Pulmonary and Critical Care Updates

Update in Lung Cancer 2007

Sarita Dubey¹ and Charles A. Powell²

¹Division of Hematology and Oncology, University of California, San Francisco, San Francisco, California; and ²Division of Pulmonary and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York

SMOKING AND LUNG CANCER RISK

Lung cancer remains the leading cause of cancer death in the world with an estimated 160,390 deaths in the United States alone in 2007 (1). Although the incidence of lung cancer in the United States appears to have increased by approximately 40,000 cases to 213,380 between 2006 and 2007, this apparent increase is actually artifactual and is the result of a one-time change in the formula used to calculate nationwide incidence. In fact, in the United States, death rates have plateaued in women and continue to decline in men, mirroring trends in smoking patterns over the past four decades.

Cigarette smoking causes lung cancer, with approximately 10 to 15% of active smokers developing lung cancer. Several recent studies have examined the role of smoking patterns and host factors in modifying the risk of lung cancer in smokers. Lubin and colleagues developed a lung cancer risk model that demonstrates that risk does not increase in a linear fashion with the number of cigarettes smoked per day (2). Instead, the excess odds ratio per pack-year is increased in lower-intensity smokers (<15–20 cigarettes/d) compared with higher-intensity smokers (>20 cigarettes/d). This finding supports other studies by this group, suggesting that the carcinogenic potential of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is reduced in individuals with higher exposure (3), as well as other studies demonstrating an inverse relationship between tobacco exposure and DNA repair capacity (4). Together with other data indicating that early age of smoking initiation is an important risk for lung cancer (5), these reports highlight the importance of public health policy efforts to reduce exposure to secondhand smoke and to prevent the initiation of cigarette smoking in children and young adults. Recent efforts to promote smoke-free environments have demonstrated promising efficacy in the attainment of these goals, as indicated by a reduction in salivary cotinine levels in New York City nonsmokers (6) and by a reduced likelihood of smoking initiation in individuals with low exposure to secondhand smoke outside of the home (7).

Approximately 10% of lung cancers occur in individuals with no prior history of tobacco smoking. To compare epidemiologic

characteristics of never-smokers with those of cigarette smoker patients with lung cancer; Wakelee and colleagues reviewed data from six prospective cohort studies from the United States and Sweden (8). Age-adjusted lung cancer incidence rates in never-smokers were higher in women (14.4 to 20.8 per 100,000 person-years) than in men (4.8 to 13.7 per 100,000 person-years), supporting findings from other case-control reports suggesting that nonsmoking women, as compared with men, have enhanced lung cancer susceptibility or have increased exposure to carcinogens from sources other than mainstream tobacco smoke. Also in agreement with earlier studies, the proportion of tumors classified as adenocarcinoma histology (range, 53–70%) was highest in never-smokers.

In comprehensive reviews of lung cancer in never-smokers, Subramanian and Govindan (9) and Sun and colleagues (10) examined molecular characteristics distinguishing tumors of never-smokers from those of smokers. Among the frequently detected molecular alterations, epidermal growth factor receptor (EGFR) mutations were more common in nonsmokers, whereas K-ras mutations, p53 transversion mutations, and p16 promoter hypermethylation were more frequent in tumors of smokers. Taken together, these data suggest that there is a significant subset of tumors in never-smokers that differ from tumors in smokers with respect to etiology, biology, and treatment response. Attention to these differences will optimize approaches for prevention, early detection, and individualized therapy for both smokers and never-smokers.

Spitz and colleagues developed an individual lung cancer risk assessment model that captures some of the complex interactions between exposures and host susceptibility factors (11). Separate models for absolute 1-year risks were developed for never-smokers, current smokers, and former smokers. In contrast to the lung cancer risk model recently reported by Bach and associates (12), the Spitz model is applicable to nonsmokers because it incorporates exposures and host susceptibility factors not included in the Bach model (e.g., environmental tobacco smoke exposure [13], family history of cancer, emphysema, dust exposure, and hay fever). Validation analysis indicated that performance of the Spitz model is comparable to other models of cancer risk. A potential application of these models that quantify individual risk is that they may optimize patient selection for screening studies. Targeting screening to individuals at increased risk will increase positive predictive value of screening tests and might provide access to nonsmokers at risk, who otherwise may not have been screened.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

As reported previously, lung cancer risk is associated with chronic obstructive pulmonary disease (COPD) (14, 15). It is not clear if this association is attributable to a shared exposure to cigarette smoke, to shared genetic susceptibility factors (16, 17), and/or to facilitation of tumor initiation and promotion by

(Received in original form January 16, 2008; accepted in final form February 5, 2008)

Supported by the National Institutes of Health (1R01CA120174), the American Cancer Society (RSG-CNE-108857), Joans Legacy Foundation, and by the Flight Attendants Medical Research Institute.

Correspondence and requests for reprints should be addressed to Charles A. Powell, M.D., Division of Pulmonary and Critical Care Medicine, Columbia University Medical Center, 630 West 168th Street, Box 91, New York, NY 10032. E-mail: cap6@columbia.edu

Am J Respir Crit Care Med Vol 177. pp 941–946, 2008

DOI: 10.1164/rccm.200801-107UP

Internet address: www.atsjournals.org

inflammation. Evidence supporting the hypothesis that the association is at least in part independent of cigarette smoking is provided by Turner and colleagues, who examined the risk for lung cancer death and COPD in 448,000 nonsmokers followed for up to 20 years in the prospective American Cancer Society Cancer Prevention Study II cohort (18). Lung cancer mortality in these nonsmokers was significantly associated with emphysema (hazard ratio [HR], 1.66) and with the combined endpoint of emphysema and chronic bronchitis (HR, 2.44).

To explore the role of inflammation in mediating lung cancer risk in COPD, Parimon and colleagues estimated lung cancer risk associated with inhaled corticosteroid (ICS) use (19). They performed a cohort study in 10,474 veterans to examine dose-dependent lung cancer risk in non-ICS users compared with ICS-users with an *a priori* cutoff dose of 1,200 $\mu\text{g/day}$ triamcinolone. The adjusted HR for lung cancer in ICS doses above 1,200 $\mu\text{g/day}$ was 0.39 (95% confidence interval [CI], 0.16–0.96). The findings of this observational study are of interest, but should be interpreted with caution. Prior observational studies have reported no significant reduction of lung cancer mortality in patients with COPD treated with ICS, (20), and phase II clinical trials (21, 22) have demonstrated no change in premalignant bronchial epithelial lesions in patients with aerodigestive cancers who are treated with ICS.

SCREENING

The debate over the utility of computed tomography (CT) for lung cancer screening continues (23–25). In contrast to the report of the International Early Lung Cancer Action Program (I-ELCAP) screening consortium in which Henschke and colleagues predicted a 92% 10-year survival rate for patients with resected stage I lung cancer (26), Bach and colleagues reported no mortality benefit in screened patients (27). Bach and colleagues examined three cohorts of screened patients and compared the observed rates of lung cancer diagnosis and mortality over 2 years with expected rates calculated from prediction models. The total number of observed lung cancer diagnoses in the screened cohorts was higher than predicted, but the number of advanced-stage lung cancer diagnoses and the number of deaths were not significantly different from those expected. These results suggest that screening may preferentially detect early-stage tumors that may be relatively clinically indolent. Direct evidence to address this possibility of overdiagnosis should be forthcoming from the ongoing randomized National Lung Screening Trial. In the absence of definitive data regarding the benefits and risks (28) of CT screening, the decision to offer screening to patients at risk remains complex and should be individualized.

The efficacy of screening can be enhanced if testing is targeted to individuals at highest risk and if the number of biopsies and resections of benign nodules is minimized (29). Recent research has identified molecular biomarkers of lung cancer risk that may provide information complementary to results of CT screening tests (30). Spira and colleagues reported gene expression signatures of nonmalignant bronchial epithelial cells acquired from noninvolved lungs from smokers with and without lung cancer (31). Their observation that the signature in patients with cancer is distinct from that in control patients suggests that an epithelial “field defect” typically associated with cigarette smoke exposure may be specific for cancer. If validated prospectively, this approach of molecular testing in epithelial cells acquired from throughout the aerodigestive tract may provide useful information for risk assessment. Other researchers have developed biomarkers of lung cancer using specimens acquired from exhaled breath (32, 33), sputum (34), and blood (35–37). The continued

development and validation of these and other biomarkers promises to improve the early detection of lung cancer and survival.

LUNG CANCER GENOMICS

Somatic DNA alterations including mutations, amplifications, deletions, and translocations are common in tumors and are required for the activation of oncogenes and the inactivation of tumor suppressor genes that drive carcinogenesis. Large-scale efforts underway to systematically characterize these alterations in lung cancer and other tumors (38, 39) have provided insights into DNA structural alterations in non-small cell lung cancer (NSCLC). Weir and colleagues comprehensively examined DNA copy number alterations in 371 lung adenocarcinoma specimens (40) and found that the top focal regions of amplification and deletion included 14q13.3, 12q15, 8q24.21, 7p11.2, and 8q21.13. These results confirmed amplifications and deletions reported in other smaller studies and also identified novel amplifications, such as that of the transcription factor *TTF-1* on chromosome 14q13.3. *TTF-1* encodes thyroid transcription factor 1, a member of the Nk-2 homeobox family that binds to and activates the promoter of thyroid- and lung-specific genes. Interestingly, other groups using similar approaches also identified *TTF-1* amplification as a frequent lung adenocarcinoma alteration, thus providing independent validation of this finding (41, 42). Kendall and colleagues extended these studies to demonstrate that *TTF-1* functions cooperatively in tumorigenicity with *PAX9* and *NKX2-8*, which are neighboring 14q13.3 transcription factors that are coamplified in lung carcinoma (41). Together, these observations link lung tumor differentiation states and histologic grade with epithelial cell developmental pathways (43, 44) and suggest that these DNA amplification events are important in mediating lung cancer initiation, differentiation, and progression.

Proof of concept that tumor mRNA profiling provides clinically significant information regarding patient outcome after resection has been established. The promise of this approach to segregate tumors and to direct patient treatment on the basis of these signatures is being prospectively tested for breast cancer in two clinical trials. For NSCLC, several predictors have been developed, which for the most part, are based on methodologically sound approaches that include independent validation (45–51) (Table 1). The signatures are heterogeneous in terms of the number of genes in the predictors and in terms of the specific genes included in each signature. This heterogeneity is expected given differences in study design, assay platform, tumor histology, and patient selection. It is not clear which predictor is best or whether specific genes or entire signatures are most important in predicting outcome. Independent comparison of the predictive accuracy of these signatures and prospective clinical trials are appropriate and are required to move this important area of research forward.

TUMOR MICROENVIRONMENT

Thirty-nine percent of patients with lung cancer present with distant metastatic disease at the time of diagnosis, and less than 2% of these patients are alive at 5 years (1). Invasion, the first and required step for metastasis, is the result of a complex cascade of molecular events, including the following: (1) tumor cell loss of cell–cell contact and increased motility, mediated in part by E-cadherin (52–53); (2) degradation of alveolar basement membrane; (3) fibroblast proliferation and fibronectin deposition (54); (4) chemokine (e.g., RANTES [regulated upon activation, normal T-cell expressed and secreted]) (55) production and chemotaxis; (5) infiltration by tumor associated macro-

TABLE 1. RECENT GENE EXPRESSION PREDICTORS OF NON-SMALL CELL LUNG CANCER OUTCOME

Classifier	Histology	Genes	Outcome	Platform
Duke metagene (46)	NSCLC, stages I, II, III	134	Recurrence	Affymetrix 133A
NCI cytokine (51)	Adenocarcinoma, stages I, II, III, IV	15	Lymph node metastasis and survival	RT-PCR
Milan 10 gene (45)	Adenocarcinoma, stage I	<i>E2F1, E2F4, HOXB7, HSPG2, MCM6, NUDCD1, RRM2, SERPINB5, SF3B1, SCGB3A1</i>	Overall survival	RT-PCR
Taiwan 5 gene (47)	NSCLC stages I, II, III	<i>DUSP6, ERBB3, MMD, STAT1, LCK</i>	Overall and relapse-free survival	RT-PCR
Toronto 3 gene (50)	NSCLC stages I, II, III	<i>CCR7, HIF1A, STX1A</i>	Overall survival	RT-PCR
Australia adenocarcinoma (49)	Adenocarcinoma stages I, II	54	Recurrence	Oligonucleotide array
Australia squamous (48)	Squamous, stages I, II, III	71	Recurrence	Oligonucleotide array

Definition of abbreviations: NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; RT-PCR = reverse transcriptase-polymerase chain reaction.

phages; and (6) angiogenesis (52, 56, 57). Recent research in these areas indicates that tumor cell invasion and metastasis of tumor cells are driven by interactions between tumor cells and their microenvironment. These findings support efforts to develop diagnostics and therapeutics that target fibroblasts, macrophages, endothelial cells, and stem cells within the tumor stromal compartment. Recent clinical trials evaluating bevacizumab (58, 59), a humanized anti-vascular endothelial growth factor (VEGF) antibody, demonstrate the importance of research focusing on the tumor microenvironment.

LUNG CANCER THERAPEUTICS

Small Cell Lung Cancer

The management of small cell lung cancer continues to feature platinum-based chemotherapy. For patients with limited disease, treatment consists of concurrent combination chemotherapy and radiation, followed by prophylactic cranial irradiation (PCI). The role of PCI in extensive disease was examined in a recent randomized study (60). When 286 patients with newly diagnosed extensive disease and any response to chemotherapy were randomized to PCI or no PCI, the cumulative risk of brain metastases was increased threefold for patients not receiving PCI (14 vs. 40%; HR, 0.27; $P < 0.001$). Despite the absence of a significant difference in the rate of extracranial progression, there was a survival improvement in the PCI arm (1-yr survival, 27 vs. 13.3%; median survival, 6.7 vs. 5.4 mo; $P = 0.003$). Notwithstanding the immediate radiation-related side effects, there was no significant effect on global health status. Thus, prophylactic cranial irradiation is now recommended for patients with extensive stage small cell lung cancer who achieve a response with chemotherapy.

NSCLC

Early-stage NSCLC. Adjuvant chemotherapy is now established as a modality that improves survival in selected early resectable NSCLC (stage II, III, and subset of IB) (61). Systemic chemotherapy has thus become standard of care, but the optimal timing of administration with respect to surgical resection (neoadjuvant vs. adjuvant) continues to be an active area of investigation. Although previous randomized clinical trials have demonstrated no statistically significant improvement in overall survival with neoadjuvant chemotherapy, they did suggest a trend toward improved progression-free survival (62, 63). Two recent, large, randomized trials of neoadjuvant chemotherapy show similar results. In one trial of 519 patients, the HR for death with neoadjuvant cisplatin-based chemotherapy versus observation was 1.02, (95% CI, 0.80–1.31; $P = 0.86$) (64). In another trial, 354 patients were randomized to receive neoadjuvant carboplatin/paclitaxel or observation. There was a trend of improvement in

progression-free survival (HR, 0.79; 95% CI, 0.6–1.04; $P = 0.98$) and in overall survival (HR, 0.83; 95% CI, 0.61–1.14) with chemotherapy (65). These studies did not reach enrollment targets and thus may have been underpowered to detect a small but significant advantage of neoadjuvant chemotherapy. Two meta-analyses have addressed this issue and concluded that preoperative chemotherapy improves survival with an HR of 0.82 (95% CI, 0.69–0.97; $P = 0.02$) in one study (66) and an HR of 0.66 (95% CI, 0.48–0.93) in the other (67). Although these studies suggest a benefit of neoadjuvant chemotherapy compared with surgery alone, they do not address the question of neoadjuvant versus adjuvant chemotherapy. Two ongoing studies in Europe and the United States will directly compare neoadjuvant with adjuvant chemotherapy to determine which is the preferred modality.

Locally advanced NSCLC. The standard of care for locally advanced NSCLC is combined-modality concurrent chemotherapy and radiation, which has been shown to lengthen survival in comparison to sequential chemoradiation. A recent phase II trial examined the role for consolidation chemotherapy after concurrent chemoradiation. The addition of consolidation therapy with docetaxel improved the median survival from 15 months in historical control subjects to 26 months in patients who completed concurrent cisplatin/etoposide-radiation therapy (68, 69). Extending this approach, the Southwest Oncology Group (SWOG) 0023 examined maintenance therapy with the epidermal growth factor gefitinib in patients who received consolidation docetaxel (70). Treatment with consolidation docetaxel was followed by randomization to gefitinib or placebo. Unexpectedly, survival was shorter in the gefitinib arm than in the placebo arm (median survival, 35 vs. 23 mo; 1-yr survival, 81 vs. 73%; $P = 0.01$), with the leading cause of death being progression of cancer, not toxicity.

The efficacy of consolidation docetaxel therapy suggested by the phase II trial was examined in a recent study that randomized patients completing cisplatin/etoposide concurrent chemoradiation to either consolidation docetaxel or to observation (71). Survival was 27% at 3 years in both groups ($P = 0.09$), but toxicity was more frequent in patients in the docetaxel arm. Thus, for locally advanced NSCLC, maintenance or consolidation therapy with docetaxel after chemoradiation with cisplatin and etoposide is not currently indicated.

Advanced NSCLC. In a phase III trial in newly diagnosed, advanced nonsquamous cell NSCLC, the addition of the monoclonal VEGF antibody bevacizumab 15 mg/kg to carboplatin/paclitaxel chemotherapy increased median survival (72). The bevacizumab dose was selected on the basis of a previous phase II trial that showed higher response rate and increased survival in patients treated with 15 mg/kg compared with 7.5 mg/kg (73). An ongoing study to reassess the optimal dose of bevacizumab

is testing doses of 7.5 mg/kg and 15 mg/kg in combination with cisplatin/gemcitabine (74). In addition, three arms are being compared: chemotherapy alone, chemotherapy with low-dose bevacizumab, and chemotherapy with high-dose bevacizumab. Preliminary results suggest that both doses of bevacizumab improve outcomes when compared with chemotherapy alone. Interim response rates for the control, low-dose, and high-dose groups were 20, 34, and 30%, respectively, and median progression-free survival was 6.1, 6.7 (HR, 0.7; $P = 0.0004$), and 6.5 months (HR, 0.78; $P = 0.125$), respectively. Although the final results of overall survival are not yet available, these early results suggest that both doses of bevacizumab have similar efficacy. In terms of toxicity, the higher dose had a slightly higher incidence of hypertension, but there was no significant difference in hemorrhage.

INDIVIDUALIZED THERAPY

As reviewed previously, biomarkers associated with lung tumor biological features have potential value to predict outcomes and treatment response as an approach to individualize therapy (75). Recently, this approach was tested for the biomarker excision repair cross-complementing group 1 (ERCC1), an enzyme involved in DNA repair. A retrospective immunohistochemical analysis of resected lung tumors showed that patients with tumors expressing low levels of ERCC1 had improved outcomes with cisplatin-based therapy, whereas those with tumors expressing higher levels had no benefit (76). In a phase III randomized study, control patients receiving cisplatin/docetaxel were compared with patients in a "genotypic" arm who were stratified according to ERCC1 mRNA status to receive either cisplatin/docetaxel if ERCC1 levels were low or docetaxel/gemcitabine if ERCC1 levels were high. Response rates for patients in the genotypic arm were higher than those seen in the control arm (50 vs. 40%, respectively; $P = 0.02$) (77).

The feasibility of clinical trials incorporating biomarker analysis of tumor biopsies is supported by the preliminary results of another ongoing trial (78). This prospective phase II clinical trial uses the results of quantitative real-time polymerase chain reaction for ERCC1 and RRM1 (ribonucleotide reductase subunit 1, which is a target of gemcitabine) mRNA levels to determine treatment regimen. All patients receive two of four study drugs (carboplatin, docetaxel, gemcitabine, or vinorelbine), but carboplatin is withheld from those with tumors highly expressing ERCC1 and gemcitabine is withheld from those with tumors highly expressing RRM1. Interim analysis has shown an overall response rate of 44%, with a 1-year survival of 59% and a median survival of 13.3 months. In addition to improved outcomes when compared with historical control subjects, the fact that 70% of patients met eligibility requirements suggests that this paradigm is clinically feasible.

These ongoing and future biomarker studies will lay the foundation for personalized medicine in the treatment of lung cancer. Before its widespread application, issues that need to be resolved include accessibility, standardization, cost, and turnaround time for biomarker testing.

Conflict of Interest Statement: S.D. has received clinical trial research support from Genentech for the amount of \$9,400 in 2007. C.A.P. received \$124,000 from Philips Research, NA, as research grants.

Acknowledgment: The authors thank Rebecca Toonkel, M.D., for editorial assistance.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Lubin JH, Caporaso N, Wichmann HE, Schaffrath-Rosario A, Alavanja MC. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. *Epidemiology* 2007;18:639–648.
3. Lubin JH, Caporaso N, Hatsukami DK, Joseph AM, Hecht SS. The association of a tobacco-specific biomarker and cigarette consumption and its dependence on host characteristics. *Cancer Epidemiol Biomarkers Prev* 2007;16:1852–1857.
4. Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, Spitz MR. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst* 2000;92:1764–1772.
5. Wiencke JK, Thurston SW, Kelsey KT, Varkonyi A, Wain JC, Mark EJ, Christiani DC. Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. *J Natl Cancer Inst* 1999;91:614–619.
6. Centers for Disease Control and Prevention. Reduced secondhand smoke exposure after implementation of a comprehensive statewide smoking ban: New York, June 26, 2003–June 30, 2004. *MMWR Morb Mortal Wkly Rep* 2007;56:705–708.
7. Centers for Disease Control and Prevention. Exposure to secondhand smoke among students aged 13–15 years—worldwide, 2000–2007. *MMWR Morb Mortal Wkly Rep* 2007;56:497–500.
8. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, Clarke CA, Holmberg L, Yong LC, Kolonel LN, Gould MK, et al. Lung cancer incidence in never smokers. *J Clin Oncol* 2007;25:472–478.
9. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007;25:561–570.
10. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers: a different disease. *Nat Rev Cancer* 2007;7:778–790.
11. Spitz MR, Hong WK, Amos CI, Wu X, Schabath MB, Dong Q, Shete S, Etzel CJ. A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007;99:715–726.
12. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, Hsieh LJ, Begg CB. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003;95:470–478.
13. Stayner L, Bena J, Sasco AJ, Smith R, Steenland K, Kreuzer M, Straif K. Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health* 2007;97:545–551.
14. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective, matched, controlled study. *Ann Intern Med* 1986;105:503–507.
15. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987;106:512–518.
16. Ben-Zaken Cohen S, Pare PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. *Am J Respir Crit Care Med* 2007;176:113–120.
17. Mannino DM. COPD and lung cancer have come a long way . . . baby. *Am J Respir Crit Care Med* 2007;176:108–109.
18. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* 2007;176:285–290.
19. Parimon T, Chien JW, Bryson CL, McDonnell MB, Udris EM, Au DH. Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:712–719.
20. Sin DD, Wu L, Anderson JA, Anthonisen NR, Buist AS, Burge PS, Calverley PM, Connett JE, Lindmark B, Pauwels RA, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005;60:992–997.
21. van den Berg RM, van Tinteren H, van Zandwijk N, Visser C, Pasic A, Kooi C, Sutedja TG, Baas P, Grunberg K, Mooi WJ, et al. The influence of fluticasone inhalation on markers of carcinogenesis in bronchial epithelium. *Am J Respir Crit Care Med* 2007;175:1061–1065.
22. Lam S, leRiche JC, McWilliams A, MacAulay C, Dyachkova Y, Szabo E, Mayo J, Schellenberg R, Coldman A, Hawk E, et al. A randomized phase IIB trial of Pulmicort Turbuhaler (budesonide) in people with dysplasia of the bronchial epithelium. *Clin Cancer Res* 2004;10:6502–6511.
23. Twombly R. Lung cancer screening debate continues despite international CT study results. *J Natl Cancer Inst* 2007;99:190–195.
24. Black WC, Baron JA. CT screening for lung cancer: spiraling into confusion? *JAMA* 2007;297:995–997.
25. Bach PB, Silvestri GA, Hanger M, Jett JR. Screening for lung cancer: ACCP evidence-based clinical practice guidelines. *Chest* 2007;132:69S–77S.

26. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–1771.
27. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. *JAMA* 2007;297:953–961.
28. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, Mandrekar JN. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology* 2007;242:555–562.
29. Gould MK, Fletcher J, Lannettoni MD, Lynch WR, Midthun DE, Naidich DP, Ost DE. Evaluation of patients with pulmonary nodules: When is it lung cancer? ACCP evidence-based clinical practice guidelines. *Chest* 2007;132:108S–130S.
30. Varela-Garcia M, Chen L, Powell RL, Hirsch FR, Kennedy TC, Keith R, Miller YE, Mitchell JD, Franklin WA. Spectral karyotyping detects chromosome damage in bronchial cells of smokers and patients with cancer. *Am J Respir Crit Care Med* 2007;176:505–512.
31. Spira A, Beane JE, Shah V, Steiling K, Liu G, Schembri F, Gilman S, Dumas YM, Calner P, Sebastiani P, et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. *Nat Med* 2007;13:361–366.
32. Mazzone PJ, Hammel J, Dweik R, Na J, Czich C, Laskowski D, Mekhail T. Diagnosis of lung cancer by the analysis of exhaled breath with a colorimetric sensor array. *Thorax* 2007;62:565–568.
33. Carpagano GE, Foschino-Barbaro MP, Spanevello A, Resta O, Carpagano F, Mule G, Pinto R, Tommasi S, Paradiso A. 3p Microsatellite signature in exhaled breath condensate and tumor tissue of patients with lung cancer. *Am J Respir Crit Care Med* 2008;177:337–341.
34. Belinsky SA, Grimes MJ, Casas E, Stidley CA, Franklin WA, Bocklage TJ, Johnson DH, Schiller JH. Predicting gene promoter methylation in non-small-cell lung cancer by evaluating sputum and serum. *Br J Cancer* 2007;96:1278–1283.
35. Yildiz PB, Shyr Y, Rahman JS, Wardwell NR, Zimmerman LJ, Shakhmourad B, Gray WH, Chen S, Li M, Roder H, et al. Diagnostic accuracy of MALDI mass spectrometric analysis of unfractionated serum in lung cancer. *J Thorac Oncol* 2007;2:893–901.
36. Patz EF Jr, Campa MJ, Gottlin EB, Kusmartseva I, Guan XR, Herndon JE II. Panel of serum biomarkers for the diagnosis of lung cancer. *J Clin Oncol* 2007;25:5578–5583.
37. Nagrath S, Sequist LV, Maheswaran S, Bell DW, Irimia D, Ulkus L, Smith MR, Kwak EL, Digumarthy S, Muzikansky A, et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature* 2007;450:1235–1239.
38. Collins FS, Barker AD. Mapping the cancer genome: pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies. *Sci Am* 2007;296:50–57.
39. Greenman C, Stephens P, Smith R, Dalgleish GL, Hunter C, Bignell G, Davies H, Teague J, Butler A, Stevens C, et al. Patterns of somatic mutation in human cancer genomes. *Nature* 2007;446:153–158.
40. Weir BA, Woo MS, Getz G, Perner S, Ding L, Beroukhi R, Lin WM, Province MA, Kraja A, Johnson LA, et al. Characterizing the cancer genome in lung adenocarcinoma. *Nature* 2007;450:893–898.
41. Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. *Proc Natl Acad Sci USA* 2007;104:16663–16668.
42. Tanaka H, Yanagisawa K, Shinjo K, Taguchi A, Maeno K, Tomida S, Shimada Y, Osada H, Kosaka T, Matsubara H, et al. Lineage-specific dependency of lung adenocarcinomas on the lung development regulator TTF-1. *Cancer Res* 2007;67:6007–6011.
43. Borczuk AC, Powell CA. Expression profiling and lung cancer development. *Proc Am Thorac Soc* 2007;4:127–132.
44. Borczuk AC, Gorenstein L, Walter KL, Assaad AA, Wang L, Powell CA. Non-small-cell lung cancer molecular signatures recapitulate lung developmental pathways. *Am J Pathol* 2003;163:1949–1960.
45. Bianchi F, Nuciforo P, Vecchi M, Bernard L, Tizzoni L, Marchetti A, Buttitta F, Felicioni L, Nicassio F, Di Fiore PP. Survival prediction of stage I lung adenocarcinomas by expression of 10 genes. *J Clin Invest* 2007;117:3436–3444.
46. Potti A, Mukherjee S, Petersen R, Dressman HK, Bild A, Koontz J, Kratzke R, Watson MA, Kelley M, Ginsburg GS, et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. *N Engl J Med* 2006;355:570–580.
47. Chen HY, Yu SL, Chen CH, Chang GC, Chen CY, Yuan A, Cheng CL, Wang CH, Terng HJ, Kao SF, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med* 2007;356:11–20.
48. Larsen JE, Pavey SJ, Passmore LH, Bowman R, Clarke BE, Hayward NK, Fong KM. Expression profiling defines a recurrence signature in lung squamous cell carcinoma. *Carcinogenesis* 2007;28:760–766.
49. Larsen JE, Pavey SJ, Passmore LH, Bowman RV, Hayward NK, Fong KM. Gene expression signature predicts recurrence in lung adenocarcinoma. *Clin Cancer Res* 2007;13:2946–2954.
50. Lau SK, Boutros PC, Pintilie M, Blackhall FH, Zhu C-Q, Strumpf D, Johnston MR, Darling G, Keshavjee S, Waddell TK, et al. Three-gene prognostic classifier for early-stage non small-cell lung cancer. *J Clin Oncol* 2007;25:5562–5569.
51. Seike M, Yanaihara N, Bowman ED, Zanetti KA, Budhu A, Kumamoto K, Mechanic LE, Matsumoto S, Yokota J, Shibata T, et al. Use of a cytokine gene expression signature in lung adenocarcinoma and the surrounding tissue as a prognostic classifier. *J Natl Cancer Inst* 2007;99:1257–1269.
52. Ceteci F, Ceteci S, Karreman C, Kramer BW, Asan E, Gotz R, Rapp UR. Disruption of tumor cell adhesion promotes angiogenic switch and progression to micrometastasis in raf-driven murine lung cancer. *Cancer Cell* 2007;12:145–159.
53. Kobayashi S, Kubo H, Suzuki T, Ishizawa K, Yamada M, He M, Yamamoto Y, Yamamoto H, Sasano H, Sasaki H, et al. Endogenous secretory receptor for advanced glycation end products in non-small cell lung carcinoma. *Am J Respir Crit Care Med* 2007;175:184–189.
54. Zheng Y, Ritzenthaler JD, Roman J, Han S. Nicotine stimulates human lung cancer cell growth by inducing fibronectin expression. *Am J Respir Cell Mol Biol* 2007;37:681–690.
55. Borczuk AC, Papanikolaou N, Toonkel RL, Sole M, Gorenstein LA, Ginsburg ME, Sonett JR, Friedman RA, Powell CA. Lung adenocarcinoma invasion in TGFβ2-deficient cells is mediated by CCL5/RANTES. *Oncogene* 2008;27:557–564.
56. McClelland MR, Carskadon SL, Zhao L, White ES, Beer DG, Orringer MB, Pickens A, Chang AC, Arenberg DA. Diversity of the angiogenic phenotype in non-small cell lung cancer. *Am J Respir Cell Mol Biol* 2007;36:343–350.
57. Fuster MM, Wang L, Castagnola J, Sikora L, Reddi K, Lee PHA, Radek KA, Schuksz M, Bishop JR, Gallo RL, et al. Genetic alteration of endothelial heparan sulfate selectively inhibits tumor angiogenesis. *J Cell Biol* 2007;177:539–549.
58. Sandler A. Bevacizumab in non small cell lung cancer. *Clin Cancer Res* 2007;13:s4613–s4616.
59. Stinchcombe TE, Socinski MA. Bevacizumab in the treatment of non-small-cell lung cancer. *Oncogene* 2007;26:3691–3698.
60. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, Postmus P, Collette L, Musat E, Senan S. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664–672.
61. Gandara DR, Wakelee H, Calhoun R, Jablons D. Adjuvant chemotherapy of stage I non-small cell lung cancer in North America. *J Thorac Oncol* 2007;2:S125–S127.
62. Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B, Braun D, Breton JL, Lemarie E, Gouva S, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002;20:247–253.
63. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, Dhingra H, De Caro L, Chasen M, McGavran M, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIa non-small-cell lung cancer. *J Natl Cancer Inst* 1994;86:673–680.
64. Gilligan D, Nicolson M, Smith I, Groen H, Dalesio O, Goldstraw P, Hatton M, Hopwood P, Manegold C, Schramel F, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;369:1929–1937.
65. Pisters K, Vallieres E, Bunn PA, Crowley J, Chansky K, Ginsberg R, Gandara DR. S990: surgery alone or surgery plus induction (IND) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): follow-up on a phase III trial [abstract 7520]. *J Clin Oncol* 2007;25:389s.
66. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol* 2006;1:611–621.

67. Berghmans T, Paesmans M, Meert AP, Mascaux C, Lothaire P, Lafitte JJ, Sculier JP. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer* 2005;49:13–23.
68. Albain KS, Crowley JJ, Turrisi AT III, Gandara DR, Farrar WB, Clark JI, Beasley KR, Livingston RB. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIb non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002;20:3454–3460.
69. Gandara DR, Chansky K, Albain KS, Gaspar LE, Lara PN Jr, Kelly K, Crowley J, Livingston R. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIb non-small-cell lung cancer: a phase II Southwest Oncology Group study (s9504). *Clin Lung Cancer* 2006;8:116–121.
70. Kelly K, Chansky K, Gaspar LE, Jett JR, Ung Y, Albain KS, Crowley J, Gandara DR. Updated analysis of SWOG 0023: a randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small cell lung cancer [abstract 7513]. *J Clin Oncol* 2007;25:388s.
71. Hanna NH, Neubauer M, Ansari R, Govindan R, Bruetman D, Fisher W, Chowhan N, Nattam S, Yiannoutsos C, Einhorn L. Phase III trial of cisplatin (p) plus etoposide (e) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (d) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): Hog lun 01-24/uso-023 [abstract 7512]. *J Clin Oncol* 2007;25:387s.
72. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilienbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
73. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF III, Gaudreault J, Damico LA, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184–2191.
74. Manegold C, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Archor V, Reck M. Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): Bo17704 [abstract 7514]. *J Clin Oncol* 2007;25:388s.
75. Dubey S, Powell CA. Update in lung cancer 2006. *Am J Respir Crit Care Med* 2007;175:868–874.
76. Olaussen KA, Dunant A, Fouret P, Brambilla E, Andre F, Haddad V, Taranchon E, Filipits M, Pirker R, Popper HH, et al. DNA repair by ercc1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006;355:983–991.
77. Cobo M, Isla D, Massuti B, Montes A, Sanchez JM, Provencio M, Viñolas N, Paz-Ares L, Lopez-Vivanco G, Muñoz MA, et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. *J Clin Oncol* 2007;25:2747–2754.
78. Simon G, Sharma A, Li X, Hazelton T, Walsh F, Williams C, Chiappori A, Haura E, Tanvetyanon T, Antonia S, et al. Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2007;25:2741–2746.