Excess mortality associated with smoking involves vascular, neoplastic, and respiratory diseases. Doll and Peto, in their classic study of British doctors who smoked, observed that those who continued smoking throughout their lifetime died ten years younger, on average, than lifetime non-smokers. Cessation of smoking by age 50 decreased the mortality rate by approximately 50%. The most recent report on smoking in the United States noted that 19.3% of adults are current smokers (21.5% males; 17.3% females), a decline from 20.9% in 2005.

Cancer death rates are also declining, according to a recent report. Since 1990, cancer deaths (age-standardized per 100,000) have declined 11% in men and 6% in women. These figures reflect prevention of 561,400 cancer deaths in men and 205,700 deaths in women. Death rates decreased for all four major cancer killers (lung, colorectal, breast, prostate). The decrease in cancer mortality stems primarily from reductions in tobacco use, increased screening, and improvements in treatment for specific cancers.

In spite of improvements in smoking prevalence and overall cancer mortality, lung cancer remains the number one cancer killer in the U.S. and most developed countries. American Cancer Society statistics for 2011 estimate that there will be 221,130 new cases of lung cancer and 156,940 deaths from lung cancer. Only 15-20% of lung cancer patients in the U.S. are diagnosed with early stage disease (Stage I and II), and these cancers are usually discovered by incidental imaging of the chest done for other reasons. If we do not screen for lung cancer, then we will wait for patients to present with symptomatic disease, and symptomatic lung cancer is seldom early stage. If we are going to shift the current paradigm for treating lung cancer, a disease in which only 16% of all new cases survive five years, then we need to develop early detection methods that give patients more curative options.
The Current Status of CT Screening For Lung Cancer

continued from page 1

Screening

Previous screening studies employing chest radiographs and/or sputum cytology failed to show any reduction in lung cancer mortality. Early studies demonstrated that when a chest x-ray was obtained within 30 days of a low-dose (radiation) computed tomography (LDCT) study, the chest x-ray missed 70-80% of the LDCT-detected lung cancers. Most recently, annual chest x-ray screening did not reduce lung cancer mortality in a randomized study of 154,901 participants, even in a subgroup of patients at high risk for lung cancer. In the past 10-15 years, a large number of clinical trials evaluated the role of LDCT screening for asymptomatic lung cancer.

Pooled data from three non-randomized studies showed that LDCT screening detected three times as many lung cancers as would have been predicted from a validated control group. The rate of detection of lung cancers in Stage I was 60-80% in numerous LDCT screening trials. There are better options for curative treatment with earlier stage disease, and these studies reported markedly improved survival (60-85% 5-year survival) for patients with lung cancer detected by LDCT. One limitation of these non-randomized trials was that it was uncertain if this stage shift resulted in fewer patients with advanced stage disease. These trials were also limited by lead time, length time, and overdiagnosis biases. Briefly, lead time bias occurs when screening identifies a cancer at an earlier time, but this does not result in a change in the date of death. Length time bias occurs when screening detects slow-growing cancers. Overdiagnosis occurs when screening detects a very slowly growing cancer that would not have led to the death of the screened individual. This would be equivalent to finding prostate cancer during a postmortem examination of an elderly male who died with prostate cancer but not from it.

The potential limitations or risks associated with LDCT screening are the large number of non-calcified nodules (NCNs) detected on screening CT scans and the necessity for follow-up imaging studies. The vast majority of NCNs are benign, but this can only be confirmed with time/follow-up. Non-calcified nodules ≥8-10 mm and enlarging nodules require further evaluation that may include PET scanning, biopsy, and/or surgical removal. The rate of surgical removal of benign NCNs ranges from 16-34% in a number of reports. LDCT screening trials have found a significant number of slow-growing nodules that are subsequently proven to be adenocarcinoma in situ (previously called bronchioloalveolar carcinoma) or adenocarcinoma with lepidic growth. It is estimated that approximately 25-30% of these slow-growing cancers have volume doubling times (VDTs) ≥400 days and may be classified as overdiagnosis (a slow-growing cancer that will not result in the patient's death). Software that calculates volumes and VDTs of NCNs detected on screening was used in the NELSON trial to identify rapidly growing (VDT <400 days) nodules that required further workup and diagnosis. Calculating VDT over a 3 month period significantly reduced the false-positive rate. More accurate and sensitive VDT analysis may one day allow shorter follow-up times than are currently recommended by the Fleischner guidelines, thus decreasing the surveillance period and radiation exposure.

Key Results of the National Lung Screening Trial

• 20% reduction in lung cancer mortality
  – LDCT screening prevents one in five deaths from lung cancer
• 6.7% reduction in all-cause mortality
• 320 persons needed to be screened with LDCT to prevent one death

(LDCT = low-dose computed tomography)
The Current Status of CT Screening For Lung Cancer

continued from page 2

detected in the chest x-ray group. By the end of the study, 1,060 and 941 lung cancers were detected in the LDCT and chest x-ray groups, respectively (Table 1). During the screening period of the study, 63% of the lung cancers detected by LDCT arm were Stage I and 70% were Stage I/II. Over 90% of the patients with Stage I lung cancers underwent surgical resection. In the chest x-ray arm, 48% were Stage I and 57% were Stage I/II.

<table>
<thead>
<tr>
<th>Table 2. Limitations and Risks of LDCT Screening for Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Detection of many NCNs that require follow-up</td>
</tr>
<tr>
<td>• Potential psychological impact of discovering a NCN</td>
</tr>
<tr>
<td>• Surgery for benign disease</td>
</tr>
<tr>
<td>• Interval cancers (screening failure)</td>
</tr>
<tr>
<td>• Lung cancer deaths in screened participants</td>
</tr>
<tr>
<td>• Potential overdiagnosis</td>
</tr>
<tr>
<td>• Risk of radiation-induced cancers</td>
</tr>
</tbody>
</table>

In the NLST, 25% of all deaths were due to lung cancer. With over 140,000 person-years of observation in each arm, there were 356 (LDCT arm) and 443 (chest x-ray arm) lung cancer deaths. This corresponded to rates of death from lung cancer of 247 (LDCT) and 309 (chest x-ray) per 100,000 person years and a relative reduction in death from lung cancer of 20.3% in the LDCT arm. There was also a significant reduction in all-cause mortality of 6.7% in the LDCT arm. The number needed to screen with LDCT to prevent one lung cancer death was 320.  

Limitations or risks of LDCT screening were identified in the trial (Table 2). A total of 24.2% of participants in the LDCT group and 6.9% participants in the chest x-ray group had abnormal screening tests. Of these abnormalities, the vast majority were false positives (not proven to be cancer). The rate of complications after a diagnostic procedure for a positive screening test was low. The rate of thoracic operations for benign disease was 24% (164 benign; 509 lung cancer).  

In the NSLT, a test was reported to be positive if it had a NCN ≥4 mm or other abnormalities suspicious for lung cancer (e.g., pleural effusion). Non-calcified nodules require interval follow-up based on their size, and this follow-up is usually performed according to the Fleischner Society guidelines for management of small pulmonary nodules. The NLST report did not provide further information about the optimal frequency and duration of follow-up of NCNs beyond the initial three CTs, but that may be the subject of further reports. I therefore recommend following the Fleischner guidelines.

A significant concern of patients is the risk of radiation-induced cancer related to screening or diagnostic x-rays. This risk was not quantified in the NLST report. The dose of radiation with the LDCT was 1.5 milliseiverts (mSv), which is lower than the dose of radiation from a typical standard chest CT (7 mSv). The American College of Radiology and the Radiology Society of North American have published risk estimates of additional fatal cancer attributable to imaging studies (RadiologyInfo.org). The risk associated with LDCT is estimated to be “very low,” which corresponds to a risk of fatal cancer of 1 in 10,000 to 1 in 100,000. The NLST reported a cumulative mortality reduction with LDCT of 30 lung cancer deaths per 10,000 screened. Thus, in this high-risk group in the NLST, the benefit of CT screening outweighed the risk of cancer associated with radiation exposure from the LDCT.

Table 1. Comparison of LDCT and CXR for Lung Cancer Screening in the NLST

<table>
<thead>
<tr>
<th></th>
<th>LDCT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal scans</td>
<td>24.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td>False-positive tests</td>
<td>96.4%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Lung cancer found during screening period</td>
<td>649</td>
<td>279</td>
</tr>
<tr>
<td>Subsequent lung cancer identified</td>
<td>411</td>
<td>662</td>
</tr>
<tr>
<td>Total lung cancers</td>
<td>1,060</td>
<td>941</td>
</tr>
</tbody>
</table>
The Current Status of CT Screening For Lung Cancer

continued from page 3

Future Directions

Biomarkers, in addition to age and smoking history, could be used to further stratify patients at high risk for lung cancer and to determine which individuals would benefit most from screening. In addition, biomarkers could be used to predict the malignant potential of NCNs found on screening CTs.

It is anticipated that we will soon be able to genotype an individual’s entire genome for $1,000. With this advance, genes associated with high risk for lung cancer could be detected. Genome-wide association studies (GWAS) have suggested that 15q 24-25 is associated with a higher risk of lung cancer, although that may be due to smoking addiction risk rather than pure lung cancer risk. Another study has suggested that two single nucleotide polymorphisms (SNPs) at 13q 31.3 may be associated with lung cancer in never-smokers. If genes associated with a high risk of lung cancer could be detected reliably with low-cost testing, this knowledge would likely influence an individual’s decisions about lung cancer screening.

Other biomarkers under study for assessing lung cancer risk include gene expression in bronchial brushings, chromosomal aneusomy, and gene methylation in sputum. Blood tests measuring serum proteins, autoantibodies to tumor antigens, microRNA, and gene expression by peripheral blood mononuclear cells are also being evaluated as biomarkers. A number of companies/centers are analyzing volatile organic compounds in exhaled breath as potential biomarkers of cancer.

Several models of lung cancer risk have been published and have an accuracy of approximately 70%. A recently reported risk model was developed based on the prostate, lung, colon, and ovarian (PLCO) screening trial. The model was externally validated in current and former smokers and had an accuracy of approximately 80%. Genomic analysis (specific risk genes) and biomarkers of some type are likely to be incorporated into future risk models to further enhance their accuracy. I would anticipate that the future of screening would be to use risk prediction models to help determine those at high risk and those at low risk. Then, based on the risk analysis, an individual and their physician will decide on whether or not to screen for lung cancer.

References

2. Vital Signs: Current Cigarette Smoking Among Adults ≥18 years in United States, 2005-2010, MMWR 2011; 60:1207-12

Disclosures

Dr. Jett reported that he has research grants pending with Oncimmune, Inc. (blood biomarkers) and iSense (breath analysis).
Cost-effectiveness of computed tomography screening for lung cancer in the United States


INTRODUCTION: A randomized trial has demonstrated that lung cancer screening reduces mortality. Identifying participant and program characteristics that influence the cost-effectiveness of screening will help translate trial results into benefits at the population level.

METHODS: Six U.S. cohorts (men and women aged 50, 60, or 70 years) were simulated in an existing patient-level lung cancer model. Smoking histories reflected observed U.S. patterns. We simulated lifetime histories of 500,000 identical individuals per cohort in each scenario. Costs per quality-adjusted life-year gained ($/QALY) were estimated for each program: computed tomography screening; stand-alone smoking cessation therapies (4-30% 1-year abstinence); and combined programs.

RESULTS: Annual screening of current and former smokers aged 50 to 74 years costs between $126,000 and $169,000/QALY (minimum 20 pack-years of smoking) or $110,000 and $166,000/QALY (40 pack-year minimum), when compared with no screening and assuming background quit rates. Screening was beneficial but had a higher cost per QALY when the model included radiation-induced lung cancers. If screen participation doubled background quit rates, the cost of annual screening (at age 50 years, 20 pack-year minimum) was below $75,000/QALY. If screen participation halved background quit rates, benefits from screening were nearly erased. If screening had no effect on quit rates, annual screening costs more but provided fewer QALYs than annual cessation therapies. Annual combined screening/cessation therapy programs at age 50 years costs $130,500 to $159,700/QALY, when compared with annual stand-alone cessation.

CONCLUSION: The cost-effectiveness of computed tomography screening will likely be strongly linked to achievable smoking cessation rates. Trials and further modeling should explore the consequences of relationships between smoking behaviors and screen participation.

EDITORIAL COMMENT: As discussed in this issue of Lung Cancer Frontiers, the National Lung Screening Trial (NLST) found that annual computed tomography (CT) screening for two years of a population at high risk for lung cancer reduced lung cancer mortality by 20% when compared to chest x-ray screening. However, the true impact of CT screening on lung cancer incidence and mortality under real-world circumstances is difficult to predict. In addition, how the NLST results might influence those at risk for lung cancer, for example individuals who still smoke, is unknown. It is conceivable that increased awareness of effective lung cancer screening might encourage smoking cessation because screening increases interaction with physicians who can emphasize the importance of quitting smoking. Alternatively, negative scans could serve as a disincentive for current smokers to quit.

The stated purpose of the article by McMahon et al. was to “estimate the cost-effectiveness of CT screening for lung cancer in the US population and to identify characteristics of lung cancer screening... with the largest influences on...
cost-effectiveness of screening.” In addition, the authors compared screening with smoking cessation programs and with combined screening and smoking cessation programs.

The authors use an established micro-simulation model, the Lung Cancer Policy Model (LCPM). This model is based on tumor registry data of lung cancer incidence, size, stage, cell type and survival. Previously, the LCPM predicted a mortality reduction of 15% in screened individuals (at six years of follow-up) compared to 20% found in the NLST (also at six years of follow-up with three yearly screens in individuals with a ≥30 pack-year smoking history).

McMahon and colleagues found that screening costs were between $126,000 and $169,000 per QALY gained. However, when they included other factors, such as incidence of radiation pneumonitis or impact of smoking cessation, the cost per QALY changed, sometimes dramatically. In a scenario where smoking cessation increased (i.e., more people quit smoking, therefore there were fewer cancers), the cost per QALY was $75,000. However, if smoking cessation decreased (and therefore cancer incidence increased), the cost increased to $880,000-$1 million per QALY.

This paper provides interesting insight into potential real-world consequences of a lung cancer screening program. The results are particularly notable in that the cost of lung cancer screening, ignoring smoking cessation rates, was greater than other screening programs in the U.S. Colorectal cancer screening, for example, costs between $13,000 and $32,000 per QALY and yearly mammography for women over 40 has a cost-effectiveness of $47,700 per QALY. These data also suggest that factors such as smoking cessation rates could have a potentially large impact on cost. Of course, these findings are estimates based on registry data and are not based on actual data from the NLST. However, as new screening programs are implemented, it will be important to try to match real-world experience with the controlled trial setting.

**Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors**


**ABSTRACT:** Lung cancers harboring mutations in the epidermal growth factor receptor (EGFR) respond to EGFR tyrosine kinase inhibitors, but drug resistance invariably emerges. To elucidate mechanisms of acquired drug resistance, we performed systematic genetic and histological analyses of tumor biopsies from 37 patients with drug-resistant non-small cell lung cancers (NSCLCs) carrying EGFR mutations. All drug-resistant tumors retained their original activating EGFR mutations, and some acquired known mechanisms of resistance including the EGFR T790M mutation or MET gene amplification. Some resistant cancers showed unexpected genetic changes including EGFR amplification and mutations in the PIK3CA gene, whereas others underwent a pronounced epithelial-to-mesenchymal transition. Surprisingly, five resistant tumors (14%) transformed from NSCLC into small cell lung cancer (SCLC) and were sensitive to standard SCLC treatments. In three patients, serial biopsies revealed that genetic mechanisms of resistance were lost in the absence of the continued selective pressure of EGFR inhibitor treatment, and such cancers were sensitive to a second round of treatment with EGFR inhibitors. Collectively, these results deepen our understanding of resistance to EGFR inhibitors and underscore the importance of repeatedly assessing cancers throughout the course of the disease.

**EDITORIAL COMMENT:** The epidermal growth factor receptor is a member of the human epidermal growth factor receptor family, a group of four trans-membrane tyrosine kinase receptors expressed on epithelial cells of many organs, including the lung. Normal functions of EGFR include epithelial growth and differentiation, cell-cell adhesion and cell migration.

Approximately 10-15% of NSCLCs harbor a mutation in *EGFR*. Most *EGFR* mutations are in the tyrosine kinase domain and result in ligand-independent activation of EGFR and unregulated signaling. Identification of these mutations forms the basis for the use of erlotinib and gefitinib, EGFR tyrosine kinase inhibitors (TKI), as lung cancer treatments. The presence of *EGFR* mutations strongly predicts a response to TKI therapy. Given the poor response of mutation-negative cancers, therapy selection based on molecular characteristics is superior to using standard clinical criteria. However, further analyses have revealed growing complexity with certain *EGFR* mutations that are associated with resistance to TKI treatment. In addition, almost all TKI-responsive lung
Cancers acquire secondary mutations rendering them resistant to further treatment, and relapse is inevitable.

In an effort to deepen our understanding of EGFR TKI resistance, the authors of this study examined biopsies of EGFR-positive patients after they had acquired TKI resistance and performed genetic and histologic analyses. Resistance to TKI therapy was defined as progressive disease on TKI treatment, despite an initial response. While they identified common EGFR resistance mutations (such as the EGFR T790M mutation and the MET amplification), they also identified more rare genetic alterations, including PI3KCA amplifications and β-catenin mutations. Interestingly, histologic analysis revealed that five of the original 37 patients had pathology consistent with SCLC upon becoming TKI resistant. In addition, three patients had histologic changes consistent with epithelial to mesenchymal transition, an aggressive phenotype. They also determined that TKI resistance could be reversed in some patients after being off TKI therapy for a period of time.

This is an interesting study that provides insight into the vexing problem of TKI resistance. Mechanisms of TKI resistance have been investigated in TKI-resistant cell lines and this analysis provides a more practical clinical perspective. Perhaps most interesting, 14% of biopsied tumors had SCLC features, while none of these tumors had neuroendocrine features prior to TKI therapy. Importantly, all specimens retained the original EGFR mutation, making a second lung primary highly unlikely. These data suggest that serial biopsies in patients receiving TKI therapy could provide information that directly impacts therapy. The five patients found to have SCLC all responded to SCLC treatment regimens. Limitations of this study include the fact that it was retrospective and therefore the time of biopsy was not standardized. However, understanding TKI resistance and the possible impact of TKI therapy on histologic subtype is an important aspect of lung cancer care.

ABSTRACT: Somatic mutations and copy number alterations (as a result of deletion or amplification of large portions of a chromosome) are major drivers of human lung cancers. Detailed analysis of lung cancer-associated chromosomal amplifications could identify novel oncogenes. By performing an integrative cytogenetic and gene expression analysis of non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) cell lines and tumors, we report here the identification of a frequently recurring amplification at chromosome 11 band p13. Within this region, only TNF receptor-associated factor 6 (TRAF6) exhibited concomitant mRNA overexpression and gene amplification in lung cancers. Inhibition of TRAF6 in human lung cancer cell lines suppressed NF-κB activation, anchorage-independent growth, and tumor formation. In these lung cancer cell lines, RAS required TRAF6 for its oncogenic capabilities. Furthermore, TRAF6 overexpression in NIH3T3 cells resulted in NF-κB activation, anchorage-independent growth, and tumor formation. Our findings show that TRAF6 is an oncogene that is important for RAS-mediated oncogenesis and provide a mechanistic explanation for the previously apparent importance of constitutive NF-κB activation in RAS-driven lung cancers.

EDITORIAL COMMENT: Somatic mutations of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) occur in up to 30% of NSCLCs, making it the most common genetic variation associated with lung cancer. The KRAS protein is a GTPase, an enzyme that regulates various intracellular signaling pathways through serine/threonine phosphorylation. A single nucleotide mutation on codon 12 or, less commonly, codons 13 and 61, results in constitutive activation of the enzyme and dysregulated signaling. The KRAS mutation is associated with a negative prognosis in lung cancer. Further understanding the mechanisms by which KRAS results in a malignant phenotype is critical.

NF-κB is a transcription factor that is constitutively active in many lung cancers and appears to be a required downstream mediator of KRAS oncogenesis. However, mechanisms leading to NF-κB activation in lung cancer are unknown, and the signal pathway tying KRAS to NF-κB has remained elusive.

This study employed large-scale cytogenetic analysis of 346 NSCLC and SCLC samples (85 cell lines and 261 primary tumors) to identify a novel candidate oncogene.

TRAF6 is an amplified oncogene bridging the RAS and NF-κB pathways in human lung cancer

involved in KRAS-driven lung cancers. Comparative genomic hybridization (aCGH), a high-throughput technique that detects DNA copy number variations, identified high-level focal copy number amplification at five locations. Four had been described previously, while site 11p13 had unknown relevance to lung cancer. Of the 26 genes in the amplified region, TRAF6 alone had significantly increased expression, suggesting that it was the putative oncogene.

TRAF6 is a member of the tumor necrosis factor (TNF) receptor family. In conducting experiments to determine the oncogenic potential of TRAF6 in cells, the authors determined that transfection and overexpression of TRAF6 enhanced cell proliferation and anchorage-independent growth, and caused cells to adopt a transformed, spindle-like morphology. TRAF6 downregulation inhibited cell growth and was primarily (though not exclusively) limited to lung cancer cell lines that harbored an overexpression mutation in either TRAF6 or KRAS, suggesting an association between the two. In mice, subcutaneous injection of cells overexpressing TRAF6 resulted in tumor development at four weeks, while TRAF6 depletion significantly impaired tumor growth. Finally, the authors confirmed that TRAF6 served as an intermediate regulator of KRAS-mediated NF-κB activation and that TRAF6 signaling was required for KRAS oncogenesis.

This study is notable for several reasons. First, it used large-scale, high-throughput genomic copy number analysis to identify a novel oncogene. Second, it identified TRAF6 as a mediator of KRAS malignancy. Lastly, it defined TRAF6 as an upstream activator of NF-κB in lung cancer. It should be noted that while almost all cells lines affected by TRAF6 inhibition had either the TRAF6 or KRAS mutation, one cell line did not, suggesting that TRAF6 might influence cancer development independent of KRAS. Most importantly, understanding KRAS oncogenesis and identification of new oncogenes has the potential to lead to new therapeutic targets.

Disclosures
Dr. Finigan reported no significant conflicts of interest with any companies or organizations whose products or services are discussed in this article.
Continuing Medical Education Events at National Jewish Health

Upcoming Live CME Events*

The 34th Annual National Jewish Health Pulmonary and Allergy Update at Keystone
Continuing Medical Education on pulmonary, asthma, allergy and immunology topics. Stay abreast of the latest knowledge and trends and gain practical information that you can apply in your practice.
Chairs: Erwin Gelfand, MD, Richard Martin, MD, Harold Nelson, MD

February 1-4, 2012, Keystone, CO

The Denver TB Course
The longest running TB course in the US, now in our 49th year! Course topics include epidemiology of tuberculosis, transmission and pathogenesis, diagnosis and treatment of tuberculosis including MDR/XDR-TB, diagnosis and treatment of latent tuberculosis infection, and vulnerable populations (e.g. children, persons with HIV).
Chairs: Shannon Kasperbauer, MD, Michael Iseman, MD

April 11-14, 2012 and October 10-13, 2012, National Jewish Health

Featured Online CME Courses*
Excessive Daytime Sleepiness
COPD Connection – Newsletter
Cardiovascular Disease in Diabetes: The Silent Killer
Eosinophilic Esophagitis: Principles & Practice

*All events listed are certified for CME and Nursing Contact Hours

To register, or to learn more about online courses and live events, go to njhealth.org/ProEd or call 800.844.2305