using an adult bronchoscope. A similar yield was also observed in 106 patients with adenocarcinoma of all sizes.

Comment: The diagnostic yield of fiberoptic bronchoscopy with an adult bronchoscope is generally < 30% for tumors ≤ 2 cm. This study is important in the light of current developments in spiral CT where the average size of the tumors detected is between 12 mm and 16 mm in diameter. The uterero-pelvic fiberscope is not ideal for bronchoscopy because of poor suctioning. However, newer bronchoscopes such as the Olympus BF-XP40 that has an outer diameter of 2.8 mm and a similar 1.2 mm biopsy channel are now available. In the

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diagnosis of peripheral lung nodules, there is now an alternative to fine needle aspiration biopsy without the risk of pneumothorax.

Lung Cancer Statistics

C A *A Cancer Journal for Clinicians* January/February, 2000 Vol 50, No. 1, brings us up-to-date on contemporary cancer statistics. Excerpts from this annual publication are cited.

Table 1 and Table 2 present reported deaths of the five leading cancer sites by age in the United States, according to sex. Lung cancer stands out in both sexes, with most deaths occurring over the age of 40. Note that in the 40 to 59 age group, there are 15,379 deaths from lung and bronchus cancer in men, and 10,088 in women. Totaling up the figures gives us 90,760 lung and bronchus deaths in men over the age of 40 and 61,455 deaths in women over that age, for a grand total of 152,215 deaths from lung and bronchus cancer. This Table does not list deaths from lung cancer in people under the age of 40, where of course, lung cancer is not a common cause of death. However, the *LCF* Editor has seen at least a dozen patients, both men and women who died of lung cancer under the age of 40. The youngest was age 29. So, we must not consider lung cancer as just a disease in old smoking men. It is a disease in both men and women, and it is now attacking younger age groups.

Table 3 shows the dismal fact that lung cancer survival has only improved 1% since 1974. It is astonishing that this is statistically significant. Compare these numbers with the improvement in survival in both whites and blacks for breast, colon, prostate, uterine cervix, and uterine corpus. Patients with all other cancers are experiencing a highly significant improvement in survival. Do we need to make a stronger case for earlier identification and intervention?

Table 1: Reported Deaths for the Five Leading Cancer Sites for Males by Age, U.S., 1997.

All Ages	<20	20-39	40-59	60-79	≥80
All Sites 281,110	All Sites 1,252	All Sites 5,467	All Sites 47,118	All Sites 161,581	All Sites 65,685
Lung & Bronchus 91,278	Leukemia 423	Non-Hodgkin's Lymphoma 723	Lung & Bronchus 15,379	Lung & Bronchus 59,558	Lung & Bronchus 15,823
Prostate 32,891	Brain & ONS 288	Leukemia 662	Colon & Rectum 4,347	Prostate 16,277	Prostate 15,511
Colon & Rectum 28,075	Endocrine System 115	Brain & ONS 625	Pancreas 2,584	Colon & Rectum 15,842	Colon & Rectum 7,459
Pancreas 13,470	Bones & Joints 86	Lung & Bronchus 512	Non-Hodgkin's Lymphoma 2,552	Pancreas 7,898	Urinary Bladder 2,900
Non-Hodgkin's Lymphoma 12,286	Non-Hodgkin's Lymphoma 86	Colon & Rectum 412	Esophagus 2,069	Non-Hodgkin's Lymphoma 6,383	Pancreas 2,843

Note: "All Sites" excludes *in situ* carcinomas except urinary bladder. ONS=other nervous system.

Source: U.S. Mortality Public Use Data Tape 1997, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999.

Table 2: Reported Deaths for the Five Leading Cancer Sites for Females by Age, U.S., 1997.

All Ages	<20	20-39	40-59	60-79	≥80
All Sites 258,467	All Sites 1,009	All Sites 6,159	All Sites 45,781	All Sites 131,274	All Sites 74,240
Lung & Bronchus 61,922	Leukemia 322	Breast 1,629	Breast 12,093	Lung & Bronchus 38,488	Lung & Bronchus 12,879
Breast 41,943	Brain & ONS 253	Uterine Cervix 629	Lung & Bronchus 10,088	Breast 18,385	Colon & Rectum 12,046
Colon & Rectum 28,621	Soft Tissue 85	Lung & Bronchus 462	Colon & Rectum 3,426	Colon & Rectum 12,799	Breast 9,835
Pancreas 14,205	Endocrine System 79	Leukemia 462	Ovary 2,801	Pancreas 7,437	Pancreas 5,045
Ovary 13,507	Bones & Joints 71	Brain & ONS 385	Uterine Cervix 1,803	Ovary 7,207	Non-Hodgkin's Lymphoma 3,859

Note: "All Sites" excludes *in situ* carcinomas except urinary bladder. ONS=other nervous system.

Source: U.S. Mortality Public Use Data Tape 1997, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999.

Table 3: Trends in Five-year Relative Cancer Survival Rates* (%) by Race and Year of Diagnosis, U.S., 1974–1995.

Site	1974 - 1976	1980 - 1982	1989 - 1995	1974 - 1976	1980 - 1982	1989 - 1995	1974 - 1976	1980 - 1982	1989 - 1995
	White			Black			All Races		
All Sites	51	52	61**	39	40	48**	50	51	59**
Breast (Female)	75	77	86**	63	66	71**	75	76	85**
Colon	51	56	62**	46	49	52**	50	55	62**
Lung & Bronchus	13	14	14**	12	12	11	13	13	14**
Prostate	68	75	93**	58	65	84**	67	73	92**
Uterine Cervix	70	68	71**	64	61	59	69	67	70
Uterine Corpus	89	83	86**	61	54	56	88	82	84**

* Survival rates are adjusted for normal life expectancy and are based on follow-up of patients through 1996.

** The differences in rates between 1974-1976 and 1989-1995 is statistically significant (P < 0.05).

Source: Surveillance, Epidemiology and End Results Program 1973-1996, Division of Cancer Control and Population Sciences, National Cancer Institute.

Genetic Alterations in Bronchial Lavage as a Potential Marker for Individuals with a High Risk of Developing Lung Cancer

Field J.K., Triantafillos L., Xinarianos G. et al. *Cancer Res* 1999;59:2690-2695.

These investigators studied DNA's from 12 microsatellite markers obtained from the bronchial lavage of 90 individuals who were referred to an early lung cancer clinic in Northwest England for suspected lung cancer. Genetic alterations were detected in 15 (35%), of 43 patients with lung cancer, but also in 11 (23%), of 47 patients with no cytological or radiological evidence of bronchial neoplasia. There were no significant differences between referring symptoms in either group, with or without genetic alterations. No correlation was found between smoking exposure and loss of heterozygosity, (LOH)/microsatellite alterations in the microsatellite markers. The most prevalent type of abnormality was LOH,

which was found through a predominance of microsatellite alterations (P=0.01). The results showed a substantial proportion of cells in the bronchial lavage from suspected lung cancer patients that carried identifiable genetic alterations. However, these alterations in bronchial lavage of individuals with no evidence of lung cancer, raise the question of whether genetic instability is a phenomena solely associated with cancer, or represents a feature of non-neoplastic disease. These results suggest that microsatellite PCR-based assays can be developed as tools for the earlier identification of genetic changes in cells exfoliating in the bronchus.

Comment: This article is cited to show temporary research in finding molecular markers of early lung cancer in expectorated sputum. Such an approach needs to be refined and made practical and commercially available to be able to identify airway cell markers indicative of central bronchogenetic markers as a complement to CT scanning for early identification, particularly in high risk groups.

“Genetic alterations were detected in 15 (35%), of 43 patients with lung cancer...”

Racial Differences in the Treatment of Early-stage Lung Cancer

Bach P.B., Cramer L.D., Warren J.L., Begg C.B. *N Engl J Med* 1999;341:1198-1205.

This study aimed to answer three questions about the treatment of early stage non-small-cell lung cancer.

1. Is there a difference in the rate of surgical treatment between white and black patients with early stage lung cancer?
2. If so, is this discrepancy still apparent once the effects of coexisting illness, socioeconomic status, insurance coverage, and availability of care influence are eliminated?
3. Does the discrepancy explain the differences in survival between black and white patients with lung cancer?

All black patients and white patients 65 years or older, diagnosed as resectable of non-small-cell carcinoma stage I or II, between 1985 and 1993, and who resided in the study areas for the Surveillance Epidemiology and End Results, (SEER), program, (10,984 patients), were enrolled. Data on the diagnosis, stage, treatment, and demographic characteristics of the patients were obtained from the SEER data base. Information on coexisting illness, type of medical coverage, and survival outcome was obtained from Medicare records.

Results: The results of surgery was 12.7 percentage points lower in survival for black patients compared with white patients (64.0% versus 76.7%, $P < 0.001$). The five-year survival rate was also lower in blacks (26.4% versus 34.1%, $P < 0.001$). However, among the patients who received surgery, survival

was similar for the two racial groups, as it was in those patients who could not have resectional surgery. Analysis in which adjustments were made for factors that are predictive of either candidacy for surgery or survival, did not alter the influence of race on the outcomes.

Conclusions: This study suggests that the lower survival rate among black patients with early stage non-small-cell lung cancer compared with white patients, is mostly explained by the lower rate of surgical treatment for blacks. Efforts to increase the rate of surgical treatment for black patients appear to be a promising way of improving survival in this ethnic group.

Comment: This interesting study again makes the point that surgery of early stage lung cancer has a good outcome. In fact, at five years, the survival rate was 50% for whites, and marginally less for blacks. Even at ten years, the survival rate for whites was 25%, including deaths from all causes, compared with blacks where it was about 20%. These outcomes are far better than the average outcome of 14% survival when lung cancer is diagnosed in all stages.

Emphysematous Lesions and Lung Function in Healthy Smokers 60 Years of Age

Tylén U., Boijesen M., Ekberg-Jansson A., Bake B., et al. *Respir Med* 2000;94:38-43.

Emphysematous lesions were evident in 44% of healthy, symptom-free smokers, according to the researchers studying the occurrence of such lesions and the relationship between pulmonary changes on high resolution computed tomography, (HRCT), and lung function tests.

The study included 57 smoking and 32 never-smoking healthy men—aged 61 or 62 years—drawn from a randomized

“Efforts to increase the rate of surgical treatment for black patients appear to be a promising way of improving survival in this ethnic group.”

epidemiological study. Full inspiration HRCT was performed with a 1.5 mm slice thickness and a 3 cm inter-slice distance. Evaluation was made by radiologists with no knowledge of the subjects' smoking history. Emphysematous lesions were visually scored. The pulmonary function tests administered included spirometry and the diffusion capacity test (D_LCO).

Emphysematous changes were demonstrated in 25 smokers, but in only one never-smoker. The most sensitive test for early emphysematous lesions was D_LCO /alveolar volume. It also correlated with radiological scoring.

The authors wrote, "HRCT may reveal emphysematous lesions in smokers before clinical symptoms have developed."

Comment: Many years ago, it was reported that 50% of smokers get symptoms of cough and sputum production resulting in the diagnosis of chronic bronchitis (Fletcher C., Peto R. The natural history of chronic airflow obstruction. *Brit Med J* 1977;1:1645-1648). However, Fletcher and his associates recognized that only 15% of smokers actually developed airflow obstruction, as judged by spirometry (Fletcher C. et al. *The Natural History of Chronic Bronchitis and Emphysema*. Oxford University Press, New York, NY 1976 pp 272), which is consistent with other observations (Olofson J., Skoogh B.E., Bake B., Svardsudd K. Mortality related to smoking habits, respiratory symptoms and lung function. *Eur J Respir Dis* 1987;71:69-76). In this country, (Gelb A.F., et al. Limited contribution of emphysema in advanced COPD. *Am Rev Respir Dis* 1993;147:1157-1161) also found a poor correlation between CT emphysema scores and either FEV_1/FVC percent, or FEV_1 percent of predicted. A strong negative correlation between diffusion capacity and CT score was present. Thus, emphysema lesions themselves may not be a major factor in the reduction in airflow. After all, airflow is a function of elastic recoil and airway resistance.

However, it is possible to have emphysema without loss of elastic recoil, and in fact, elastic recoil loss without emphysema, which sometimes occurs in alpha-1 antitrypsin deficiency states. The bottom line is that the spirometer measures airflow limitation of clinical significance and is the only practical tool for the early detection and intervention in COPD.

Historical Vignette

John Hutchinson, a surgeon, invented the spirometer. He coined the term, vital capacity, i.e., the capacity for life. John Hutchinson was a very precise man and a violinist of some reputation. His exacting observations allowed him to learn that the vital capacity was directly related to height and inversely related to age. In his first paper published in 1846, he reported on measurements in 2,130 individuals, including deceased patients (On the capacity of the lungs and on the respiratory function with a view of establishing a precise and easy method of detecting disease by the spirometer. *Med Chir Tr London* 1846;29:137). He recognized that reductions in vital capacity predicted premature morbidity and mortality. Hutchinson became a consultant to the insurance industry of London. He recommended that the vital capacity should be used in actuarial predictions. Hutchinson's invention was initially acclaimed. "We have no hesitation in recording our deliberate opinion, that it forms one of the most valuable contributions to physiological science that we have seen for some time. In all future investigations, the name of Mr. Hutchinson must receive honorable notice" (Bishop P. J. A bibliography of John Hutchinson. *Med Hist* 1977;21:384-396).

But Hutchinson's instrument was not widely accepted in London or anywhere else and still remains absent from most physicians' offices and clinics. Since this is so, it is reasonable to conclude that John Hutchinson was frustrated when he

"The most sensitive test for early emphysematous lesions was D_LCO /alveolar volume."

"If the vital capacity is so important in clinical medicine, why don't all physicians have a spirometer in their offices, just as they have a sphygmomanometer, an EKG machine, a clinical thermometer..."

(Spirometer, *continued*)

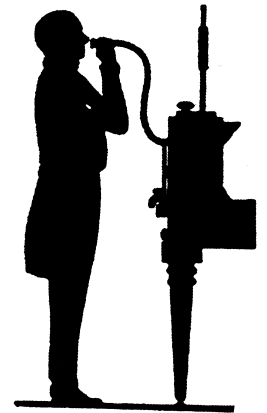
left his wife and three children and emigrated to Australia at age 41. At this time, he abandoned all further scientific study of his device. Toward the end of his life, he moved to Fiji where he died at age 50, possibly from tuberculosis. The British Thoracic Society and The Thoracic Society of Australia erected a monument to the memory of John Hutchinson in 1980 (see Figure).

In 1980, it was reported that the vital capacity was a powerful prognostic indicator in the Framingham study of 5,209 men over the age of 30. "This simple office procedure is a useful predictor of pulmonary disease and cardiac failure and can effectively select groups of persons destined for premature death. Since the vital capacity predicts cardiovascular as well as non-cardiovascular mortality, this pulmonary function measurement seems truly a measure of living capacity useful for insurance and underwriting purposes."(Kannel W.B., et al. The value

of measuring vital capacity for prognostic purposes. *Trans Am Life Ins Med Dir of Am* 1980;64:66).

If the vital capacity is so important in clinical medicine, why don't all physicians have a spirometer in their offices, just as they have a sphygmomanometer, an EKG machine, a clinical thermometer, and a tape measure? This deficit in the wide application of simple spirometry in the offices and clinics of primary physicians continues to be amazing. It is now well established that spirometric abnormalities are predictive of a several-fold increased risk of lung cancer, compared with subjects at otherwise equal risk and with normal measures of airflow, as presented elsewhere in this issue of *LCF*.

It is hoped that the dearth of office spirometry will be corrected by the efforts of the National Lung Health Education Program, (NLHEP). The spirometry statement of the NLHEP has just been published in the April issue of *Chest*.



John Hutchinson and a version of his spirometer

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