Chemoprevention of Lung Cancer

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Lung cancer is the leading cause of cancer death in the United States, and the majority of diagnoses are made in former smokers. While avoidance of tobacco abuse and smoking cessation clearly will have the greatest impact on lung cancer development, effective chemoprevention could prove to be more effective than treatment of established disease. Chemoprevention is the use of dietary or pharmaceutical agents to reverse or inhibit the carcinogenic process and has been successfully applied to common malignancies other than lung. Despite previous studies in lung cancer chemoprevention failing to identify effective agents, our ability to determine higher risk populations and the understanding of lung tumor and premalignant biology continues to advance. Additional biomarkers of risk continue to be investigated and validated. The World Health Organization/International Association for the Study of Lung Cancer classification for lung cancer now recognizes distinct histologic lesions that can be reproducibly graded as precursors of non-small cell lung cancer. For example, carcinogenesis in the bronchial epithelium starts with normal epithelium and progresses through hyperplasia, metaplasia, dysplasia, and carcinoma *in situ* to invasive squamous cell cancer. Similar precursor lesions exist for adenocarcinoma, and these pre-malignant lesions are targeted by chemopreventive agents in current and future trials. At this time, chemopreventive agents can only be recommended as part of well-designed clinical trials, and multiple trials are currently in progress and additional trials are in the planning stages. This review will discuss the principles of chemoprevention, summarize the completed trials, and discuss ongoing and potential future trials with a focus on targeted pathways.

Keywords: lung cancer; chemoprevention; premalignancy

Lung cancer is now the leading cause of cancer death in both men and women in the United States, as well as being the leading cause of cancer death worldwide (1). The current 5-year survival rate in the United States for lung cancer is a discouraging 15%, and while there has been an interval improvement in survival over the last several decades, the survival advances seen in other common malignancies have not been realized in lung cancer. One reason for the discouraging survival statistics is that the majority of lung cancer subjects present with late-stage disease and are not curable by current therapies. With the advent of new biologically targeted therapeutic agents, treatment of advanced lung cancer should continue to improve (2), but effective chemopreventive agents are sorely needed. Approximately 90% of lung cancer cases are attributable to tobacco smoking. Recent decreases in smoking have led to a downturn in lung cancer death rates in the United States, but smoking rates continue to increase worldwide. It is well known that the incidence of lung cancer decreases only slowly after smoking cessation, ensuring that the lung cancer epidemic will

continue for many years. Smoking cessation is clearly the most effective intervention to reduce lung cancer risk, but ex-smokers still carry a significant risk and, in the United States, the majority of lung cancers are diagnosed in former smokers (3). Additional strategies to reduce the burden of lung cancer in former smokers are needed, and because the large majority of lung cancers are non-small cell lung cancer (NSCLC), chemopreventive efforts have chosen to focus on these histologic types of lung cancer.

Similar to many solid organ tumors, lung tumorigenesis results from a series of genetic and epigenetic alterations in pulmonary epithelial cells. The World Health Organization/International Association for the Study of Lung Cancer classification for lung cancer now recognizes distinct histologic lesions that can be reproducibly graded as precursors of NSCLC (4). By reproducibly identifying and focusing therapy on premalignant stages of the disease, rather than the current focus on invasive lung cancer, effective treatment and improved survival may become a more attainable goal (5). Our understanding of lung cancer biology continues to improve, and this has led to a proliferation of targeted therapies that may prove to be important chemotherapeutic and chemopreventive agents. Clinical experience has also illustrated that chemopreventive agents may have dramatically different results in current and former smokers (6) and many trials either exclude current smokers or analyze these subjects separately.

Chemoprevention is defined as the use of dietary or pharmaceutical interventions to slow or reverse the progression of premalignancy to invasive cancer (7). Chemoprevention has been validated as effective in selected groups at high risk for breast (tamoxifen), prostate, colon (celecoxib), and skin cancers, but not for lung cancer (8–10). Many of the principles that have proven effective in chemoprevention of other common malignancies are likely applicable to lung cancer, and therapeutic advances may target pathways that are altered in pre-malignant stages of disease.

PRINCIPLES OF CHEMOPREVENTION

The term “chemoprevention” was coined by Sporn and coworkers in 1976 to describe either pharmacologic or dietary interventions that would interfere in the carcinogenic process, resulting in a decreased cancer risk (7). Lung carcinogenesis can involve 20 to 30 years, and more recent studies have appropriately chosen to evaluate the effects of treatment on premalignant lesions or inhibition of the carcinogenic progression. Chemoprevention studies can be further subdivided into three distinct areas (primary, secondary, and tertiary), and current investigations in each area should advance the field. Primary chemoprevention measures the development of cancer in a high-risk population (for instance, current or former smokers who have airflow limitation on spirometry), while secondary chemopreventive studies examine the development of cancer in subjects with precursor lesions (for example, severe dysplasia on an endobronchial biopsy or atypical adenomatous hyperplasia [AAH] on a transthoracic needle biopsy). Tertiary chemoprevention studies examine the development of lung cancer in subjects with a previous cancer.

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Development of agents follows the standard progression of phased clinical trials. Phase I trials focus on safety, pharmacokinetics, and pharmacodynamics, with particular emphasis on drug effects. Phase II trials begin to evaluate efficacy and are randomized, double-blind, placebo-controlled studies that emphasize the evaluation of biomarkers and other potential surrogate endpoint biomarkers for cancer prevention. A biomarker is defined as a characteristic that is objectively measured or evaluated as an indicator of a pathogenic process or a response to a therapeutic intervention. The development and validation of biomarkers is particularly important for lung cancer prevention studies, as invasive cancer progresses over many years and longitudinal studies with the development of lung cancer as an endpoint can take decades to complete. Phase III trials are large, randomized, blinded, placebo-controlled trials with the goal of delaying the development of cancer, and continuing to evaluate efficacy and toxicity. The NCI and FDA have developed general strategies for developing chemopreventive agents. This typically involves the initial *in vitro* studies, progressing to animal tumorigenesis studies, and then concluding with phased human trials. Animal models of lung tumorigenesis allow for more thorough preclinical testing that should result in only the most promising agents progressing to human trials. Murine adenocarcinoma models have many similarities to human adenocarcinoma in terms of histology, mutations, and gene expression patterns (11), and agents currently employed in the majority of trials have proven efficacious in animal testing.

Chemoprevention has been applied with some early success to individuals at high risk for breast, prostate, and colon cancer, but there is no currently available chemoprevention for lung cancer. In fact, certain agents (β -carotene, *n*-acetyl cysteine) have been shown to increase cancer risk in current smokers (12, 13). Retinoids have received the most attention in the past as potential lung cancer chemopreventive agents (14). A large body of epidemiologic, genetic, and cell biology data suggested that supplementation with β -carotene would be protective, although preclinical animal studies were not very supportive. No one would have predicted that the two large trials (the ATBC and CARET trials) conducted in the 1990s would each show a statistically significant increase in lung cancer incidence ($\sim 20\%$) associated with β -carotene supplementation (particularly in current smokers) (6, 15). While a disappointing result, β -carotene supplementation applied on a large scale without the foresight of a clinical trial would have been disastrous.

At present, there are four major approaches to choosing promising agents for study in lung cancer chemoprevention trials: observational studies, analysis of the effects of drugs or targeted agents on cancer or dysplastic cell biology, preclinical animal models of lung carcinogenesis, and intermediate endpoint trials in humans. Since we currently have no validated lung cancer chemoprevention agents, none of these strategies is a reliable predictor.

Definition of High-Risk Groups

Three requirements must be met for clinically effective chemoprevention. First, an adequately high-risk population must be readily identifiable (and historically this has proven challenging for lung cancer). Second, effective agents with a tolerable side effect profile must be available. Side effects for chemoprevention agents must be minimal, given that annual risk for cancer development is small. Subjects enrolled in tertiary chemoprevention trials have a previous history of cancer, and therefore more toxicity may be tolerated in chronically administered chemopreventive agents. This is a particularly important group of patients, as the risk of developing a second primary lung cancer after resection can be as high as 1 to 2% per year (16). Third,

endpoints to the clinical trials must be identified, defined, and validated in terms of demonstrating reduction in cancer development. For tertiary trials this can be cancer incidence, but for secondary prevention trials intermediate biomarkers must be present and have an acceptable risk of progression. For lung cancer, one could argue that there is no current gold standard biomarker, and that histology is used in a similar paradigm to the development of other epithelial cancers. Histologic changes may not prove to be the best biomarker, and advances in genomics, proteomics, and molecular imaging studies may increase our understanding and better refine endpoints.

One in nine smokers eventually develops lung cancer (17), and epidemiologic studies have been able to more accurately identify high-risk populations. The development of COPD (as evidenced by airflow obstruction on spirometry) and lung cancer have a common genetic basis, as current and former smokers with airflow obstruction have a significant increase in lung cancer incidence (18, 19). Bach and colleagues developed and validated a model of lung cancer risk based on age, sex, and tobacco smoke and asbestos exposure history (20). Clinical experience has shown that significant variation in risk within smokers is evident, with 50% of lung cancers occurring in the highest risk quartile and only 8% in the lowest risk quartile (20). Risk of developing lung cancer in the upper quartile is up to 1.5% per year (20). A model similar to that described by Bach that incorporates airflow obstruction into the calculation of risk for lung cancer would be a significant advance. The University of Colorado SPORE in Lung Cancer recruited and followed a cohort of high-risk current and ex-smokers with airflow obstruction (21). The overall rate of incident lung cancer in this group was 1.85 per 100 person-years, or six times that required for tamoxifen chemoprevention of breast cancer (0.3% per year) (22, 23). Therefore, high-risk groups for lung cancer can easily be identified on the basis of age, smoking history, exposure to asbestos, pulmonary function, and family history. A very recent published report also showed an association of spiral computed tomography (CT) detected emphysema and risk of developing lung cancer (odds ratio [OR], 3.56; 95% confidence interval [CI], 2.21–5.73) (24). This association was maintained after controlling for airflow limitation. Ongoing genetic testing should further clarify and aid in better defining lung cancer risk in the near future and improve the ability to identify even higher risk subpopulations. For example, a comprehensive study of somatic mutations in 188 human lung adenocarcinomas identified 26 genes mutated at significantly high frequencies and provided information on new signaling pathways involved in lung tumorigenesis, and may help to identify new chemopreventive and chemotherapeutic targets (25).

Intraepithelial Neoplasia

Similar to other common cancers, lung cancer develops as the result of predictable histologic and genetic abnormalities. The development of squamous cell lung cancer in the central bronchial epithelium starts with normal epithelium and progresses through hyperplasia, metaplasia, dysplasia, carcinoma *in situ* to invasive squamous cell lung cancer. The term "intraepithelial neoplasia" (IEN) has been used to describe the precursor lesions (most often moderate to severe dysplasia) that precede the development of carcinoma *in situ* and invasive cancer (26, 27). The presence of IEN, which is most reliably detected with fluorescence bronchoscopy (28, 29), can then be used to define high-risk cohorts, and the genetic abnormalities present in IEN can be used to define cancer risk and assist in the selection of agents for trials. The natural history of endobronchial dysplastic lesions is difficult to predict, as some of them may be completely removed at the time of biopsy. Published reports have stated that 37% of severe dysplasias persist or progress (30), and 50% of

carcinoma *in situ* lesions transition to invasive squamous cell lung cancer (31). Most importantly, these severely dysplastic lesions can be targets of chemopreventive trials and, because they typically contain fewer genetic derangements and signaling abnormalities, they may be more amenable to treatment.

The premalignant lesions for adenocarcinomas (BAC and invasive adenocarcinomas) are microscopic proliferations of atypical pneumocytes that are termed atypical adenomatous hyperplasias (AAH) (32, 33). These lesions may be detected on high-resolution CT as ground glass opacities. AAH contain many of the genetic alterations seen in invasive adenocarcinoma (including Kras mutations, p53 mutations, epidermal growth factor receptor mutations [34], and loss of heterozygosity on chromosomes 3p, 9p, 17p, and 16q) (32). Promoter hypermethylation has also been observed in AAH, and advanced histologic grade was associated with more hypermethylation of tumor suppressor genes (35, 36). It is not known at what frequency AAH progress and how these can be reliably modeled for preclinical testing. This may be better determined as the number of AAH lesions undergoing longitudinal clinical evaluation increases coinciding with improved thoracic imaging modalities employed in screening trials.

PREVIOUS TRIALS

No agents have been validated as effective for lung cancer chemoprevention (37). The only intervention that has been shown to be effective in reducing risk of lung cancer is smoking cessation, most impressively demonstrated prospectively in the Lung Health Study. In this large study smokers were assigned to smoking cessation intervention programs or no smoking cessation intervention, with a resultant 55% reduction in lung cancer risk observed in successful quitters (38). Early lung cancer chemoprevention trials were based on epidemiologic data which suggested that diets high in vitamin A reduced risk (39). Several large randomized primary and secondary prevention trials were conducted. Three large trials in primary prevention evaluated β -carotene plus retinol, β -carotene and/or α -tocopherol, or β -carotene alone. Three other trials investigated secondary prevention strategies by administering retinyl palmitate, retinyl palmitate and/or N-acetylcysteine (NAC), or 13-*cis* retinoic acid (6, 12, 13, 37). Unfortunately, the results from these trials were also disappointing. No protective effect against lung cancer was observed, and two trials suggested that these agents could increase the risk of lung cancer in current smokers (12, 13). Only smoking cessation correlated with a significant reduction in squamous metaplasia (40). In addition, a recent meta-analysis of the large β -carotene trials (ATBC, CARET, Physician's Health, and Women's Health) found an increased risk of lung cancer in current, not former, smokers who received β -carotene (OR, 1.21; 95% CI, 1.09–1.34) (41). Thus, high doses of a single antioxidant vitamin do not appear to be a viable chemopreventive strategy. In addition, these trials were based only on epidemiologic data and required thousands of participants and considerable resources to complete.

Phase III chemoprevention trials evaluating isotretinoin or vitamin A/NAC in patients with a prior lung or head and neck cancer resected for cure have been completed and required fewer patients, but none have shown a reduction in lung cancer incidence (13, 42). A number of preclinical studies have demonstrated that corticosteroids, either administered systemically or by inhalation, can decrease chemical carcinogen induced pulmonary adenoma formation in mice (43), but human trials have only yielded negative results. Other completed trials that have failed to yield positive results include the findings that (1) anethole dithiolethione (an organosulfur compound that increases glutathione-S-transferase and additional phase II enzymes) did not reverse bronchial dysplasia (44), and (2) inhaled budesonide in smokers with dysplasia did not induce histologic regression (45).

Phase II intermediate endpoint trials are currently being conducted, and these trials have emerged as one strategy for prioritizing agents for longer and more expensive phase III chemoprevention trials containing a lung cancer endpoint. As discussed above, there are no established intermediate biomarkers for lung cancer prevention trials, although IEN or dysplasia has been proposed as an endpoint for studies of squamous cell carcinoma (5) and AAH lesions may also exhibit a spectrum that would allow for progression to be monitored (46). Validation of intermediate endpoint biomarkers will rely on a proven chemoprevention treatment, and even then uncertainties remain as to whether they will be predictive of outcome (47, 48). However, given the difficulties in choosing agents for phase III chemoprevention trials, modulation of biologically plausible intermediate endpoint biomarkers is one rational factor, among others, in prioritizing agents for more thorough testing. Metaplasia index and sputum cytologic atypia have been used in some trials, but they have also not been validated (40, 49, 50). Metaplasia has been criticized, as it can occur as a response to injury and is less specific for tobacco smoke exposure than dysplasia. The histologic grading of dysplastic endobronchial lesions was used in several recent trials, but the best scoring methodology for assessing changes in bronchial histology has not been established (44, 45, 51), although many of the current trials are attempting to use similar criteria. The use of more advanced biological and molecular markers remains an area of active investigation (26), and many current trials are providing biological samples for advanced testing.

PRECLINICAL STUDIES

One area of definitive advancement in chemoprevention is in preclinical testing. Historical chemoprevention studies would have benefited from animal studies. Mice develop pulmonary adenomas that progress to adenocarcinomas in response to a number of agents, including ethyl carbamate, nicotine-derived carcinogens, or tobacco smoke exposure (52, 53). In addition, investigators have developed a number of transgenic models in which viral oncogenes or transforming ras mutants are selectively and conditionally expressed in lung tissue (54). The murine tumors developed in these models have many similarities to human adenocarcinoma, ranging from specific markers to gene expression patterns (52, 55). Models of squamous cell lung cancer have also been developed, and some models (for example, NTCU) also results in dysplastic lesions that are similar to those found during bronchoscopy and can therefore be used to evaluate one proposed surrogate endpoint in preclinical studies (56, 57). More recent chemoprevention trials rely on preclinical testing in animals and this should allow for improved screening of potential agents prior to clinical trials.

CURRENT TRIALS

There are a number of chemoprevention trials currently being conducted, and the majority of these are phase II trials based on epidemiologic and preclinical studies. The ongoing studies summarized below are based on molecular pathways and were identified as "actively recruiting" on the NIH-sponsored clinical trial website (<http://clinicaltrials.gov>).

COX Inhibitors

Alterations in eicosanoid production have been associated with many types of cancer, including lung cancer. Inhibition of

cyclooxygenase (COX-1 and COX-2, PGH₂ synthase) activity decreases eicosanoid production and prevents lung cancer in animal models (58). A large number of COX-2-dependent genes are involved in lung tumorigenesis (reviewed in Reference 59), and COX-2 can be up-regulated in IEN and many NSCLC. Therefore, studies evaluating the role of COX-2 inhibition (celecoxib) are currently enrolling, but preliminary results are not available. A separate Phase II trial evaluating the effects of nonspecific COX inhibitor sulindac on endobronchial histology has also been initiated.

Iloprost

PGI₂ is a PGH₂ metabolite with antiinflammatory, antiproliferative, and potent antimetastatic properties. Preclinical studies in transgenic mice with selective pulmonary prostacyclin synthase overexpression showed significantly reduced lung tumor multiplicity and incidence in response to either chemical carcinogens or exposure to tobacco smoke (60, 61). Iloprost, a long-lasting oral prostacyclin analog, also inhibits lung tumorigenesis in wild-type mice. These studies formed the basis of an NCI-sponsored double-blind, placebo-controlled clinical chemoprevention trial in which subjects at high risk for lung cancer are being treated with iloprost or placebo. The primary endpoint for the trial is endobronchial histology, and subjects have fluorescence bronchoscopy performed at study entry and after 6 months of treatment. Enrollment has been completed and results should be available in 2009.

Leukotriene Modifiers

Tobacco carcinogens can increase 5-lipoxygenase (5-LO), leukotriene B₄, and COX-2. 5-LO expression increases in lung cancer, and 5-HETE (one product of 5-LO) augments the growth of lung cancer cell lines (62). Inhibition of 5-LO and 5-LO-activating protein (FLAP) inhibits lung tumorigenesis in murine studies (63), and a chemoprevention trial with the 5-LO inhibitor zileuton has been initiated.

Selenium

The use of selenium for cancer prevention has been an area of considerable interest, as it improves cellular defense against oxidative stress (64). The Nutritional Prevention of Cancer trial tested selenium for the prevention of nonmelanoma skin cancer, and while it did not prevent skin cancer, the subjects in the trial exhibited a 44% decrease in lung cancer incidence (64). Further analysis of the trial determined that selenium supplementation decreased lung cancer incidence only in the tertile with the lowest baseline plasma selenium levels (65). The ongoing SELECT (Selenium and Vitamin E Cancer Prevention Trial) trial for prostate cancer chemoprevention has established lung cancer as a secondary endpoint. SELECT trial participants were recently suspended from taking supplements due to a lack of efficacy in preventing prostate cancer and concerns about long term toxicity.

Green Tea and Broccoli Sprout Extracts

Green tea extract contains multiple polyphenols (including polyphenol E), and the protective effects in cancer chemoprevention arise from the inhibition of cytochrome p450 (thereby blocking the bioactivation of carcinogens) and the activation of phase II detoxifying enzymes via the MAPK pathway (66). Broccoli sprout extract contains phytochemicals that also activate phase II detoxifying enzymes and protect against oxidative stress-induced DNA damage. Trials of oral supplementation with both agents are also currently being conducted, particularly in premalignant lesions with specific genetic alterations.

FUTURE TRIALS AND ENDPOINT BIOMARKERS

Advances in our understanding of the early events in lung tumorigenesis naturally has led to the discovery of important pathways that can be targeted by potential chemopreventive agents. Future trials must build upon the results of the current trials, and it remains vitally important to identify and validate intermediate endpoint biomarkers to allow for a more rapid evaluation of novel agents. One list of potential pathways that can be targeted is contained in Table 1, and below are a couple of examples of classes of agents that may be evaluated in the future. Pathway targeted chemotherapeutic agents may also play an important role.

Future trials will also need to be based on improved biomarkers of both risk and response. Validated intermediate endpoints will allow for shorter trials that do not have cancer as an endpoint, but these intermediate biomarkers need to meet the following requirements: expression correlates with disease course; expression is different between normal and pre-malignant tissue; and evaluation must be reproducible. Examples of biomarkers being evaluated are Ki67, p53, EGFR expression, and gene methylation. These biomarkers must ultimately be validated in prospective clinical trials.

PPAR γ Agonists

Prostacyclin analogs like iloprost selectively increases PPAR γ activity both in nontransformed epithelial cells and in NSCLC. In human NSCLC cell lines, activation of PPAR γ by pharmacologic agents, or by molecular overexpression, strongly inhibits transformed growth, as assessed by colony formation in soft agar (67, 68). In addition, NSCLC cells overexpressing PPAR γ exhibit significantly less invasiveness and metastasis compared with control cells both *in vitro* and in a rat orthotopic lung xenograft model (67). The thiazolidinediones (TZDs) are oral PPAR γ agonists, and lung cancer incidence in diabetics on PPAR γ agonists was decreased 33% when compared with diabetics on non-PPAR γ -modulating medications (69). TZDs have also been shown to induce 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the enzyme that inactivates the anti-apoptotic and immunosuppressive PGE₂ by conversion to 15-keto prostaglandins (70). A recent report has shown that PPAR γ overexpression chemoprevents murine lung cancer (71). This class of agents will likely be employed in future chemoprevention trials.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that mediates the akt signaling pathway. Human lung

TABLE 1. CURRENT AND POTENTIAL FUTURE TARGETS FOR LUNG CANCER CHEMOPREVENTION STUDIES

Current
Prostacyclin analogs (75)
COX inhibitors (76)
PPAR γ agonists (71)
mTOR inhibitors (74, 77)
Corticosteroids (78, 79)
Future
Farnesyltransferase inhibitors (80)
EGFR inhibitors (81)
Rexinoids (82)
Ras inhibitors (83)
Fatty acid synthase inhibitors (84)
Demethylating agents (85)
Angiogenesis inhibitors (86)

Definition of abbreviations: COX = cyclooxygenase; EGFR = epidermal growth factor receptor; mTOR = mammalian target of rapamycin.

cancers, as well as dysplastic endobronchial lesions (72), have been shown to exhibit activation of the akt/mTOR pathway. Tobacco-specific carcinogens also activate this pathway (73, 74) and mTOR inhibitors (rapamycin and sirolimus) can successfully induce cell cycle arrest. Phase I studies evaluating the mTOR inhibitors are in the planning stage.

Combinatorial Agents

Due to the potentially large number of genetic and metabolic derangements in pre-malignant lesions, combinations of agents may prove to be the most effective route to chemoprevention. This could largely be directed by genetic or proteomic abnormalities detected in the dysplastic lesions, and similar to personalized lung cancer chemotherapy, chemoprevention may also be directed on the basis of specific “signatures” (gene expression, proteomics, etc.) being present in biopsy specimens from high-risk individuals. The most effective chemoprevention may depend on abnormalities found in biological specimens.

CONCLUSIONS

Despite advances in lung cancer chemotherapy, there is a pressing need for effective lung cancer chemoprevention beyond smoking cessation. The understanding of molecular changes present in pre-malignant lesions continues to progress and this has resulted in more targeted single-agent prevention studies. In addition, higher-risk subjects can now be identified (including tobacco history, occupational history, airflow limitation, and family history), and trials can be enriched for these subjects. The lung chemoprevention field still needs validated secondary endpoint biomarkers, and the current trials are evaluating histology from lung biopsy specimens, along with targeted markers in specific pathways. Eventually, phase III trials with lung cancer as the primary endpoint are needed before chemoprevention agents can be recommended for widespread use in high-risk populations. These trials are difficult, expensive, and time-consuming, and the above-outlined strategies should assist in prioritizing agents for Phase III trials. Information from epidemiology, cell biology, preclinical models, and phase II intermediate endpoint trials all may be useful to inform choices of agents for definitive phase III chemoprevention trials. It is clear that we must continue to promote successful smoking cessation and tobacco control. Lung cancer chemoprevention research will advance more quickly as the number of subjects involved in clinical trials increases, and at the current time subjects should only be encouraged to use chemopreventive agents in the context of a clinical trial.

Conflict of Interest Statement: R.L.K. and other investigators have a patent application on the use of prostacyclin analogues for cancer chemoprevention.

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