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Lung cancer chemoprevention: current status and future prospects

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Abstract

Lung cancer is the leading cause of cancer death worldwide, making it an attractive disease for chemoprevention. Although avoidance of tobacco use and smoking cessation will have the greatest impact on lung cancer development, chemoprevention could prove to be very effective, particularly in former smokers. Chemoprevention is the use of agents to reverse or inhibit carcinogenesis and has been successfully applied to other common malignancies. Despite prior studies in lung cancer chemoprevention failing to identify effective agents, we now have the ability to identify high-risk populations, and our understanding of lung tumour and premalignant biology continues to advance. There are distinct histological lesions that can be reproducibly graded as precursors of non-small-cell lung cancer and similar precursor lesions exist for adenocarcinoma. These premalignant lesions are being targeted by chemopreventive agents in current trials and will continue to be studied in the future. In addition, biomarkers that predict risk and response to targeted agents are being investigated and validated. In this Review, we discuss the principles of chemoprevention, data from preclinical models, completed clinical trials and observational studies, and describe new treatments for novel targeted pathways and future chemopreventive efforts.

Introduction

The term cancer chemoprevention was first introduced into the medical literature in 1976 by Michael Sporn and was defined to be the use of dietary or pharmaceutical interventions to slow or reverse the progression of pre-malignancy to invasive cancer. In this landmark publication,¹ Sporn discussed the evidence supporting the potential efficacy of retinoids in preventing lung cancer, a hypothesis that has subsequently undergone significant clinical testing with largely null or harmful outcomes in patients. For cancer chemoprevention to succeed, a high-risk population needs to be identifiable and agents that are both efficacious

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Competing interests

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and associated with tolerable adverse effects must be available. For prevention of lung cancer, individuals at high risk can be readily identified using simple clinical features.^{2,3} Unfortunately, no pharmacological or dietary intervention has been demonstrated to reduce lung cancer risk. Smoking cessation is currently the only known intervention effective in reducing the risk of lung cancer.⁴

Lung cancer is the leading cause of cancer death in the world, with an estimated 1,387,400 deaths in 2011,⁵ making it an attractive target disease for cancer chemoprevention. In the USA, over 200,000 lung cancer diagnoses were made in 2012 and the 5-year overall survival for patients is a dismal 16%.⁶ Although gradual improvements in survival have been achieved, this advance has not matched those seen for other common malignancies, such as breast, prostate and colon cancer, partly as a result of lung cancer patients often presenting at an advanced stage where surgical cure is no longer feasible. Early detection is critical for improving outcomes, and lung cancer screening using low-dose CT scans has been shown to be effective in reducing mortality by 20%.⁷ Although this is a major advance in preventing deaths from lung cancer, even with the widespread introduction of CT screening, overall survival remains low, with less than 20% of patients living beyond 5 years. Populations at high risk for lung cancer, with an annual incidence of up to a 2%, can be readily identified using easily obtainable information, including smoking history, previous history of a tobacco-induced cancer, pulmonary function, and family history.^{3,8,9} More sophisticated risk assessment models have been developed, which include capacity for DNA repair, but these models do not add greatly to the previously described models.⁹ For breast cancer, a predicted annual incidence of 0.3% is an indication for consideration of chemoprevention treatment, so the potential population for lung cancer chemoprevention is comparatively large.

The vast majority of lung cancers diagnosed in the USA (85–90%) are associated with exposure to tobacco smoke.¹⁰ Therefore, prevention of smoking initiation is clearly the most effective intervention that can be applied to reduce the burden of lung cancer. Smoking cessation has been demonstrated to decrease lung cancer and prolong life.^{4,11} Most recently, this was shown in the Million Women Study in the UK, where female smokers who continued to smoke beyond the age of 40 lost at least 10 years of lifespan.¹² In contrast to other smoking-related diseases, former heavy smokers retain a significant risk of developing lung cancer years after smoking cessation. Currently in the USA, more than 50% of lung cancer occurs in former smokers.^{13,14} Studies have shown that response to chemopreventive agents may differ between current and former smokers, with a more favourable response in the latter.^{15,16} Therefore, limiting chemoprevention clinical trial enrolment to former smokers or analysis of the two groups separately remains a reasonable strategy.

In this Review, we provide an overview of previous clinical trials that assessed lung cancer prevention as the primary goal. We will also discuss strategies for identifying new agents for lung cancer prevention, including modulation of intermediate end point biomarkers, pre-clinical models and observational studies. Finally, we will summarize our vision of novel ways to move the field forward.

Human pulmonary carcinogenesis

Lung cancer is currently divided into histological classifications of small-cell carcinoma and the non-small-cell carcinoma types of adenocarcinoma, squamous-cell carcinoma, and large-cell undifferentiated carcinoma. Adenocarcinoma and squamous-cell lung cancer make up the vast majority of lung cancer cases, and are the only cell types for which premalignant histology has been well characterized. For both of these subtypes of lung cancer, multistep carcinogenesis involving genetic and epigenetic alterations in pulmonary epithelial cells has been demonstrated.¹⁷ However, a consistent progression of events has not been clearly established.

For squamous-cell lung cancer, progression through a series of histological changes, which can be sampled by bronchoscopy, has been described. These changes, classified by the WHO, include reserve cell hyperplasia, squamous metaplasia, mild, moderate and severe dysplasia, and carcinoma *in situ* (Figure 1).¹⁸ The lesions can be reproducibly graded,¹⁸ but the risk of progression of each lesion to invasive squamous-cell lung cancer has not been well established because this process is difficult to study and, therefore, remains controversial. Several studies have suggested that assessment of the accumulation of genetic alterations—assessed by fluorescence *in situ* hybridization (FISH),¹⁹ PCR-based loss of heterozygosity,²⁰ comparative genomic hybridization²¹ or sequence analysis²²—might provide important prognostic information beyond that of the level of histological dysplasia.²³ Amplification of genes encoded on chromosome 3q26,²¹ including *SOX2*, *PIK3CA* and *TP63*, has been identified as an early event in the development of squamous-cell lung cancer, with *SOX2* amplification occurring before the other genetic changes.²⁴

The premalignant biology of adenocarcinoma is more difficult to investigate than that of squamous-cell lung cancer, since lesions are only accessible by surgical resection or percutaneous needle biopsy. Adenocarcinoma seems to be preceded by a premalignant lesion (atypical adenomatous hyperplasia) and the preinvasive lesion (adenocarcinoma *in situ*, formerly known as broncho-alveolar carcinoma), which progresses to invasive adenocarcinoma.²⁵ In some cases, specific *EGFR* or *KRAS* mutations might precede the development of invasive squamous cell or adenocarcinoma.^{26–28}

In 1953, Slaughter *et al.*²⁹ introduced the term ‘field cancerization’ to describe the frequent occurrence of widespread premalignant histological changes and second primary neoplasms in smokers with oral cancer. It is now widely accepted that field cancerization also occurs in the lower respiratory tract during pulmonary carcinogenesis, with the molecular correlates of widely dispersed epithelial cells harbouring mutations in either *TP53* or *EGFR* associated with squamous-cell or adenocarcinoma premalignancy, respectively.^{22,26} *EGFR* or p53 protein overexpression has been reported in premalignant dysplasia,^{27,30} and expression is most pronounced in more-advanced lesions (that is, severe dysplasia and carcinoma *in situ*).

Chemoprevention

Carcinogenesis is a complex process, involving carcinogen exposure and activation, DNA adduct formation, inflammation, oxidative stress, mutation and epigenetic alterations, which lead to the acquisition of the hallmarks of cancer.³¹ These hallmarks include: sustained

proliferative signalling; growth suppression evasion; cell death resistance; replicative immortality; angiogenesis; invasion or metastasis; reprogrammed energy metabolism, and immune evasion. All these hallmarks arise as a result of genomic instability.

Chemoprevention efforts have been directed at all of the carcinogenic processes, as well as at many of these intrinsic features of cancer (Figure 1). Both adenocarcinoma and squamous-cell carcinoma of the lung are genetically complex and heterogeneous, making chemoprevention with an agent targeted to specific driver mutations unlikely to be widely effective, except perhaps in the setting of definable premalignant lesions (ground glass opacities or endobronchial dysplasias) with established mutations in targetable proteins.^{32,33} Loss of function of the p53 tumour-suppressor protein might be the most common mutation in squamous cell and adenocarcinoma, but approaches to restore p53 function have yet to be therapeutically translated. We speculate that the most broadly effective chemoprevention approaches will target general processes, such as suppression of inflammation, interference with autocrine or paracrine growth stimulation, restoration of epithelial differentiation and polarity, augmentation of apoptosis, improved immune surveillance, and suppression of invasion or angiogenesis.

Phase III chemoprevention trials

Chemoprevention efforts fall into three distinct subgroups: primary, secondary and tertiary. Primary chemoprevention involves patients at increased risk, but without a previous history of cancer. Secondary chemoprevention studies enroll individuals with increased risk and evidence of premalignancy. For lung cancer, this usually refers to sputum cytological atypia and/or endobronchial dysplasia. Recent studies have also focused on individuals with ground glass opacities on CT scan suggestive of adenocarcinoma *in situ* or atypical adenomatous hyperplasia.^{34–36} Tertiary chemoprevention trials have the end point of a second primary tumour in individuals with a previous tobacco-induced aero-digestive cancer. A number of phase III chemoprevention trials, including primary, secondary and tertiary studies, have been reported in the past two decades (Table 1). Unfortunately, the results of phase III lung cancer chemoprevention trials can be summarized succinctly: aspirin,^{37–39} retinyl palmitate,⁴⁰ 13-*cis*-retinoic acid,⁴¹ vitamin E,⁴² a multivitamin and mineral supplement,⁴³ and selenium⁴⁴ are all ineffective; beta-carotene seems to be harmful in current smokers.¹⁶

As the discouraging results of phase III lung cancer chemoprevention trials have accumulated, investigators and funding agencies have adopted increasingly stringent criteria for assessing a treatment in a phase III trial.⁴⁵ Although all criteria cannot be applied to every putative agent, evidence supporting efficacy of a chemopreventive intervention ideally should be derived from multiple sources, including mechanistic, preclinical, observational and phase II studies with intermediate or surrogate end points. In addition, ideal chemopreventive agents would be well tolerated, inexpensive, and perhaps also treat comorbid disease (such as chronic obstructive pulmonary disease [COPD], diabetes mellitus, pulmonary hypertension, or atherosclerosis) in high-risk individuals. Currently, no interventions other than smoking cessation have been shown to reduce lung cancer risk, so we believe that efficacy should take precedence over these ancillary characteristics as attempts are made to discover ways to reduce lung cancer risk.

Early phase trials

Although phase III clinical trials represent the definitive means of demonstrating efficacy in terms of reducing cancer incidence and mortality, phase II cancer prevention trials rely on intermediate end points that are meant to predict these outcomes. The terms ‘surrogate end point’ and ‘intermediate end point’ are not synonymous. A surrogate end point is obtained earlier, potentially less invasively, and at lower cost than a true end point, but serves as a substitute for the true outcome. An intermediate end point should be integrally involved in the disease process (carcinogenesis in this case), and expression should differ between normal and at-risk subjects and correlate with disease course.⁴⁶

Owing to the lack of an effective chemoprevention agent for lung cancer (Table 1), no intermediate end point biomarkers have been validated as surrogate end points according to the Prentice criteria.⁴⁷ Therefore, intermediate end points for phase II chemoprevention trials are largely chosen on the basis of biological plausibility. Premalignant histology is the most-widely accepted intermediate end point, but has several weaknesses. The WHO classification focuses largely on squamous-cell precursor lesions, which are accessible to bronchoscopic biopsy.¹⁸ Whether an effect on these squamous precursor lesions might carry over to premalignant adenocarcinoma lesions is speculative. The complexity of branching airway anatomy and small calibre of higher division airways makes bronchoscopic inspection of the entire epithelial surface impossible. It is extremely rare to biopsy a premalignant dysplasia that subsequently develops into an invasive squamous-cell carcinoma, so accurately predicting the progression of premalignant lesions (except possibly for carcinoma *in situ*) is infrequent and controversial. Although endobronchial histology has a poor correlation with lung cancer risk, the addition of biomarkers of genetic alteration (including chromosomal aneusomy detected by FISH, PCR-detected loss of heterozygosity or gene-copy number changes detected by comparative genomic hybridization or single nucleotide polymorphism array) are promising.^{19–22} Proliferation index, most commonly measured by Ki-67 immunostaining, is a similarly plausible, but unvalidated intermediate end point biomarker.⁴⁸ A number of novel biomarkers have been developed that might be validated and could be used in phase II chemoprevention trials. These include a transcriptomic signature derived from endobronchial or nasal brushings,^{49,50} biopsy proteomics,⁵¹ serum proteomics,⁵² and the analysis of volatile organic compounds in exhaled breath.⁵³

Several phase II chemoprevention trials have been completed (Table 2), although few have met their primary end point. Two negative phase II trials of 13-*cis*-retinoic acid, with histological end points,^{54,55} have been published and the results are consistent with the negative phase III trial of 13-*cis*-retinoic acid in individuals with a previous lung cancer diagnosis.⁴¹ This consistency at least suggests that phase II trials might help identify potential chemopreventive agents that should not progress to phase III testing. To date, the only trials to have met the primary end point are those assessing iloprost (a drug to treat pulmonary arterial hypertension that produced histological improvement⁵⁶) and celecoxib (decreased Ki-67 levels in two trials^{57,58}). In the iloprost trial, Ki-67 level was a secondary end point and was not decreased by iloprost treatment. However, there were considerable differences between the celecoxib and ilo-prost trials. In the celecoxib trials, dysplasia was

either extremely infrequent or not reported, and the iloprost trial evaluated a cohort with an approximately 70% incidence of dysplasia. Expression of Ki-67 was assessed largely in the normal bronchial epithelium in the celecoxib trials and in more-advanced lesions in the iloprost trial. As no intermediate end points have yet been validated to be predictive of chemopreventive efficacy, it is not clear if either the modulation of histology or Ki-67 index is informative.

Although most phase II trials have assessed histological or proliferative intermediate end points in the central airways, three trials evaluated CT-detected pulmonary nodules in response to inhaled corticosteroids.^{34–36} CT-detected nodules were not the primary end point in two of these trials, but were included in exploratory analyses that indicated efficacy of inhaled corticosteroids, and led to a third trial with nodules as the primary end point. The latter trial,³⁴ was negative in that nodules were not decreased by inhaled corticosteroids. This potentially exciting new end point might represent atypical adenomatous hyperplasia or adenocarcinoma *in situ*, which presents as ground glass opacities on thoracic CT scan. However, this end point lacks specificity as other pulmonary conditions, including infection, organizing pneumonia, hypersensitivity pneumonitis, and desquamative interstitial pneumonia, can also cause ground glass opacities.⁵⁹ Short-term trials assessing the response of the ground glass component of semi-solid pulmonary nodules that will undergo resection might address this lack of specificity, but we are not aware of any such trials that are ongoing or planned.

The phase I trial that assessed myoinositol had no control group, but gave promising results when compared to historical controls.⁶⁰ Of interest, gene-expression profiling of bronchial brushings identified increased expression of PI3K in association with lung cancer or dysplastic lesions.⁶¹ Myoinositol inhibits PI3K, and elevated expression of genes involved in PI3K signalling identified patients who responded to myoinositol. These data indicate that the personalization of chemoprevention may be possible, as is the case for treating lung cancer with targeted agents.⁶¹ Results of an ongoing randomized controlled phase II trial of myoinositol will be of great interest.

Preclinical studies

Similar to other common cancers, animal models of non-small-cell lung cancer have been extensively used to study lung carcinogenesis and perform preclinical studies involving chemopreventive agents. Multiple, well-characterized models of murine adenocarcinoma are available, including initiator-promoter carcinogenesis,⁶² mutant *KRAS*⁶³ or *EGFR*⁶⁴ and the use of complete carcinogens.^{65–67} Tobacco smoke is a mouse lung carcinogen and can reproducibly induce pulmonary adenocarcinomas, but it is a labour-intensive and expensive model.⁶⁸ More recently, a chemically induced squamous-cell lung carcinoma model has been described, and histopathological analysis of serial lung sections in this model revealed a range of lung pathology, including squamous-cell carcinoma, carcinoma *in situ*, and varying levels of bronchial dysplasia.⁶⁹ Immunohistochemical studies on the premalignant lesions show staining that corresponds to analogous human lesions.⁷⁰ Gene expression similarities between human and murine adenocarcinoma have been described;⁷¹ these comparisons have not yet been made for the squamous-cell carcinoma model.

Eicosanoids represent a large family of bioactive lipid molecules that signal through autocrine and paracrine pathways and have been implicated in cancer initiation, progression and metastasis (Figure 2).⁷² Prostaglandin I₂ (PGI₂, prostacyclin) is a member of the eicosanoid family that has anti-inflammatory, antiproliferative, anti-metastatic, and potent chemopreventive properties.⁷³ The chemopreventive effects of PGI₂, or its analogue iloprost, are independent of the canonical cell surface receptor (prostacyclin receptor), but rather involve the activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ).⁷⁴ PPAR γ ligands inhibit the growth of lung cancer cell lines *in vitro* and in xenograft models, resulting in decreased proliferation, increased apoptosis, and promotion of differentiation (which may allow for the use of targeted therapeutics).^{75,76} Furthermore, multiple animal carcinogenesis studies have demonstrated that PPAR γ ligand treatment inhibits lung tumour development and can induce apoptosis.^{77,78} The observed tumour inhibition occurs in the setting of mutated *TP53*, thereby mirroring the most-common human genetic abnormality found in lung cancer. The addition of the PPAR γ ligand pioglitazone to the inhaled steroid budesonide further improved the efficacy associated with either agent alone and was shown to decrease tumour load by 90% in animals exposed to the cigarette smoke carcinogen benzo(a)pyrene.^{78,79} Mice overexpressing lung-specific PPAR γ developed 70% fewer tumours than wild-type controls when exposed to carcinogens.⁷⁴

Chemopreventive interventions have been assessed in murine preclinical models. Inhaled and systemic glucocorticoids,⁸⁰ myoinositol,⁸⁰ overexpression of PGI₂,⁸¹ dietary administration of iloprost,⁷⁴ overexpression of PPAR γ ,⁷⁴ dietary administration of pioglitazone⁷⁸ and the VEGF inhibitor vandetanib,⁸² as well as the anti-oestrogen fulvestrant, have all proved efficacious in murine models.⁸³ The effect of COX inhibitors on lung cancer prevention has also been tested in murine models. The COX inhibitor indomethacin was found to be effective,⁸⁴ but the COX-2 selective inhibitor celecoxib was not.⁸⁵ Additionally, rexinoids, agents that activate nuclear retinoid X receptors, and triterpenoids⁸⁶ have been shown to prevent murine adenocarcinoma, both alone and when used in combination.^{87,88}

Observational studies

Observational studies on the relationship of aspirin use and lung cancer are inconsistent; any positive reports are at odds with the results of randomized controlled studies including the Physicians' Health Study³⁷ and Women's Health Study.³⁸ Recently, a meta-analysis of case-control and cohort studies of aspirin in the prevention of vascular events was published in which the association between aspirin use and the incidence of several cancers was analysed. Regular use of aspirin was associated with a reduced risk of colorectal cancer (odds ratio = 0.62, 95% CI 0.58–0.67; $P < 0.0001$), but only a trend towards protection from lung cancer was identified.⁸⁹ Another meta-analysis of 15 observational studies (six case-control studies and nine prospective cohort studies) also failed to demonstrate a protective effect of aspirin for the prevention of lung cancer.⁹⁰ A third meta-analysis of randomized controlled studies of daily aspirin versus no aspirin for the prevention of vascular events in which individual patient data on risk of cancer death was available yielded interesting results.⁹¹ The 20-year risk of death from lung cancer was significantly decreased in trials

with scheduled aspirin treatment for 5 years or longer, with hazard ratios (HR) of around 0.70. This effect was entirely due to a reduction in deaths from adenocarcinoma and was seen only in longer-duration studies (5 years or more) with long-term follow up. Although these studies are not definitive, they do raise the hypothesis that to demonstrate the chemopreventive effect of aspirin on lung cancer, more than 5 years of treatment and long-term follow up might be needed.

Pulmonary inflammation is thought to be one factor leading to lung cancer. Therefore, it is perhaps not surprising that systemic and inhaled treatment with the anti-inflammatory agents corticosteroids have chemopreventive efficacy in murine models.⁸⁰ A cohort study of patients being treated in Department of Veterans Affairs outpatient clinics reported that those receiving high-dose inhaled corticosteroids and exhibiting good compliance had a reduced risk of lung cancer (HR = 0.39, 95% CI 0.16–0.96) compared to controls.⁹² These results are in agreement with a meta-analysis of interventional studies of inhaled corticosteroids assessing COPD outcomes in which a trend towards protection from lung cancer mortality (HR = 0.47, 95% CI 0.22–1.00) was noted (D. Sin, personal communication). The short period of observation of these trials (mean 26 months) limits their applicability to lung cancer chemoprevention.

The thiazolidinedione class of anti-diabetic agents, including rosiglitazone and pioglitazone, act through the PPAR γ nuclear receptor, as does the prostacyclin analogue iloprost.⁷⁴ Two large observational studies have compared lung cancer incidence in patients with type II diabetes mellitus treated with thiazolidinediones versus other agents, and both have reported an approximate 33% reduction in lung cancer risk ($P = 0.003$ – 0.001) in the thiazolidinedione-treated patients.^{93,94} However, a third large cohort study from the Kaiser Permanente Northern California Diabetes Registry did not find an association between the use of pioglitazone and decreased risk of lung cancer.⁹⁵

There has been considerable interest in the anti-diabetes agent metformin as a cancer chemoprevention agent. One of the previously described analyses also evaluated metformin use and found a protective effect similar (20–50%, $P = 0.001$) to that observed with the thiazolidinediones.⁹⁴ However, published observational studies examining the association between metformin use and lung cancer risk have had mixed results, with two studies reporting that metformin does not have a protective effect.^{96–98} By contrast, two systematic reviews and meta-analyses have concluded that the use of metformin in patients with type II diabetes mellitus is associated with significantly lower risk of lung cancer incidence.^{99,100} Metformin has also been demonstrated to be chemo-preventive in preclinical models.¹⁰¹ Putative mechanisms for a chemopreventive effect include decreased levels of insulin and insulin-like growth factor and energy stress leading to inhibition of liver kinase B1 (LKB1)/AMP activated protein kinase (AMPK) signalling.¹⁰²

The role of oestrogen in lung carcinogenesis has attracted considerable attention.¹⁰³ In the Women's Health Initiative randomized controlled trial, use of oestrogen plus progestin resulted in increased lung cancer mortality.¹⁰⁴ However, use of oestrogen alone in the same study did not increase either incidence or death from lung cancer.¹⁰⁵ An observational study of the California Teachers Study cohort found no association between either oestrogen or

oestrogen plus progestin and the risk of lung cancer.¹⁰⁶ A second study of the NIH-AARP Diet and Health Study cohort also found a similar lack of association between oestrogen or oestrogen plus progestin and lung cancer risk.¹⁰⁷ The aromatase inhibitor exemestane was compared to the anti-oestrogen tamoxifen in a randomized controlled trial of women with breast cancer who had been treated for 2–3 years with tamoxifen.^{108,109} Exemestane treatment resulted in significantly improved breast cancer disease-free survival and there were fewer lung cancer deaths (4 versus 12) in the exemestane group compared to the tamoxifen group. However, this did not achieve statistical significance owing to the small number of events. Thus, although there is some tantalizing data from both preclinical and clinical studies that treatment with aromatase inhibitors might prevent lung cancer, further investigation is needed.

Finally, a large number of epidemiological studies assessing the relationship between diet and lung cancer incidence have been performed. Almost universally, these demonstrate an inverse correlation between diets that are high in fruit and vegetables and lung cancer incidence.¹¹⁰ Whether this association represents a true protective action or is the result of other variables associated with fruit and vegetable intake is unclear because no interventional studies have been reported in which dietary manipulations have reduced the incidence of lung cancer.

Future chemoprevention efforts

Agents that have now been clearly shown to lack promise in lung cancer chemoprevention trials, based on null or harmful results in phase III trials, include beta-carotene, aspirin, retinol, multivitamin and mineral supplements, vitamin E, retinyl palmitate, 13-*cis*-retinoic acid, N-acetyl cysteine and selenium (Table 1). Several of these agents are dietary antioxidants, making the general approach of antioxidant administration unattractive without further data supporting efficacy. Aspirin has had negative results in phase III trials, but a recent meta-analysis of randomized trials of aspirin for prevention of vascular events suggests that an intervention period of 5 years or more and prolonged follow up might be necessary to demonstrate a reduction in lung cancer risk.⁹¹

Chemoprevention agents currently under investigation that have substantial support for incorporation into phase III trials are limited. Inhaled corticosteroids might be the lead agent class because their use is supported by positive data from observational and preclinical studies. However, phase II trials assessing these agents with end points of either dysplasia or nodule growth have been negative,³⁵ although the lack of specificity surrounding the use of pulmonary nodules as an intermediate end point softens this negative factor. Inhaled corticosteroids are currently used as a treatment for patients with COPD, which is an independent risk factor for lung cancer.¹¹¹ Phase III trials with COPD-specific end points have not shown a robust reduction in lung cancer incidence, but the design of these trials, with an average follow-up period of only 26 months, is not ideal for the assessment of cancer chemoprevention.^{112–114} Consideration should be given to the initiation of a phase III chemoprevention trial of inhaled corticosteroids for the prevention of lung cancer with a longer duration.

The use of the antidiabetic agents pioglitazone and metformin for chemoprevention is also supported by both preclinical and observational studies (albeit with mixed results). A phase II trial of pioglitazone or placebo with the end point of dysplasia is currently underway.¹¹⁵ Prostacyclin analogues, specifically iloprost, act through the same PPAR γ nuclear receptor as pioglitazone and other thiazolidinediones,¹¹⁶ so there is some observational support for these agents. In addition, iloprost is effective in preclinical experiments and is the only agent to have demonstrated improvement in endobronchial dysplasia in a phase II trial. The next step to assess the effectiveness of iloprost for chemoprevention would be longer term trials with lung cancer as an end point.

Improved methods for risk assessment, beyond the current models based on clinical and demographic characteristics, would allow chemoprevention trials to be more efficiently designed.^{2,3,9} While the current models may be improved by the incorporation of genetics or biomarkers, specific markers have not been validated as providing a major improvement in risk assessment. Furthermore, the currently available risk models allow the identification of individuals with approximately a 2% yearly risk of developing lung cancer. Currently, the field of lung cancer chemoprevention is more in need of the development of new agents than improved risk models.

Clearly, the translation of preclinical findings into clinically effective chemoprevention of lung cancer has been difficult and largely disappointing. High-throughput screening and functional genomics¹¹⁷ could be used to identify new promising approaches for chemoprevention, but we are not aware of such applications to date. As lung carcinogenesis is a complex, multistep process involving both the epithelium and stroma, new approaches for lung cancer chemoprevention will still need to be evaluated in preclinical animal models and ultimately in the clinical setting.

The lung is a unique organ, in that there is a long history of therapeutic agents being administered via the inhalational route. Inhalational administration can be more effective than systemic administration and minimizes adverse effects.¹¹⁸ The potential use of inhaled agents in early phase chemoprevention trials does raise some issues regarding the necessity for and interpretation of traditional end points, such as blood levels of drug. With the exception of inhaled corticosteroids, we are not aware of clinical trials using inhaled agents for lung cancer chemoprevention.^{34–36} Furthermore, inhaled treatment in preclinical models is difficult and often results in different patterns of drug distribution compared to those seen in humans.¹¹⁹ However, inhaled chemoprevention is an attractive approach going forward as it maximizes drug delivery to the target organ and minimizes systemic effects.¹¹⁸

Personalized medicine has been exemplified by the success of targeted therapy in treating molecularly defined subsets of patients, most commonly with specific driver mutations. The complexity of genetic mutations in both adenocarcinoma and squamous-cell lung cancer,^{32,33} coupled with the difficulty in detecting and analysing premalignant lesions, are challenges to personalized chemoprevention for lung cancer. It might be possible to define common pathways in early carcinogenesis, such as PI3K activation or p53 inactivation, which are shared by significant fractions of the at-risk population and might be targeted in a directed fashion provided effective agents are identified. Myoinositol has been proposed as

an agent that may be useful for targeting individuals specifically with premalignant lesions characterized by activated PI3K signalling, and an ongoing trial is testing this hypothesis.⁶¹ Alternately, phenotypes such as airway or parenchymal inflammation, incipient angiogenesis, tissue hypoxia, or excessive growth factor expression, might be defined, each of which would respond best to a different intervention.^{82,120,121}

Conclusions

Lung cancer is the leading cause of death from cancer worldwide and a disease for which high-risk individuals can be readily identified. Even after smoking cessation is accomplished, former smokers are at significant residual risk of developing lung cancer. These factors make lung cancer an ideal target for chemoprevention. Attempts to discover and validate chemopreventive agents have been frustrating; however, there are a number of interesting compounds that might be effective. These include inhaled glucocorticoids, myoinositol, prostacyclin analogues and thiazolidinediones. Advances in driver-mutation targeted treatment of lung cancer might provide insight into targets and potential chemotherapeutic agents for future trials. Personalized chemoprevention is likely to be targeted more to phenotypes, such as airway inflammation, alveolar hypoxia, or incipient angiogenesis, than to specific driver mutations. Validating biomarkers of risk and response will be critical to advancing the field.

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Review criteria

The PubMed database was searched for articles with no restriction on date. The search terms used included: “lung cancer”, “chemoprevention”, “animal models”, and the various chemopreventive agents in past and current trials (summarized in Tables 1 and 2), “trials”, “biomarkers”, “tobacco smoke”, “pre-malignant airway lesions” and “carcinogenesis”. Only articles published in English were considered, and the final PubMed search was conducted on 2 April 2013.

Key points

- The annual risk for lung cancer in patient populations readily identifiable using simple clinical and demographic characteristics approaches 2%; therefore, the potential for chemoprevention in this common cancer is high
- No chemopreventive agents have been shown to be efficacious for lung cancer, despite numerous leads from observational studies
- Smoking cessation remains the only intervention proven to reduce lung cancer risk
- Lung cancer is a heterogeneous malignancy from a mutational standpoint; focusing on frequently altered pathways may be a promising strategy because molecular targeting of chemoprevention to specific mutations is challenging
- Chemoprevention targeted to phenotypes expressing specific carcinogenic influences, including inflammation, angiogenesis, hypoxia and epithelial differentiation, appears most likely to succeed phenotypes

Figure 1. Potential tobacco smoke induced carcinogenic processes for chemopreventive intervention. Hallmarks in the development of squamous-cell lung cancer as the bronchial epithelium proceeds through pathological stages in the progression to CIS. Tobacco cessation and chemopreventive agents can promote repair and block progression. Abbreviation: CIS, carcinoma *in situ*.

Figure 2.

Schematic pathway of the cyclooxygenase pathway showing conversion of arachidonic acid to prostanoids. The fatty acid arachidonic acid is released from the membrane phospholipids by several forms of phospholipase A₂, which have previously been activated by one of a range of stimuli. The free arachidonic acid is converted to the cyclic endoperoxides prostaglandin G₂ and prostaglandin H₂ by the sequential COX and HOX actions of PGHS-1 or PGHS-2; these isoforms both have dual COX and HOX activity. Aspirin inhibits the conversion of free arachidonic acid to prostaglandin G₂ by inhibiting the COX activity of PGHS-1 or PGHS-2. Prostaglandin H₂ is converted into a range of prostanoids by tissue-specific isomerases; therefore, the inhibition of this pathway prevents (or reduces) the downstream activation of a superfamily of G-protein-coupled receptors by these prostanoids. Prostacyclin binds to both a transmembrane G-protein coupled receptor and to PPAR γ , a nuclear receptor. Abbreviations: ASA, acetylsalicylic acid; COX, cyclooxygenase; HOX, hydroperoxidase; NSAIDs, nonsteroidal anti-inflammatory drugs; PGHS, prostaglandin H synthase; PPAR γ , peroxisome proliferator-activated receptor γ .

Table 1

Phase III chemoprevention trials

Intervention	Chemoprevention setting	<i>n</i>	Results
Aspirin	Primary	5,139	Negative ³⁹
		22,071	Negative ³⁷
		39,876	Negative ³⁸
Beta carotene	Primary	29,133	Harmful (RR=1.18) ⁴²
		22,071	Negative ¹⁵
Beta carotene and retinol	Primary	18,314	Harmful (RR=1.28) ¹²²
Multivitamins and minerals	Primary	29,584	Negative ⁴³
Vitamin E	Primary	29,133	Negative ⁴²
Retinyl palmitate	Tertiary	2,592	Negative ⁴⁰
13- <i>cis</i> -retinoic acid	Tertiary	1,166	Negative ⁴¹
N-acetyl cysteine	Tertiary	2,592	Negative ⁴⁰
Selenium	Tertiary	1,772	Negative ⁴⁴

Abbreviation: RR, relative risk.

Table 2

Early phase intermediate end point chemoprevention trials

Intervention	End point	<i>n</i>	Outcome
13- <i>cis</i> -retinoic acid	Metaplasia	40	Negative ⁵⁵
	Dysplasia	100	Negative ⁵⁴
Fenretinide	Metaplasia	82	Negative ¹²³
Etretinate	Sputum atypia	150	Negative ¹²⁴
Beta carotene	Sputum atypia	1,067	Negative ¹²⁵
Vitamin B12/folate	Sputum atypia	73	Negative ¹²⁶
Budesonide	Dysplasia	112	Negative for primary end point; nodules decreased in treatment group ³⁵
	Nodule size	202	Negative ³⁴
Fluticasone	Nodule size and number	201	Negative ³⁶
Anethole dithiolethione	New dysplastic lesions	101	Negative for primary end point; rate of worsening lower in treatment group ¹²⁷
Iloprost	Dysplasia	152	Positive in former smokers only (improvement in airway endobronchial histology) ⁵⁵
Celecoxib	Ki-67	204	Positive (decreased Ki-67 labelling in former smokers) ⁵⁶
	Ki-67	101	Positive (decreased Ki-67 labelling in former smokers) ⁵⁷
Myoinositol	Dysplasia	26	Promising, was a phase I trial with historical controls ⁵⁹