Background: Bronchial epithelial proliferation as measured by Ki-67 immunostaining is a biologically plausible intermediate endpoint biomarker of lung cancer risk, but has not been validated. We designed a study to determine factors associated with increased bronchial epithelial proliferation and whether increased epithelial proliferation is associated with endobronchial dysplasia, chronic obstructive pulmonary disease or lung cancer.

Methods: Cross-sectional study of 113 subjects undergoing white light and autofluorescence bronchoscopy; 27 never smokers, 27 current or ex-smokers with normal spirometry, 31 current or ex-smokers with COPD and 28 current, ex- or never smokers with lung cancer. Ki-67 expression was determined by immunohistochemistry on all evaluable biopsy sites without carcinoma. A Ki-67 index was defined as the percent of cells expressing Ki-67. Relationships between Ki-67 index and demographic variables, smoking, histology and the presence of COPD and/or lung cancer were determined.

Results: Results for both maximal and mean Ki-67 index are similar, so only the former are reported. Average maximal Ki-67 index was higher in current smokers than either ex-smokers or never smokers (48.0% vs 30.6% vs 22.6%; p<0.001). Males had higher Ki-67 index than females, (39.9% vs 23.6% p<0.001). Compared to subjects without disease (Ki67 index = 30.0%) maximal Ki-67 index was not significantly elevated (p = 0.44) in subjects with either lung cancer (Ki67 = 39.1%) or COPD (Ki67 = 38.9%).

Conclusions: Current smoking and gender are major determinants of Ki-67 index. No increase in Ki-67 index was found in the non-malignant epithelium of patients with lung cancer or COPD. Although Ki-67 index may provide insight into the short-term effects of chemoprevention agents on cell proliferation, its lack of association with lung cancer or COPD raise question about its utility as a surrogate endpoint in clinical trials.

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Epidermal Growth Factor Receptor (EGFR) inhibition with gefitinib is synergistic with prostacyclin synthase overexpression in chemopreventing murine lung cancer

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Background: Chemically induced murine adenocarcinomas contain many of the same histological and genetic alterations found in human adenocarcinomas, affirming the importance of murine tumorgenesis models. Increased pulmonary PG12 (prostacyclin) by lung-specific overexpression of prostacyclin synthase (PGIS) chemoprevents lung cancer in chemically induced and cigarette smoke exposure models, suggesting that PG12 plays a role in the development of NSCLC. Alterations in EGFR by mutation or increased copy number are identified in a subset of lung cancers, and targeted therapies with tyrosine kinase inhibitors (TKIs) are currently in clinical use for NSCLC. We hypothesized that the TKI gefitinib would provide synergistic chemoprevention of murine lung cancer when combined with PGIS overexpression.

Methods: PGIS overexpressors and their wild-type littermates were given a single intraparitoneal (i.p.) injection of urethane. After one week, body-weight based i.p. injections of gefitinib were given in doses of 50mg/kg (n=45), 100mg/kg (n=41) or vehicle alone (tween 80R, n=43) three times per week. Serial body weights were followed during the experiment, and at the time of sacrifice (18 weeks after urethane) lung tissue and tumors were collected. Lung tissue was snap frozen, stored in formalin or RNA later, or immediately used for analysis of PGE2 and 6-keto PGF1α (the stable metabolite of PG12) eicosanoid levels. Additional overexpressing and wild-type animals (n=12 in each group) received gefitinib for two weeks only, after which lung tissue was harvested for studies to determine if EGFR inhibition was successful. Western blots for p-Erk, p-Src, and p-Akt were performed on lung homogenates from all treatment groups.

Results: PGIS overexpressors, when compared with transgene negative littermates, showed significant decreases in tumor multiplicity consistent with our prior studies. A further reduction in tumor multiplicity (1.13 ± 0.29 vs. 2.29 ± 0.32 tumors/mouse, p=0.0149) was observed in the 50mg/kg treatment group versus the vehicle alone. No additional effects were realized in the 100mg/kg treatment group (2.00 ± 0.32 tumors/mouse, p=0.5340). No significant differences in tumor burden or eicosanoid levels were observed among the experimental groups. Analysis of p-Erk, p-Src, and p-Akt in PGIS treated animals showed decreases in the 50mg/kg treatment group, while the 100mg/kg group showed a paradoxical return of p-Src. Western blot analyses of p-Ten and cleaved caspase 3 continue to be performed.

Conclusions: Animals tolerated i.p. injection at doses of 50mg/kg and 100mg/kg. Lung homogenates from gefitinib-treated mice showed a decrease in p-EGFR following EGF exposure, demonstrating successful inhibition of EGFR in our model. At a dose of 50mg/kg, treatment with gefitinib was synergistic with PGIS overexpression in decreasing tumor multiplicity. The observed increases in p-Src in both wild-type and PGIS mice in the 100mg/kg treatment group suggest a mechanism of adaptation to EGFR inhibition. Future investigations into the synergy of prostacyclin manipulation and EGFR inhibition are planned.

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Individual screening of lung cancer in france: results of EDIFICE study

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Objectives: EDIFICE study was aimed at improving knowledge of the French population adherence to screening tests for the four most frequent cancers: breast, colon-rectum, prostate and lung cancers. The results pertaining to lung cancer are summarised below.

Methods: This was an observational survey conducted in France among a representative sample of 1 504 subjects aged 40 to 75 years without history of cancer and among a representative sample of 600 general practitioners (GPs).

Results: Individual screening for lung cancer using chest radiography had been performed by 6% of subjects (of whom 51% were women). Compared with the unscreened subjects, more screened subjects were smokers (33% versus 23%; p<0.05). Cancer screening had often been initiated by the GP (22%) or the company doctor (21%). Regarding the screened subjects’ profile, mean age was 54.5 years; their socio-profes-
Polymorphisms in the epidermal growth factor receptor gene and the risk of primary lung cancer

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The Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor that mediates the intracellular effects of growth factors, such as EGF, transforming growth factor α and neuregulins, and thus plays an important role in the development and progression of cancer. Polymorphisms in the EGFR gene may influence EGFR production and/or activity, thereby modulating susceptibility to lung cancer. To test this hypothesis, we first examined the frequencies of 39 candidate polymorphisms in the EGFR gene in 27 healthy Korean individuals. After that, we selected five polymorphisms (127378C>T, 142285G>A, 162093G>A, 181946C>T, and 187114T>C) that have variant allele frequencies greater than 10%, and genotyped the five polymorphisms by a PCR-RFLP assay in 582 lung cancer patients and in 582 healthy controls that were frequency-matched for age and gender. Of the 5 polymorphisms studied, the 181946C>T genotype distribution was significantly different between the cases and controls (P = 0.04), with the frequency of the variant T allele being significantly lower in the cases than in the controls (35.4% vs 40.3%, P = 0.01). Compared with the frequency of the variant T allele being significantly lower in the controls (P = 0.04), with the frequencies of the genotype, the 181946 TT genotype was associated with a significantly decreased risk of lung cancer (adjusted OR = 0.63, 95% CI = 0.45-1.75, P = 0.73; P = 0.08, test for homogeneity). Consistent with the results of the genotyping analysis, the 127378C>T polymorphism, could be used as markers for the genetic susceptibility to lung cancer.

EGFR, ERBB2 and K-ras mutations in Korean non-small cell lung cancer patients

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The epidermal growth factor receptor (EGFR), and its family members play an important role in the development and progression of lung cancers. It has been reported that somatic mutations in the tyrosine kinase domain of the EGFR or ERBB2 genes occur in a subset of patients with lung cancer. We searched for mutations of the EGFR, ERBB2 and K-ras genes in surgically resected non-small cell lung cancers (NSCLCs) to determine the prevalence of these mutations in Korean lung cancer patients. In addition, we examined the relationship between the mutations and clinico-pathologic features of lung cancers. Mutations of the EGFR, ERBB2 and K-ras genes were determined by PCR-based direct sequencing in 115 surgically resected non-small cell lung cancers. EGFR mutations were present in 20 patients (17.4%). All EGFR mutations were found in adenocarcinomas (20 of 55 adenocarcinomas, 36.4%). The ERBB2 mutation was found in one adenocarcinoma of the 115 NSCLCs (overall 0.9%; and 1.8% of 55 adenocarcinomas). K-ras mutations were found in six (5.2%) of the 115 NSCLCs [two (3.3%) of 60 squamous cell carcinomas; and four (7.3%) of 55 adenocarcinomas]. EGFR mutations in adenocarcinomas were more frequent in females (P = 0.02) and never-smokers (P = 0.004). EGFR mutations in adenocarcinomas were not associated with pathologic stage in never-smokers, whereas they were more frequent in pathologic stage II-IV than in stage I in ever-smokers (P = 0.01). Of the 55 adenocarcinomas, 25 (45.5%) had mutations of either one of the three genes, and EGFR mutations were never found in tumors with ERBB2 or K-ras mutations. These findings suggest that the EGFR mutation frequently occurs in Korean lung cancer patients, and that the ERBB2 mutation is rare. Further studies are needed to investigate the role of EGFR mutations in the carcinogenesis of adenocarcinoma among smokers.

Urinary N1,N12-Diacetyl spermine (DiAcSpm) as a tumor marker for non-small cell lung cancer

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