Lung cancer chemoprevention: current status and future directions

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Abstract Lung cancer is the leading cause of cancer death in the world. In the United States, lung cancer causes more death per annum than colorectal, breast, and prostate cancers combined. While smoking prevention and cessation are essential strategies against lung cancer, they are often ineffective, and former smokers remain at lower, yet persistent risks. The magnitude of the tobacco epidemic and burden of lung cancer will continue to escalate globally, underscoring the importance of advancing chemoprevention research. Recently, exciting results from phase 2b randomized control trials are beginning to emerge. Advancements in understanding clinical tumor biology, diagnostic technology, and bioinformatics will continue to propel significant progress in the field. This update will provide a general overview of the background and rationale for lung cancer chemoprevention, review important results from historical trials, summarize key findings from recently completed studies, and discuss ongoing clinical trials and future directions for lung cancer chemoprevention.

Keywords Lung cancer · Chemoprevention · Carotinoids · Retinoids · Vitamin E · Selenium · Budesonide · Arachidonic acid · Ki-67 · Bronchial dysplasia · Surrogate end point biomarker · Cyclooxygenase-2 inhibitors · Celecoxib · PGE₂ · Aspirin · Iloprost · Myoinositol · PPAR-gamma agonists · Tea extracts · Isothiocyanates · Personalized approach

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Introduction

Over the past century, advancements in medicine, technology, and health care have led to dramatic epidemiologic transition as a country evolves through the process of modernization. Whereas infections and nutritional deficiencies used to account for the leading causes of premature death and morbidity, with the advent of antimicrobials and improvement of nutrition and health care, these causes are increasingly being replaced by chronic, noncommunicable diseases, including cancer. Globally, known risk factors for chronic diseases have dramatically increased, including tobacco consumption, changing diets, level of physical activity, and environmental and air pollution. Among these risk factors, tobacco use is the single most important preventable risk to human health and an important cause of premature death worldwide [1]. Smoking causes approximately 90% of lung cancer, the leading cause of cancer death in the world.

In spite of significant advancements in anti-cancer therapy, lung cancer continues to account for the majority of cancer-related deaths in the world [2, 3]. The high mortality is primarily due to the fact that the majority of the cases are diagnosed at a late invasive stage when curative treatment is no longer possible. Whereas smoking prevention and cessation remain essential in the overall strategy for lung cancer prevention, these approaches have notable limitations. Even when smoking cessation is successful, former-smokers continue to be at significant risk. Today at least half of all new lung cancers are diagnosed in former smokers [4–6]. Such revelations have led to intensified research in chemoprevention, which entails the use of an agent to impede the carcinogenic process and prevent cancer from developing in individuals at increased risk. Chemoprevention focuses on biological changes associated with the development and early progression of cancer. In contrast to chemotherapy, chemoprevention aims to impede the carcinogenic processes by targeting molecular

pathways that drive cancerization, thereby preventing the development of invasive cancer. Such an approach provides a powerful platform to advance scientific understanding of tumor biology, from which safe and highly efficacious interventions can be derived.

First coined by Sporn and colleagues [7], chemoprevention is defined as “the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer.” Since that time the potential of chemoprevention in reducing mortality risk has been realized in common epithelial cancer; the best example is the use of tamoxifen for breast cancer. Positive phase 3 trial findings have been demonstrated in breast, colon, and prostate cancers [8–11]. Results from phase 3 lung cancer chemoprevention trials over the past two decades, however, had been disappointing. These include the Alpha-Tocopherol, Beta-Carotene (ATBC) trial, Carotene and Retinol Efficacy Trial (CARET), Lung Intergroup Trial (LIT) using 13-*cis* retinoic acid [12–15], the EUROSCAN trial using retinyl palmitate and/or N-acetylcysteine [16], the Linxian study using four different combinations of vitamin and minerals [17], and a recent randomized controlled trial (RCT) using selenium [18] (Table 1).

Comparatively, the lungs and bronchi make up a far more intricate organ system comprised of complex anatomic architecture, tissues, and cell types that function not only for gas exchange, but serve as first line of defense against inhaled pathogens and noxious stimuli and mediate and regulate inflammatory responses, as well as immune functions. The respiratory tree is continually and directly exposed to high levels and vast numbers of harmful matters. As such, it is not surprising that chemoprevention of bronchogenic carcinomas

presents far greater challenges than malignancies of other solid organs. Nonetheless, many of the principles and strategies that have proven effective in chemoprevention of other common malignancies apply to lung cancer.

Lung carcinogenesis and biomarkers

Lung tumorigenesis results from lengthy, complex interactions between genetic predisposition and environmental influences. Malignant transformation begins with initiation, in which exposure of the respiratory epithelium to carcinogens leads to mutations in oncogenes, tumor suppressor genes, and DNA repair genes. While the human body has tremendous capacity to compensate for the damages caused by these harmful matters, continued exposures fuel the process of promotion, which is orchestrated by a series of genetic and epigenetic alterations in respiratory epithelial cells, aberrant interactions with other cell types, and imbalances of the network of biologic response modifiers, including cytokines, growth factors, and eicosanoids in the lung microenvironment. These alterations manifest as malignant phenotypic changes characterized by resistance to apoptosis, uncontrolled cellular proliferation, enhancement of angiogenesis, suppression of anti-tumor immunity, and increased epithelial mesenchymal transition. Collectively these mechanisms facilitate the driving force of cancerization, which is a multi-step process marked by progressions of premalignant changes in the respiratory epithelium [19–21].

According to the field carcinogenesis theory, exposure of the entire respiratory epithelium can lead to malignant transformation at multiple, independent sites. With sufficient genetic

Table 1 Phase 3 lung cancer chemoprevention trials

Study	Agents	1 ⁰ End point	Outcome
ATBC 1994	β-carotene/vitamin E	Lung cancer	(–)
CARET 1996	β-carotene/retinal	Lung cancer	(–)
NCI Intergroup 2000	13cRA	Second primaries	(–)
EUROSCAN 2000	Retinol/NAC	Second primaries	(–)
Linxian 2006	4 diff combinations of vitamins/mineral	Lung cancer mortality	(–)
MDACC 2010	Selenium	Second primaries	(–)
Results of large-scale RCT-based study for lung cancer chemoprevention			
UK Physicians' Health Study 1988	Aspirin	Lung cancer	(–)
US Physicians' Health Study 1988	Aspirin	Lung cancer	(–)
US Physicians' Health Study 1996	β-carotene	Lung cancer	(–)
US Women's Health Study 2005	Aspirin	Lung cancer	(–)
Meta analysis of 8 RCT 2011	Aspirin	Lung cancer mortality	(+)

instability and promotion, some of these sites may eventually evolve into cancer. Furthermore, these aberrant molecular and cellular changes can be identified in respiratory secretions, exfoliated cells, tissue, and blood samples using molecular and biochemical techniques, the modulations of which may be useful as surrogate biomarkers of response to anti-neoplastic agents. As our understanding of lung cancer biology and diagnostic technologies continues to advance, more refined risk assessment with targeted therapeutic approach toward personalized chemopreventive strategy to maximize efficacy, as well as favorable risk-benefit ratios, is becoming increasingly tangible.

Past experiences and challenges: productive failure is the key to success

Most of the historic phase 3 lung cancer chemoprevention trials were launched based on findings from epidemiologic, observational studies. While disappointing, important information and lessons learned from these studies continue to shape and improve the designs of subsequent trials. Several plausible explanations have been derived to account for decades of failed attempts to translate epidemiologic and preclinical clues into successful chemopreventive approaches for lung cancer.

Inaccurate interpretations of epidemiologic findings

The observation that diets high in carotenoids-rich fruits and vegetables are associated with reduced lung cancer risks led to several large-scale, phase 3, randomized, placebo-controlled trials using high-dose beta-carotene or retinoids [12–15]. Unfortunately, these agents actually increased the risk of lung cancer in active smokers while showing a potential benefit in former and never smokers. Such revelations have important public health implications. Before such definitive findings, supplementations with high-dose carotenoids and retinoids were becoming common practices for disease prevention, which would have substantially contributed to much higher mortality risk in active smokers. Experience from these studies also illustrated the formidable challenges in reversing carcinogenic process and premalignancy in the setting of continued tobacco exposure [22]. Because chemopreventive agents may exert differential effects in current and former smokers, many contemporary trials either exclude current smokers or analyze these subjects separately [23].

Limitations of preclinical models

Presently, the discovery, selection, and development of promising agents for lung cancer chemoprevention trials follow five general approaches: 1) identification of suggestive clues

and molecular targets involved in lung carcinogenesis from observational, case-control, and/or preclinical studies; 2) *in vitro* evaluation of the effects of drugs or targeted agents on cancer or pre-malignant cell biology; 3) *in vivo* preclinical animal models of lung carcinogenesis or xenografts of human lung cancer; 4) phase 1 and 2 clinical trials using surrogate end point biomarkers (SEBM) in humans; and 5) phase 3 RCT using cancer incidence as end points.

In vitro preclinical models are often uni-dimensional, unable to account for the complex interactions between varying cell types that normally occur *in vivo*. They are frequently limited by *in vitro* artifacts, thus requiring higher than physiologic relevant doses to achieve efficacy [24]. They also cannot completely simulate the complex, *in vivo* issues associated with metabolism and bioavailability. Preclinical mouse models are often inadequate, given tremendous biological, interspecies variations, and the inability of mouse model to account for the heterogeneity of human lung tumor biology. As such, efficacy in murine models frequently fails to translate successfully into human studies. For example, 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 [25], but human trials have only yielded negative results [26].

In addition to the aforementioned issues, several formidable obstacles stand in the way of progress for successful translations of promising chemopreventive agents. Even in high-risk groups such as heavy smokers, the actual incidence of lung cancer is still quite low—approximately 10%–15% [4]. In a chronic disease with such a complex biology that takes decades of carcinogenic exposure and molecular cellular damage for the malignant phenotype to manifest clinically, timely evaluation of promising chemopreventive agents and completion of trials is impossible to achieve if the primary end point is cancer incidence. Such an end point requires huge sample sizes, lengthy follow-up, and tremendous resources. To this end, intermediate end points have long been used in early-phase lung chemoprevention trials to access efficacy.

Lack of validated SEBM

To further complicate the matter, there are no validated SEBM that can reliably predict lung cancer incidence at present. Even the use of bronchial pre-neoplastic lesions as SEBM is fraught with controversies, including the potential of spontaneous reversal of pre-neoplasia and more recently, issues pertaining to sampling with serial bronchial biopsies of the same site that may completely remove the preneoplastic lesions at baseline bronchoscopy [26]. Conceivably if the preneoplastic lesions are completely removed at baseline, as the biopsy sites wound heals, the mucosa will be replaced by relatively normal tissue. Because the development of preneoplastic change is expected to be a lengthy process, it is highly probable that histopathology

from serial biopsy of the same bronchial site after 6 months may not accurately reflect the driving force of cancerization in the lung milieu. Such notion is consistent with the fact that the placebo groups in many phase 2 lung cancer chemoprevention trials also showed histopathologic improvement post treatment [26, 27•]. In view of all the caveats associated with repeated sampling of the bronchial epithelium, it is likely that only large changes in the resolution of bronchial pre-neoplasia may provide sufficient evidence to continue the development of the preventive agent. Further limitation with bronchial histopathology is the fact that bronchial pre-neoplasias are precursors of squamous cell carcinoma, which is no longer the most common NSCLC cell type. As such, the utility of bronchial histopathology as the primary SEBM for lung cancer chemoprevention trials has recently been challenged.

In addition to modulation of histopathology, many chemopreventive trials have used markers causally linked to lung carcinogenesis as SEBM, including the assessment of Ki-67. Ki-67 is a proliferation marker expressed in all phases of the cell cycle except in resting cells [28]. Elevated Ki-67 LI has been reported to be a unfavorable prognostic factor in NSCLC [29]. Because abnormal epithelial proliferation is a hallmark of tumorigenesis and increased Ki-67 expression has been seen in bronchial biopsies where preneoplastic changes are lacking [30], measuring Ki-67 LI in bronchial tissues as a SEBM for a chemopreventive agent with antiproliferative properties may circumvent, to some extent, the potential problems associated with mechanical removal. In a three-arm, double-blind, placebo-controlled RCT among former smokers to examine the effects of a 3-month treatment of 9-cis-retinoic acid (RA), 13-cis-RA, and α -tocopherol, or placebo, both treatments were associated with a significant reduction of bronchial Ki-67 LI, a secondary end point of the study [31].

NSCLC can arise centrally in the proximal bronchial epithelium (predominantly squamous cell carcinoma) or peripherally in the distal bronchoalveolar respiratory epithelium (predominantly adenocarcinoma). Most published, randomized, double-blind, placebo-controlled phase 2b lung cancer chemoprevention trials have focused on evaluating SEBM on the central bronchi. The phase 2b study with budesonide was the first published study to use both low-dose chest CT scans with fluorescence bronchoscopy for SEBM assessment. The study showed a small but statistically significant decrease in the proportion of CT-detected nodules in the budesonide-treated group [26], leading to an RCT with budesonide using serial chest CT for primary end point assessment in patients with CT-detected high-risk lung nodules [32].

Defining favorable risk-benefit ratio of the chemopreventive agent

Because the intent of chemoprevention is to prevent a disease from developing in high-risk individuals that are still relatively

healthy, tolerance of risks associated with such an intervention must be kept to a minimum, in contrast to chemotherapy. For example, the chemoprevention field suffered an enormous blow from the well-publicized cardiovascular (CV) risk associated with cyclooxygenase-2 (COX-2) inhibitors and other NSAIDs [33, 34]. Although the increase in CV risk associated with COX-2 inhibitors seems to occur mainly in those individuals with elevated baseline CV risk factors [35], the general enthusiasm for COX-2 inhibitors for chemoprevention has nonetheless been severely dampened. These types of concerns also contribute to the conduct of studies with marginally active compounds given at suboptimal, pharmacologically ineffectual doses.

The difficulty with recruitment and retention of high-risk human subjects

As mundane the issues may seem, no clinical studies will ever come to fruition without timely recruitment and retention of suitable human subjects to allow accurate end point assessment [36]. This is an important aspect of trial design and grant proposal that is often overlooked, lacking appropriate attention and funding for implementation. Most phase 2 RCT for lung cancer chemoprevention entail multiple layers of screening, diagnostic evaluation, treatment, and follow-up, requiring high level of coordination between and time investment from both the investigative team and subjects to successfully complete the trials.

A lack of personalized approach to lung cancer prevention

In view of the heterogeneity of human biology, no drug is anticipated to exert the same effects on every individual. Such a realization has given rise to the concept of personalized medicine, which is based on identifying the molecular characteristics of an individual that will maximize the probability of a favorable therapeutic response to a medication. Application of personalized approach in lung cancer chemoprevention has lagged behind targeted therapy for lung cancer and chemoprevention of other common epithelial cancers.

Encouraging new findings

After decades of hard work and disappointments, positive primary end point findings from phase 2b RCT are emerging. All of the interventions in some way targeted the arachidonic acid (AA) metabolic pathways. Two of these trials targeted the COX-2 pathway using a specific inhibitor celecoxib [27•, 37•]; the other used a prostacyclin analog iloprost. One of the celecoxib study involved exclusively former smokers [27•], the other two included both former and current smokers [37•, 38•].

RCT with celecoxib

Ample preclinical data suggest that the COX-2/prostaglandin E₂ (PGE₂) signaling pathway plays a pivotal role in conferring the malignant phenotype [39]. Produced primarily by the action of COX on the AA liberated from membrane phospholipids, overproduction of PGE₂, which is predominantly generated by up-regulation of COX-2, is associated with a variety of well-established carcinogenic mechanisms [40–43]. COX-2 expression has also been shown to be a poor prognostic indicator in non-small cell lung cancer (NSCLC) [44]. In animal models, inhibition of COX-2 and PGE₂ synthesis suppresses lung tumorigenesis [45, 46]. These data support the anti-neoplastic effect of COX-2 inhibitors and provide the rationale for evaluating their potential as chemoprevention agents for bronchogenic carcinoma.

The first RCT with celecoxib was published by Kim and colleagues in 2010 [37•]. Current or former smokers with at least a 20 pack-year (pack-year = number of packs of cigarettes per day times number of years smoked) smoking history were randomized into one of four treatment arms (3-month intervals of celecoxib then placebo, celecoxib then celecoxib, placebo then celecoxib, or placebo then placebo) and underwent bronchoscopies with biopsies at baseline, 3 months, and 6 months. Celecoxib was initially administered orally at 200 mg twice daily and the protocol subsequently increased the dose to 400 mg twice daily. The 204 patients randomized were primarily current smokers (79.4%). The primary end point was modulation of bronchial Ki-67 expression (a cellular proliferation marker) from baseline to 3 months by celecoxib. High-dose celecoxib significantly decreased Ki-67 labeling in former smokers and current smokers compared with placebo, after adjusting for metaplasia and smoking status ($P=0.02$), with stronger reduction of Ki-67 observed in former smokers.

Results from the second RCT with celecoxib were recently published by our group [27•]. In a phase 2a single-arm trial of celecoxib for lung cancer prevention in active smokers, we showed that celecoxib downregulated PGE₂ and interleukin 10 (IL-10) production in alveolar macrophages from active smokers [47], and 6 months of celecoxib treatment significantly downregulated Ki-67 in bronchial epithelial tissue obtained from 20 heavy smokers [48]. These promising results were followed up with a phase 2b RCT of celecoxib for lung cancer prevention in former smokers. Former smokers (age ≥ 45 , ≥ 30 pack-years of smoking, ≥ 1 year of sustained abstinence from smoking) were recruited and randomized into two arms (6 months of celecoxib then placebo, 6 months of placebo then celecoxib). Oral celecoxib at 400 mg twice daily was administered. The primary end point was bronchial Ki-67 labeling index (Ki-67 LI) after 6 months of treatment. Of 137 randomized subjects,

101 completed both baseline and 6-month bronchoscopies and were evaluable for the primary end point analysis (52 placebo, 49 celecoxib). Celecoxib significantly decreased Ki-67 LI by an average of 34%, whereas placebo increased Ki-67 LI by an average of 3.8% ($P=0.04$; t test). The beneficial effect on Ki-67 LI was even greater in the celecoxib arm (versus placebo) in a mixed-effects analysis ($P=0.0006$).

Celecoxib did not have significant effect on histopathology outcomes, although there is a trend favoring celecoxib in maximum histopathology score. Additionally, celecoxib significantly reduced plasma c-reactive protein, interleukin-6 mRNA and protein and increased 15(S)-hydroxy-eicosatetraenoic acid (15-HETE) levels in bronchoalveolar lavage (BAL) samples. Furthermore, the baseline ratio of COX-2 to 15-hydroxyprostaglandin dehydrogenase (15-PGDH) mRNA in BAL cells was a significant predictive marker of Ki-67 response to celecoxib ($P=0.002$). The balance of COX-2 and 15-PGDH determines the ultimate level of PGE₂, which likely contributes to the driving force of cancerization in the lung microenvironment; such a balance has been suggested to play a role in the responsiveness of an individual to COX-2 inhibition [49]. Findings from our trial not only confirm the antiproliferative effects of high-dose celecoxib on the bronchial epithelium, indicating the importance of appropriate dosing to achieve antineoplastic effects, but also provide additional evidence for simultaneous, favorable modulations of a number of secondary SEBM. Collectively, these findings reflect the efficacy of COX-2 inhibition on the driving force of cancerization in the lung microenvironment.

This study also incorporated low-dose helical CT for baseline screening and secondary end point assessment at 12 months, in 76 participants who crossed over to the other study arm at 6 months (all of whom had received 6 months of celecoxib at the end of a 12-month treatment period). Hard on the heels of the definitive randomized controlled National Lung Screening Trial (NLST) showing that screening high-risk current or former smokers with CT scans reduced lung-cancer mortality by 20%, we found that the decreases in Ki-67 LI correlated with a reduction and/or resolution of lung nodules on CT in our participants. We acknowledge the diagnostic limitation of CT scans for peripheral precursor lesions in the lungs, the noncomparative nature of our CT data, and the fact that a recent RCT of budesonide with a primary end point assessed by CT did not show improvement [50]. Nonetheless, our findings suggest that oral celecoxib is biologically active in the respiratory epithelium both centrally and peripherally. The earlier budesonide trial did not report any such correlative results. This is the first report providing evidence that a systemically administered agent may be capable of globally impeding the driving force of cancerization in the lungs, beyond the central airways.

RCT with Iloprost

Another approach for targeting the arachidonic acid pathway was conducted by Keith and colleagues [38•] using a prostacyclin (PGI₂) analogue. PGI₂ is a metabolite of PGH₂ (derived from AA by the action of COX) with anti-inflammatory, anti-proliferative, and potent anti-metastatic properties. Human lung cancer studies have shown that prostacyclin synthase expression is low in most lung cancers and low expression is associated with a worse outcome [51, 52]. 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 [53]. Iloprost, a long-acting oral prostacyclin analog, also inhibits lung tumorigenesis in wild-type mice. Based on these findings, the investigators launched a multi-centered RCT sponsored by the NCI and Lung Cancer Specialized Program of Research Excellence (SPORE) consortium. The primary end point for the trial is endobronchial histopathology, and heavy former and current smokers with sputum atypia were randomized, undergone fluorescence bronchoscopy performed at study entry and after 6 months of treatment with oral iloprost. These patients were required to have sputum atypia and thus were at a higher risk for central bronchial preneoplastic lesions than were patients of the celecoxib trials, who were not so required.

The accrual goal of 152 subjects was reached and 125 completed both bronchoscopies (60/75 iloprost, 65/77 placebo). Within each subject, the results were calculated by using the average score of all biopsies (Avg), the worst biopsy score (Max), and the dysplasia index (DI). Change in Avg was the primary end point, evaluated in all subjects, as well as in current and former smokers. Baseline histology was significantly worse for current smokers than former smokers. When compared with placebo, former smokers receiving oral iloprost exhibited a significantly greater improvement in Avg (0.41 units better, $P=0.010$), in Max (1.10 units better, $P=0.002$), and in DI (12.45%, $P=0.006$). No histologic improvement occurred in current smokers. Ki-67 was a secondary end point of this trial and was slightly, non-significantly reduced in the airways of former smokers of the iloprost arm, further reinforcing the importance of smoking status in lung cancer prevention.

Ongoing RCTs in lung cancer chemoprevention

Myoinositol

Myoinositol is a glucose isomer derived from grains, seed, and fruit. It is a precursor of several second messengers including diacylglycerol, which regulates some members of the protein kinase C family, inositol-1,4,5-triphosphate, which modifies

intracellular calcium levels, and phosphatidylinositol-3,4,5-bisphosphate, which is involved in signal transduction. In a phase 1 study in smokers with bronchial dysplasia, myoinositol significantly increased the rate of regression of preexisting dysplastic lesions (91% vs 48%; $P=0.014$), using the regression rate of the placebo subjects from another recently completed clinical trial from the same investigators with the same inclusion/exclusion criteria as a comparison [54]. Myoinositol had also been reported to inhibit the PI3K pathway in vitro, and PI3K activity was found to be decreased in the airway of high-risk smokers who had significant regression of dysplasia after treatment with myoinositol [55]. In addition, myoinositol decreased endogenous and tobacco carcinogen-induced activation of Akt and ERK in immortalized human bronchial epithelial cells, which decreased cell proliferation and induced a G(1)-S cell cycle arrest. Significant decreases in Akt and ERK phosphorylation were observed in bronchial dysplastic lesions following myoinositol treatment in heavy smokers [56]. All of these findings support the ongoing phase 2 multicenter study sponsored by the NCI Mayo Clinic Cancer Prevention Network (ClinicalTrials.gov identifier: NCT00783705).

PPAR-gamma agonist

PPAR-gamma (PPAR- γ) is a nuclear hormone receptor that acts as a ligand-activated transcription factor and plays a pivotal role in regulating adipocyte differentiation, glucose and lipid homeostasis, and intracellular insulin-signaling events [57]. Transcriptional activities of PPAR- γ are regulated by fatty acid binding. PPAR- γ has been receiving growing interest for its involvement in carcinogenesis. Ligands of PPAR- γ induced differentiation and apoptosis by NSCLC [58]. Reduced PPAR- γ expression within the tumor is associated with poor prognosis in lung cancer patients. Synthetic PPAR- γ agonists such as the thiazolidinedione (TZD) class of anti-diabetic drugs can inhibit growth of NSCLC cells in vitro, and block tumor progression in xenograft models [59]. Preclinical studies in NSCLC, colon, and prostate cancer cell lines have also implicated the involvement of PPAR- γ in mediating apoptosis with 15-HETE, an AA metabolite of 15-lipoxygenase (15-LOX). PPAR- γ agonists have been demonstrated to exhibit anticancer properties in colon, breast, and prostate cells [60–62]. Furthermore, the reductions of 15-LOX, 15-HETE, and PPAR- γ activity have been shown to contribute to lung carcinogenesis [63]. Recent reports of lung, prostate, and colon cancer rates in diabetic veterans receiving PPAR- γ agonists revealed a 33% decrease in lung cancer incidence compared to none users [64], suggesting that PPAR- γ activation may be useful in lung cancer chemoprevention. A phase 2 RCT using the PPAR- γ agonist pioglitazone is actively recruiting subjects. Subjects will have quantitative high-resolution thoracic CT scan and a fluorescent bronchoscopy at

study entry and after 6 months on drug or placebo. The primary outcome is endobronchial histology and determining if pioglitazone can retard progression. Secondary end points related to the PPAR- γ signaling pathway will also be analyzed (ClinicalTrials.gov identifier: NCT00780234).

Other agents of interest

Tea extracts

Many epidemiological studies and laboratory experiments suggest that tea consumption protects against chronic diseases, such as cardiovascular disease and cancer [65–67]. Tea contains high levels of flavonoids, including catechins and other polyphenols. These phytochemicals are thought to play key roles in mechanisms that may provide health benefits [68–71]. Through these mechanisms, tea has demonstrated significant antineoplastic effects in animal models of lung, skin, esophageal, and gastrointestinal cancers [72–74]. For example, green tea has been shown to inhibit lung tumor development in A/J mice treated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen found in tobacco [75]. Green tea and EGCG has also been shown to inhibit breast and lung cancer in murine xenografts [24, 76]. The potential of GTE for lung cancer chemoprevention is being evaluated in a phase 2 RCT, the results of which are pending (ClinicalTrials.gov identifier: NCT00363805; NCT00573885).

Whereas the majority of the work evaluating the antineoplastic effects of tea has been done on green tea, the potential health benefits of white tea and its advantage over green tea are becoming increasingly recognized. In a recent report, our group reported that white tea extract (WTE) was more efficacious than green tea extract (GTE) in the induction of apoptosis in NSCLC cell lines, through the upregulation of 15-LOX, 15-HETE, and PPAR- γ , supporting further evaluation of the potential of WTE for lung chemoprevention in future clinical trials [77].

Isothiocyanates

Isothiocyanates, such as phenethyl isothiocyanate (PEITC) and sulforaphane, have been shown to inhibit carcinogenesis and are potential chemopreventive agents [78]. They have been shown to inhibit carcinogenesis through inhibition of cytochrome P450 enzymes, which oxidize compounds such as benzo[a]pyrene and other polycyclic aromatic hydrocarbons (PAHs) into more polar epoxy-diols. These compounds can then cause mutation and induce cancer development. A randomized trial evaluating PEITC as a modifier of nicotine-derived nitrosamine ketone (NNK) metabolism in smokers is currently recruiting subjects (ClinicalTrials.gov identifier: NCT00691132).

Other modulators of the arachidonic acid pathway

RCTs involving the 5-lipoxygenase inhibitor zileuton (ClinicalTrials.gov identifier: NCT00056004) and the NSAID sulin-dac, a nonspecific COX inhibitor, were conducted recently, pending publication of results (ClinicalTrials.gov identifier: NCT00368927). A recent meta-analysis of eight RCTs of daily aspirin to reduce the risk of vascular disease found a 20%–30% reduction in lung cancer mortality in people taking daily aspirin for 5 or more years [79•].

Organosulfurs

Oltipraz and anethole dithiolethione (ADT) are two organosulfur compounds belonging to the dithiolethione class. Oltipraz was studied in a phase I lung cancer chemoprevention trial with early termination due to hepato-toxicity [80, 81]. ADT is available in Europe and Canada for the treatment of xerostomia due to radiation. A phase IIb trial with ADT in smokers with bronchial dysplasia was performed in 2002. The progression rate of pre-existing dysplastic lesions by two or more grades and/or the appearance of new lesions was statistically significantly lower in the ADT group than the placebo group in both the person-specific (32% versus 59%) and lesion specific analysis (8% versus 17%) [82]. However, due to undesirable side effects of abdominal bloating and flatulence, a phase III trial of ADT was not conducted.

Protein kinase C inhibitor

In lung cancer cells, enzastaurin, a protein kinase C- α (PKC- α) inhibitor, had demonstrated inhibitory activity on intracellular signaling proteins [83]. Enzastaurin, had being studied in a phase IIb lung cancer chemoprevention trial in former smokers, result of which is pending (ClinicalTrials.gov identifier: NCT00414960).

Future directions

Due to a variety of social and political factors, support for lung cancer research pales in comparison with other common epithelial cancers. The dismal prognosis and disappointing results from previous screening trials with chest x-ray and chemoprevention studies have also discouraged many talented individuals from pursuing a career in the field. As a result, progress in lung cancer research and management has generally lagged behind other common solid cancers. While the focus on smoking prevention and cessation should be maintained and intensified, efforts on exploring new frontiers for research and clinical management deserve equal emphasis, without which advancement and innovations will be

impossible. With developing countries contributing to much of the tobacco epidemics, the global burden of lung cancer will continue to escalate for decades to come; such an epidemiologic transition in the Western society is now predictably occurring at an accelerated pace in the developing world. The magnitude of the problem underscores the urgency for the development of innovative chemopreventive strategies.

Inventive trials methods, such as adaptive design, marker assessment, and data analysis, should be employed in early-phase clinical studies. For the detection of central precursor lesions, better imaging techniques including noninvasive methods to detect and follow endobronchial premalignancy, such as autofluorescence-guided optical coherence tomography (OCT), may help bypass the potential sampling issue associated with biopsy, allowing for more accurate assessment of the natural history and effects of chemoprevention on these lesions [84]. For detection of small peripheral lesions, the development of molecular imaging coupled with the target of interest, such as COX-2–targeted imaging using positron emission tomography (PET) or single photon emission computed tomography (SPECT) tracers, promises the potential of detecting COX-2–expressing lesions and enhances predictive information for responsiveness to COX-2 inhibitors [85–87].

The use of a sophisticated model system for end point analysis, such as mixed effect model analysis in our celecoxib trial, clearly demonstrates that the higher the baseline Ki-67 LI, the more likely a treatment response is observed. The association of Ki-67 responders having higher BAL cell COX-2/15-PGDH than non-responders also presents a new direction for a more focused trial design in the future with celecoxib—for instance, restricting inclusion of subjects to those with elevated baseline bronchial Ki-67 LI and BAL cell COX-2/15-PGDH. An elevated baseline bronchial proliferative index should reflect a stronger driving force of cancerization in the lung microenvironment or higher risk for lung cancer at the molecular level, whereas an elevated BAL cell COX-2/15-PGDH may increase the likelihood of responding to COX-2 inhibition [27•].

The lack of validated SEBM for early-phase lung cancer chemoprevention trials continues to curtail progress in the field. Studies of typical phase 2 SEBM such as histopathology and Ki-67 will need to be validated within the context of phase 3 cancer end point trials [88]. In view of the complexity of lung cancer biology, favorable alterations in a combination of biomarkers rather than in any single biomarker will be required to achieve the level of sensitivity and specificity adequate for routine screening and therapeutic monitoring. To this end, application of system biology combining clinical characteristics, cellular and molecular phenotype derived from high-throughput technology such as gene expression profile, epigenetic alterations (methylation patterns and microRNA expression), proteomics and metabolomics, will allow more

refined risk assessment, development of prediction model, and personalized approach to intervention to maximize efficacy and minimize treatment-related risks.

In line with these ideas, Gold and colleagues proposed another approach, “reverse migration,” to accelerate the development of chemopreventive agents. This approach involves importing agents, targets, and study designs to personalize interventions developed in advanced cancer to cancer prevention—for example, using the model from the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial of personalized lung cancer therapy for personalized lung cancer prevention [89•]. BATTLE is the first completed prospective, biopsy-mandated, biomarker-based, adaptively randomized study in 255 pretreated lung cancer patients. Following an initial equal randomization period, chemo-refractory NSCLC patients were adaptively randomized to erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib, based on relevant molecular biomarkers analyzed in fresh core needle biopsy specimens. Overall results include a 46% 8-week disease control rate (primary end point), confirm prespecified hypotheses, and show an impressive benefit from sorafenib among mutant-*KRAS* patients. BATTLE establishes the feasibility of a new paradigm for a personalized approach to lung cancer clinical trials (Kim, ClinicalTrials.gov numbers: NCT00409968, NCT00411671, NCT00411632, NCT00410059, and NCT00410189). Development of this approach in tertiary prevention of second primary lung cancer with the above targeted agents will be the first logical step [90].

Analogous to treatment of other chronic noncommunicable diseases such as diabetes, the use of combination chemopreventive regimen with agents targeting various known carcinogenic pathways may prove to be more advantageous than a single agent, and allow the use of smaller doses to achieve synergy, minimize side effects, and sustain long-term benefits. Development of appropriate inhalational agents may also reduce the chance for systemic toxicity, although adherence with treatment, including the proper use of inhalational techniques, may interfere with consistent drug delivery to the lungs and efficacy. Exploration of old drugs with established track record of tolerability, such as metformin, which has been shown to inhibit cellular growth and proliferation, is also of future interest [91–93]. Table 2 lists potential molecular targets for lung cancer chemoprevention.

The success of the iloprost study helps illustrate the importance of collaborative efforts from lead investigators with expertise in specialized areas of translational research. Forging alliances by cooperative trial groups with synergistic programmatic approaches can overcome the challenges with recruitment, and improve and accelerate the development of the next generation of translational research approaches to lung cancer chemoprevention.

Table 2 Molecular targets for lung cancer chemoprevention

Potential molecular targets for lung cancer chemoprevention

COX-2
 PGI₂
 PPAR-gamma
 PI3K
 mTOR
 5-LOX
 15-LOX
 EGFR
 Tyrosine kinase
 Methylation
 Angiogenesis
 Histone deacetylase

Conclusions

Despite decades of disappointment, the invaluable lessons we learned from past failures have established the path toward success. Recognizing the power of prevention and early detection, future studies will continue to build upon prior experiences. In view of the complexity of the pathogenesis of lung cancer, biomarker-driven approaches based on sound understanding of clinical tumor biology, combined with advanced diagnostic technology and systematic application of bioinformatics, promise to propel progress in the field. With dedication, creativity, open-mindedness, hard work, and perseverance, the development of practical, personalized paradigms for lung cancer chemoprevention is well within reach and will soon become a reality.

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