Lung Cancer Chemoprevention: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Lung Cancer Chemoprevention*

ACCP Evidence-Based Clinical Practice Guidelines
(2nd Edition)

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Background: Lung cancer is the most common cause of cancer death in the United States. Cigarette smoking is the main risk factor. Former smokers are at a substantially increased risk for lung cancer compared with lifetime never-smokers. Chemoprevention is the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis. This article reviews the major agents that have been studied for chemoprevention.

Methods: Articles of primary, secondary, and tertiary prevention trials were reviewed and summarized to obtain recommendations.

Results: None of the phase III trials with the agents beta carotene, retinol, 13-cis-retinoic acid, alpha-tocopherol, N-acetylcysteine, or acetylsalicylic acid has demonstrated beneficial, reproducible results. For facilitating the evaluation of promising agents and for lessening the need for a large sample size, extensive time commitment, and expense, focus is now turning toward the assessment of surrogate end point biomarkers for lung carcinogenesis. With the understanding of important cellular signaling pathways, various inhibitors that may prevent or reverse lung carcinogenesis are being developed.

Conclusions: By integrating biological knowledge, more trials can be performed in a reasonable time frame. The future of lung cancer chemoprevention should entail the evaluation of single agents or combinations that target various pathways while working toward identification and validation of intermediate end points.

Key words: acetyl salicylic acid; apoptosis; biomarkers; chemoprevention; cyclooxygenase-2 inhibitors; lung cancer; proliferation; protein kinase C; selenium; signal transduction pathways; tyrosine kinase inhibitors; vitamin A; vitamin E

Abbreviations: ADT = anethole dithiolethione; ATBC = alpha Tocopherol Beta-Carotene; CARET = Beta-Carotene and Retinol Efficacy Trial; CI = confidence interval; COX = cyclooxygenase; HOPE = Heart Outcomes Prevention Evaluation; HR = hazard ratio; LOX = lipoxygenase; MCM2 = minichromosome maintenance factor 2; PG = prostaglandin; PGI = prostacyclin; PKC = protein kinase C; RR = relative risk; SEB = surrogate end point biomarker

The number of newly diagnosed cases of lung cancer in the United States in 2007 is estimated to be 213,380. Lung cancer causes more death (160,390) than colorectal cancer (52,180), breast cancer (40,910), and prostate cancer (27,050) combined.1 The annual worldwide incidence of lung cancer is > 3,000,000 and continues to rise. The single most important risk factor is smoking. Approximately 20% of the US adult population continues to smoke. In those who smoke, the risk for lung cancer...
is on average 10-fold higher than in lifetime never-smokers (defined as a person who has smoked < 100 cigarettes in their lifetime). There were 45.4 million former smokers in the United States in 2003. Although smoking prevention and cessation remain essential in the overall strategy for lung cancer prevention, former smokers continue to have an elevated risk for lung cancer for years after quitting. In fact, more than one half of lung cancers occur in those who have stopped smoking.

At the time of diagnosis, the majority of patients have stage IIIB to IV disease, which carries a 5-year survival of < 5%. Efforts to improve this dismal outcome have more recently been directed at chemoprevention to reduce the incidence and mortality of lung cancer.

The rationale for chemoprevention is based on two main concepts, multistep carcinogenesis and “field cancerization,” which can be used to explain the process of lung carcinogenesis as it occurs over time and throughout the entire bronchoalveolar epithelium. Multistep carcinogenesis is based on the theory that the progression of normal bronchoepithelial cells to a malignant lesion entails a multistep process involving numerous morphologic and molecular modifications. A series of alterations that lead to malignant transformation with unregulated clonal expansion and cellular proliferation occur over time. The morphologic correlate of multistep carcinogenesis is the progression of bronchial epithelium from hyperplasia to metaplasia to increasing grades of dysplasia and carcinoma in situ onward to invasive carcinoma. Specific genetic abnormalities that correlate with the morphologic steps that are involved in the evolution to malignancy have been described.

Physiologically, proliferation of bronchoepithelial cells is required to replace cells lost at the lumen and to repair epithelial damage caused by environmental influences. To control proliferation in response to tissue damage, a complex system of intercellular communication that includes epithelial cells, stroma, and inflammatory cells has evolved. The vehicles of communication are growth factors, cytokines, peptides, and lipid metabolites and their respective cellular receptors. Their functions include induction and suppression of not only proliferation but also migration, contact inhibition, angiogenesis, apoptosis, and antitumor immunity. Reactive oxygen species that are generated during inflammation can result in DNA damage and may thus trigger or accelerate carcinogenesis.

In 1953, it was first established that many areas of the aerodigestive tract are simultaneously at risk for cancer formation as a result of exposure to carcinogens. This concept is known as field cancerization and serves to explain the synchronous presence of various premalignant and malignant lesions at different locations in the aerodigestive tract of the same person. The high rate of second primary cancers in individuals who underwent curative treatment for an aerodigestive malignancy provides further evidence for field cancerization.

Tobacco exposure is among the most preventable causes of morbidity and mortality in the United States. It includes smokeless tobacco and pipe and cigar use. The most important of these is cigarette smoke. It has been estimated that the majority of lung cancer is associated with cigarette smoking. Given the harm associated with tobacco use, it is important not only to promote the cessation of tobacco use but also to prevent the initiation.

For reducing the incidence of smoking, tobacco prevention is also an imperative public health focus. The key is to provide early information about the harms of tobacco exposure to middle and high school students. Policies and programs exist and continue to be developed to educate youth on the harms of tobacco use given its potential for dependency and associated morbidity and mortality.

Advocacy efforts have been increasingly successful at limiting tobacco use and public exposures to environmental tobacco smoke. Some of these methods include strict regulation of tobacco advertisements, increases in tobacco taxes, and comprehensive smoking bans for indoor and public outdoor areas.

Another major public health focus in the United States is tobacco cessation. Numerous cessation programs are available for those who would like to quit. These range from behavioral therapy to pharmacologic interventions. As an essential aspect of all primary care practices, all patients should be asked about smoking status, and counseling and advice should be provided when needed. This has been associated with an increase in smoking cessation. By providing mutual support, behavior modifications, and coping skills, group therapy has been found to be an effective method. The use of pharmacologic interventions such as all forms of nicotine replacement (including nicotine spray, gum, and patches), bupropion, and varenicline (partial agonists of nicoenic acetylcholine receptors) have been effective in increasing smoking cessation rates. Other techniques, such as acupuncture and hypnosis, to date, have not been effective.

Smoking cessation results in a decrease in precancerous lesions from 27 to 7%. For those who have quit smoking for 10 years (15 years), the risk for lung cancer may be 30 to 50% (80 to 90%) less than that of current smokers.

Many options are available to help with smoking cessation. Physicians are strongly encouraged to
discuss these options with their patients to develop individualized cessation plans. Still, half of lung cancers occur in those who have stopped smoking. To help reduce the incidence of lung cancer, recent efforts have been directed to chemoprevention. Chemoprevention is defined as the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis.\textsuperscript{19} The first and most powerful step in lung cancer chemoprevention is avoidance of continued carcinogen exposure, for instance, through smoking cessation. However, people who have smoked in the past and have successfully quit have a substantially higher risk for lung cancer development than people who are lifetime never-smokers.\textsuperscript{19} Chemoprevention as a means of reducing cancer incidence has been successful for breast cancer and prostate cancer.\textsuperscript{20, 21} For lung cancer, chemoprevention is an area that needs further exploration for proper recommendations to be formed. This article discusses the methods used to obtain articles and grade recommendations. It is organized into sections: (1) high-risk populations, (2) various chemopreventive interventions investigated to date, (3) arachidonic acid pathway studies, (4) studies using other pathways, and (5) future studies.

**Materials and Methods**

In 2005 to 2006, a panel of experts corresponded to update the previous recommendations on the use of lung cancer chemoprevention agents. The panel consisted of investigators who were experienced in the formulation, design, and execution of chemoprevention clinical trials. Deliberations were resolved to establish guidelines for practitioners to use for patients at high risk for lung cancer.

For obtaining various lung cancer chemoprevention guidelines, a systematic review of the literature was performed (see “Methods and Grading” chapter). These guidelines were focused on primary, secondary, and tertiary lung cancer chemoprevention studies that were mostly funded by the National Cancer Institute. Additional information was obtained by performing a literature search of the PubMed and Medline databases and review of the Thoracic Oncology NetWork reference lists. For establishing study quality, recommendations were organized by the panel of experts on the writing committee and then graded by the standardized American College of Chest Physicians methods (see “Methodology for Lung Cancer Evidence Review and Guidelines Development” chapter). Before final approval, this chapter was reviewed by all panel members, which included a multidisciplinary team that consisted of thoracic surgeons, medical oncologists, radiation oncologists, and pulmonologists, followed by review by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. Following are key considerations in designing chemoprevention trials for lung cancer.

**Identification of Candidate Agents**

The selection of chemoprevention agents involves a careful process. First, sufficient in vitro and animal model data should exist to support the use of a specific agent. The use of specific agents should not be based solely on epidemiologic data. Recent advances in tumor biology have resulted in the development of agents that target specific cellular pathways that are thought to be crucial for tumor development and progression. Therapies can now be directed at various steps that are involved in carcinogenesis. Agents that target DNA repair may prevent or reverse the initial development of mutations that frequently are found in bronchial atypia. Rather than prevent the initiation process, other agents may inhibit promotion or progression. As more evidence and data are obtained regarding the molecular pathways that are involved in these processes, these agents may serve as realistic targets for future drug development and therapeutic interventions.

Other issues must be considered when selecting agents for chemoprevention trials. A favorable safety profile must be associated with the chosen drug because it may be used for prolonged periods of time in a putatively healthy, albeit high-risk, population to prevent disease. Agents should be easy to administer such that compliance will be high. In addition, the agent should be readily available and affordable.

**Populations at Risk for Lung Cancer**

Chemoprevention trials can be divided into three types: primary prevention, secondary prevention, and tertiary prevention. In primary prevention trials, participants have no evidence of lung cancer. Such trials are targeted at high-risk individuals, for instance, those with a significant smoking history. Secondary prevention studies involve the use of participants who have evidence of premalignancy, such as sputum atypia or dysplasia on bronchial sampling. Individuals who have a history of being cured from their primary lung cancer are the focus of tertiary prevention trials (second primary tumor prevention). The practical rationale for selecting high-risk individuals is to reduce the sample size and duration of therapy. However, it is important to recognize that individuals who are at high risk, such as active smokers with ongoing smoke exposure, may have a different biology of disease than former smokers. As a result, the outcome of a trial may be adverse in one group (smokers) yet beneficial in another (former smokers). In the end, the ultimate goal of lung cancer chemoprevention is to reduce disease incidence and mortality. Within each trial category, guidelines are needed for enrollment criteria.

**Smoking and Risk for Lung Cancer**

Chemoprevention trials typically focus on high-risk populations. The main criteria for selection of patients to lung cancer chemoprevention trials are based on smoking history. In addition, airway obstruction and environmental factors, such as asbestos exposure, family history, and obstructive disease, have well-established hazard ratios (HRs) for lung cancer risk and have been used as factors for identifying special cohorts (see “Epidemiology of Lung Cancer” chapter).\textsuperscript{22} Case-control studies\textsuperscript{23–25} linking smoking to lung cancer became available in the 1950s. These were confirmed by prospective cohort studies\textsuperscript{26–29} that supported the conclusion that smoking causes lung cancer. Many studies\textsuperscript{30} have demonstrated that a longer smoking duration, younger age of initiation, and a higher number of packs per day increase the risk for lung cancer. The 12-year follow-up data of the American Cancer Society’s Cancer Prevention Studies followed > 1 million individuals and included smokers, nonsmokers, and former smokers. An individual with a history of smoking ≥ 40 cigarettes a day for 35 to 39 years has a mortality risk from lung cancer of 19.45 compared with an individual who has...
a history of 1 to 9 cigarettes daily for 20 to 24 years, whose lung cancer-related mortality risk is 1.26.\textsuperscript{31} When evaluating numerous trials, individuals with a $\geq 30$-pack-year smoking history have higher rates of lung cancer.\textsuperscript{39} There seems to be a continuum between risk and 10, 20, and 30 pack-years of smoking; still, no one level has been accepted as a definitive threshold for what is considered high risk. What is known is that the risk for lung cancer for nonsmokers is significantly less than the risk for smokers.

**Dysplasia and Risk for Lung Cancer**

The progression from a benign to a malignant lesion in the bronchial epithelium involves a multistep process. Changes occur in concert at both the molecular and the cellular levels, enhancing the ability of a cell to proliferate, evade cell death, and invade the basement membrane. Before becoming invasive, morphologic descriptions include hyperplasia, metaplasia, dysplasia, and carcinoma \textit{in situ}. In general, hyperplasia and metaplasia are not necessarily premalignant, because these lesions can spontaneously regress and can be found after trauma or along with chronic inflammation. Dysplasia and carcinoma \textit{in situ} are considered the principal premalignant lesions, although these, too, can spontaneously regress, albeit at a lower frequency than hyperplasia and metaplasia.\textsuperscript{32} Specific genetic alterations are associated with the steps involved. Wistuba et al\textsuperscript{33} demonstrated an increase in molecular abnormalities, including loss of heterozygosity, when lesions progressed from normal to carcinoma \textit{in situ}. Molecular characteristics of dysplastic lesions that seem to be associated with progression to carcinoma \textit{in situ} are high telomerase activity, increased Ki-67 labeling index, and p53 positivity.\textsuperscript{34} These may correlate with an increased risk for subsequent carcinoma, although this has not been clearly demonstrated.

Saccomanno et al\textsuperscript{35} demonstrated that sputum atypia could be seen 4 to 5 years before the development of lung cancer. A population with sputum atypia is at increased risk for lung cancer development.\textsuperscript{36,37} On the basis of these observations, the National Cancer Institute sponsored three lung cancer screening trials in the 1970s using chest radiograph and sputum cytology as screening tools. One of these trials, conducted at Johns Hopkins University ("the JHU cohort"), addressed the utility of sputum cytology as a screening tool. The study showed that 10% of participants with moderate atypia on sputum cytology and no overt evidence for lung cancer developed lung cancer up to 9 years later. Of those with severe atypia, lung cancer developed in $\geq 40\%$ during the same time period.\textsuperscript{38}

**Second Primary Lung Cancer**

The development of second primary tumors is common in patients with previously treated lung cancer. After resection of a lung cancer, there is a 1 to 2% risk for a second lung cancer per patient per year.\textsuperscript{39} Those who do have a second lung cancer have a median survival of 1 to 2 years and a 5-year survival of approximately 20%.\textsuperscript{39} As such, chemoprevention in this population is an important area of research.

**RESULTS**

**Vitamins as Chemoprevention Agents With Lung Cancer as an End Point**

**Beta Carotene Use in Former and Current Smokers and Those With Asbestos Exposure: A diet rich in fruits and vegetables (at least three servings per day) is associated with a lower cancer incidence as based on epidemiologic data. The $\alpha$ Tocopherol $\beta$-Carotene (ATBC) study\textsuperscript{40} randomly assigned 29,133 people to receive beta carotene, $\alpha$ tocopherol, both, or placebo. Study participants averaged 57.2 years of age, 20.4 cigarettes per day, and 35.9 years of smoking. They were followed up for 5 to 8 years. The incidence of lung cancer in the study group was 18% higher than in the placebo group ($p < 0.01$). When this trial was completed, a second trial to evaluate beta carotene was under way. The Beta-Carotene and Retinol Efficacy Trial (CARET) evaluated high-risk current and former smokers with a $\geq 20$-pack-year history of smoking ($n = 14,254$) or with asbestos exposure and a 15-pack-year smoking history ($n = 4,060$). Forty percent of the $\geq 20$-pack-year smoking history group were women. The participants were randomly assigned to receive either a combination of beta carotene and vitamin A or placebo. An early analysis was performed because of the finding of the ATBC trial. The relative risk (RR) for lung cancer in the active treatment group was 1.28 (95% confidence interval [CI], 1.04 to 1.57; $p = 0.02$). In a subgroup analysis, the RR for lung cancer in current smokers was 1.40 (95% CI, 1.07 to 1.87), whereas the RR in participants who were no longer smoking at the time of randomization was 0.80 (95% CI, 0.48 to 1.31). As a result of these findings, the CARET was terminated 21 months early. Both of these trials demonstrated a higher incidence of lung cancer in those who had received the beta carotene.

In the United States, the Physicians Health Study evaluated 22,071 physicians who ranged in age from 40 to 84 years\textsuperscript{41}; 11% were current smokers, and 39% were former smokers. The participants were randomly assigned to beta carotene or placebo. There was no difference in lung cancer rates in those who received the beta carotene (82 lung cancers in the beta carotene group vs 88 in the placebo group).

The Women’s Health Study explored the use of 50 mg of beta carotene every other day vs placebo in 39,876 women who were $\geq 45$ years old. Thirteen percent of the women were smokers. The study was terminated early, and the median treatment duration was 2.1 years. There was no significant difference in the development of any site-specific cancer including lung cancer (30 cases vs 21 cases, respectively).\textsuperscript{42}

**RECOMMENDATION**

1. For individuals with a smoking history $\geq 20$ pack-years or a history of lung cancer, the use of beta carotene supplementation is not recom-
mended for primary, secondary, or tertiary chemoprevention of lung cancer. Grade of recommendation, 1A

Vitamin E Use in Men With a Smoking History: Epidemiologic data support that vitamin E (α-tocopherol) has antitumor properties such that individuals with high levels of vitamin E are less likely to have cancer. The ATBC study\(^40\) was published in the New England Journal of Medicine in 1994. It involved 14 study sites, mainly based in Finland. More than 29,000 high-risk participants were randomly assigned to α-tocopherol, beta carotene, both, or placebo. The participants were men who ranged in age from 50 to 60 years and had smoked at least five cigarettes per day. The primary end point was diagnosis of lung cancer, and the secondary end point was diagnosis of any cancer. Participants were followed up for 5 to 8 years. There was a nonsignificant reduction in the incidence of lung cancer by 2%.

The Heart Outcomes Prevention Evaluation (HOPE) trial was an international, randomized, double-blind, placebo-controlled trial that evaluated participants who were ≥55 years of age and had vascular disease or diabetes from 1993 to 1999. The trial was extended to 2003 and was known as the HOPE TOO trial. A total of 9,541 participants enrolled in the HOPE trial, and 7,030 continued on the HOPE TOO trial. The participants were treated with 600 IU of vitamin E every other day vs placebo in the vitamin E arm were found to have a higher rate of heart failure (p = 0.03). The Women’s Health Study explored the use of 600 IU of vitamin E every other day vs placebo in 39,876 women who were ≥45 years of age and were followed up for 10.1 years. There was no significant difference in lung cancer incidence between the treatment and placebo arms (RR, 1.09; 95% CI, 0.83 to 1.44).\(^44\)

Vitamin A in Current or Former Smokers: Epidemiologic data supported the idea that fruits and vegetables that are high in vitamin A lower the incidence lung cancer. In 1996, the results of the CARET were published.\(^45\) This study evaluated 18,314 high-risk patients with either >20 years of smoking or >15 years of smoking and a history of asbestos exposure. Participants were randomly assigned to vitamin A and beta carotene or placebo. Participants were either current smokers or smokers who had quit in the previous 6 years. This study found a RR of 1.28 (p = 0.02) for lung cancer in the treatment arm compared with placebo.

13-Cis-Retinoic Acid in Patients With Stage I Lung Cancer: Preclinical and early clinical studies have suggested that retinoids have chemopreventive effects. A large randomized trial\(^46\) of 1,166 participants who had stage I lung cancer that was treated with curative intent were randomly assigned to received placebo or isotretinoin. HRs were 1.08 (95% CI, 0.78 to 1.49) for time to second primary tumor, 0.99 (95% CI, 0.76 to 1.29) for recurrence, and 1.07 (95% CI, 0.84 to 1.35) for mortality. Isotretinoin did not decrease the incidence of second primary tumors. In a subgroup analysis, current smokers who were treated with isotretinoin had increased mortality compared with former smokers and nonsmokers (HR, 1.56; 95% CI, 1.09 to 2.24; p = 0.01).

N-Acetylcysteine: Preclinical data have demonstrated that N-acetylcysteine has antitumor properties. A large clinical study\(^47\) evaluated this agent in 1,023 patients who had non-small cell lung cancer (pT1-T3, N0-1, or T3, N0) that was treated with curative intent. Patients were randomly assigned to N-acetylcysteine, retinyl palmitate (vitamin A), both, or no intervention. The primary end points were recurrence, death, or second lung cancer. No significant differences were noted between the groups.

Other Agents for Chemoprevention

Acetylsalicylic Acid: There is literature supporting a protective role of aspirin and nonsteroidal antiinflammatory drugs on development of cancer. Three major trials have been conducted, which evaluated the use of acetylsalicylic acid in lung cancer prevention. The UK Physicians’ Health Study was a 6-year, randomized trial that evaluated 5,139 healthy male doctors who were receiving 500 mg/d aspirin.\(^48\) Eleven percent were current smokers, and 39% were former smokers. The lung cancer death rate in the aspirin group was 7.4/10,000 person-years vs 11.6/10,000 person-years in the placebo group. This difference was not statistically significant. In 1989, the results of the United States Physicians Health study\(^49\) was published. This study evaluated 22,071 physicians and did not demonstrate a decreased rate of lung cancer in participants who had taken aspirin.

More recently, the results of the Women’s Health Study\(^50\) were published; this was a randomized trial of 39,876 US women who were treated with either 100 mg of aspirin or placebo every other day.
Approximately 13% were current smokers, and 35.8% were former smokers. There was an average of 10.1 years of follow-up. Lung cancer was a secondary end point. Lung cancer developed in a total of 205 participants. The RR for lung cancer in the aspirin group was 0.78, which did not reach statistical significance.

**Recommendation**

2. For individuals who are at risk for lung cancer and patients with a history of lung cancer, the use of vitamin E, retinoids, N-acetylcysteine, and aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer. Grade of recommendation, IA

**Surrogate End Point Biomarkers Under Development**

Double-blind, randomized, phase III trials are considered the “gold standard” for proof of superiority of a novel therapy over current standard of care. Lung cancer incidence should be the primary end point. Because of the large number of required participants and long intervention/follow-up time, such trials pose a formidable challenge to conduct successfully from a logistical as well as a financial perspective.

To allow for testing of an increased number of promising agents over a short period of time, the use of surrogate end point biomarkers (SEBs) is being explored as an alternative to cancer incidence. However, because such trials do not use a definitive clinical end point (eg, cancer incidence), promising results obtained require confirmation in a phase III design.

The identification of SEBs that are reliably associated with cancer incidence is of paramount importance. Examples of SEBs currently used include premalignancy by morphologic criteria and proliferative markers by immunohistochemistry, specifically Ki-67 and minichromosome maintenance factor 2 (MCM2). Other potential SEBs are molecules targeted by the specific agents under investigation.

Biomarkers that are under study include dysplasia, Ki-67, MCM2, and others. However, no surrogate marker has been validated; therefore, use of such markers is limited to phase II efficacy trials that require subsequent confirmation in a phase III trial using cancer incidence and/or mortality as the end point.

Dysplasia has long been used as a SEB for lung cancer in many chemoprevention trials. Carcinogenesis involves a progression from a precancerous lesion to invasive disease. Not all dysplasia will progress to cancer. There are data to suggest that 58% of dysplastic lesions will regress spontaneously. A statistically significant change must occur in the bronchoepithelium for chemopreventive agents to have a noticeable impact. On histopathologic review, a complete or near-complete regression of dysplasia in the treatment vs control arm should be demonstrated.

Given the importance of dysregulated proliferation to the carcinogenesis process, several proliferation indexes have been studied as potential SEBs. Ki-67 is an epitope of a nuclear protein recognized by the MIB-1 monoclonal antibody. The protein is frequently expressed throughout the cell cycle of proliferating cells and has not been detected in nonproliferating cells. During interphase, Ki-67 is located primarily in nucleolar and perinucleolar regions in association with condensed chromatin. The function of the Ki-67 protein is still unknown, although it seems to be required for cell progression through the cell cycle. MCM2 is a new proliferation marker and one of six members of the MCM protein family. These serve as components of “licensing factor,” which is essential for initiation of DNA replication and for limiting replication to one round per cell cycle.

The MCM proteins are also associated with replication forks and are likely to stimulate the unwinding of the parental DNA strands at these forks.

Other markers under investigation include molecular end points such as epidermal growth factor receptor, human epidermal growth factor 2 receptor, p53, Bcl2/Bax, and telomerase, among others. Proteomics and GeneChip arrays are platforms under investigation for SEB development. However, marker validation remains a major challenge to ensure reproducibility and clinical relevance for any of the SEBs in lung cancer chemoprevention trials.

For instance, it has been reported that plasma levels of folate are lower in smokers with bronchial metaplasia than in those with normal mucosa. In 1988, a randomized, controlled, prospective intervention trial in smokers with bronchial metaplasia was published. Seventy-three men with at least a 20-pack-year history of smoking were stratified according to smoking level and randomly assigned to placebo or folate, 10 mg, and hydroxocobalamin, 500 μg. Therapy was administered for 4 months, and patients were followed up by direct cytologic comparison. The supplemental group did show significantly greater reduction in atypia (p = 0.02). However, results from this study are limited by the rate of spontaneous variation in the sputum samples, the small sample size, and the short duration of therapy.
Arachidonic Pathway and Lung Cancer Chemoprevention

Arachidonic acid is metabolized to prostaglandins (PGs) and prostacyclin (PGI) by the cyclooxygenase (COX) pathway, whereas leukotrienes are formed via the lipoxygenase (LOX) pathway. Their end products are thought to be involved in carcinogenesis.

Two isoforms of COX exist: COX-1 and COX-2. COX-1 exists in most cells and is constitutively active. In contrast, COX-2 is induced by inflammatory and mitogenic stimuli that lead to increased PG formation in inflamed and neoplastic tissues.61,62 Despite having similar structures, COX-2 can be selectively inhibited.

Evidence exists to support arachidonic pathway modulation for inhibition of carcinogenesis. Corticosteroids are known modulators of the eicosanoid-signaling pathway. Synthesized glucocorticoids have been demonstrated to block the development of cancer in A/J mice with induced pulmonary adenomas. COX-2 expression has been demonstrated in premalignant and malignant bronchial cells.63 Higher levels are associated with a poor prognosis in those with non-small cell lung cancer.64,65 It has been demonstrated in mouse models that by inhibiting COX-2 with celecoxib, the rate of growth of lung cancer and number and size of metastasis could be decreased.66 The expression of COX-2 has been shown to enhance tumorigenesis by regulation of growth factor receptor,70,71 invasion via CD4472–74 and survivin78,79 and insulin-like growth factor,80–82 and apoptosis via lipin183–88 and antitumor immunity via interleukin-10 and -12.83–88 However, not all preclinical carcinogenesis models have shown chemopreventive efficacy.89

5-LOX is an enzyme involved in the conversion of arachidonic acid to leukotrienes. Leukotrienes are proinflammatory and enhance cell adhesion.90 Leukotrienes seem to affect the development and progression of lung cancer. This is based on data demonstrating that 5-LOX is expressed in lung cancer.91 5-LOX inhibitors reduced the multiplicity and incidence of lung tumors in mice,92 and 5-LOX metabolites may play a role in angiogenesis.93

Lung Cancer Chemoprevention Trials With Arachidonic Acid Pathway Modulators

Several studies have been completed and are ongoing to evaluate the use of arachidonic acid pathway modulators for lung cancer chemoprevention. The following is an overview of these trials.

Budesonide: Lam et al94 evaluated the use of inhaled budesonide, a corticosteroid that is used for the treatment of asthma, in 112 smokers with bronchial dysplasia and found no effect on bronchial dysplastic lesion or on the prevention of new lesions. A modest decrease in p53 and Bcl2 protein expression in bronchial samples was noted as well as a slightly higher rate of resolution of lung nodules on CT.

Celecoxib for Primary Chemoprevention of Lung Cancer in High-Risk Smokers: Several clinical trials to address the use of celecoxib for lung cancer prevention are underway. The results of a pilot, phase IIA trial in high-risk smokers performed at University of California, Los Angeles suggested that celecoxib may reduce PGE2 production, inhibit immunosuppression, and modulate SEBs. A follow-up, larger phase IIb trial focusing on heavy former smokers is evaluating the effect of celecoxib on cellular and molecular events associated with lung carcinogenesis. Another phase IIb trial of celecoxib in current and former smokers is being conducted at MD Anderson Cancer Center.

Other Arachidonic Pathway Metabolites: A clinical trial of the 5-LOX inhibitor zileuton is under way at the Karmanos Cancer Institute to address the effect of zileuton on bronchial dysplasia (primary end point) and multiple molecular markers (secondary end points) in at-risk smokers or patients with curatively treated aerodigestive cancers. Another metabolite of arachidonic acid is PGI. It has been demonstrated that up-regulation of PGI resulted in decreased tumorigenicity in mice that were exposed to carcinogens.30 The University of Colorado is enrolling participants in a phase II, randomized clinical trial to evaluate the effectiveness of iloprost, a PGI analog. End points include the comparison of phenotypic modulation of bronchial epithelium between the two groups, as well as evaluation of multiple molecular markers.

Recommendation

3. For individuals who are at risk for lung cancer or have a history of lung cancer, budesonide, COX-2 inhibitors, 5-LOX inhibitors, and PGI analogs are not recommended for use for primary, secondary, or tertiary lung cancer chemoprevention outside the setting of a well-designed clinical trial. Grade of recommendation, 2C

Impact of Information Regarding Cardiovascular Risk Associated With COX-2 Inhibitors: In late 2004, unfavorable news was released regarding an in-
creased cardiovascular risk with the use of COX-2 inhibitors rofecoxib and celecoxib. The Vioxx GI Outcomes Research Study\textsuperscript{97} evaluated 8,076 patients who had rheumatoid arthritis and received rofecoxib vs naproxen; the RR for a cardiac event associated with rofecoxib was 2.38 (p = 0.002). The Celecoxib Long-term Arthritis Safety Study\textsuperscript{98} involved 8,059 patients with both osteoarthritis and rheumatoid arthritis and compared celecoxib with nonsteroidal antiinflammatory drugs; in this trial, no significant difference in cardiovascular events was demonstrated between the two groups.

In 2001, Merck started the Adenomatous Polyp Prevention on Vioxx trial\textsuperscript{99}, which was stopped early because of the finding of an increased risk for adverse thrombotic cardiovascular events after 18 months of therapy over placebo during an interim analysis. One study\textsuperscript{100} in chemoprevention of colorectal cancer also reported an increased cardiovascular risk with prolonged use of celecoxib. The finding led to the suspension of the aforementioned clinical trials in lung chemoprevention in late December 2004. In February 2005, after careful consideration, the Food and Drug Administration concluded that the benefits of celecoxib outweigh the potential risks in properly selected and informed patients. Advisors to the Food and Drug Administration also recommended that COX-2 inhibitors continue to be studied in the treatment and prevention of cancer. With the addition of new monitoring guidelines as well as exclusion criteria to safeguard the well-being of study participants, it is believed that the potential benefits from the studies outweigh the risks.

Future Directions for Chemoprevention

**Selenium:** Epidemiologic data have demonstrated an association between high selenium exposure and a reduction in lung cancer risk.\textsuperscript{101} The mechanism of action is thought to be related to oxidative stress pathways, modification of gene expression through DNA methylation, and suppression of COX-2 and 5-LOX expression.\textsuperscript{102–104}

The Nutritional Prevention of Cancer trial\textsuperscript{105} was designed to evaluate the role of selenium in reducing the incidence of nonmelanomatous skin cancer. The trial did not demonstrate a decrease in skin cancer but did show a 26% decrease in lung cancer risk. A phase IIA chemoprevention trial using selenium was completed at the Moffitt Cancer Center to evaluate toxicity and modulation of biomarkers in current and former smokers. Although selenium was very well tolerated, analysis of samples from the 14 individuals who completed the trial showed no alterations in the biomarkers that were assessed (p53 by immunohistochemistry in sputum, proliferating cell nuclear antigen and p16 by immunohistochemistry in bronchial biopsies, and apoptosis by terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine nick-end labeling in bronchial biopsies.

Easter Cooperative Oncology Group protocol E5597 is a phase III, double-blind, placebo-controlled study of selenium (200 \( \mu \)g of L-selenomethionine) in the prevention of second primary lung cancers in patients who have had a complete resection of a pathologically staged T1/N0M0 non-small cell lung cancer. The primary end point of the trial is the incidence of second lung cancers. Intermediate biomarkers are also studied as potential surrogates for lung cancer. This is a national, multiinstitutional, cooperative group trial with an accrual goal of 1,960 patients. The study is powered to detect a 40% relative decrease in the 2.0% annual incidence rate of second lung cancers in this cohort of patients and is still in the accrual stage.

**Organosulfurs:** The organosulfur compounds oltipraz and anethole dithiolethione (ADT) belong to the dithiolethione class. They have antitumor activity as a result of their antioxidant, chemopreventive, chemotherapeutic, and radiopreventive properties.\textsuperscript{106} Furthermore, oltipraz was thought to inhibit macromolecule adducts of carcinogens by inducing phase II detoxifying enzymes.\textsuperscript{107} For further investigation of this in relation to tobacco, a phase I chemoprevention trial using oltipraz was initiated. Participants received 0, 200, or 400 mg/wk oltipraz for 12 weeks and were followed up with bronchoscopies at 1 and 12 weeks. No significant difference was found between the two groups, but the oltipraz group did have substantial toxicity. In an earlier trial\textsuperscript{107,108} oltipraz was combined with N-acetylcysteine. This trial was stopped early as a result of hepatotoxicity.

ADT is available in Europe and Canada for the treatment of xerostomia as a result of radiation. In 2002, data from a randomized phase II study\textsuperscript{109} that evaluated ADT vs placebo for secondary chemoprevention of lung cancer was published. Although there was no statistical difference in histologic regression of bronchial dysplasia, there was a statistical difference in the progression rate: 8% vs 17%.\textsuperscript{109}

**Recommendations**

4. For individuals at risk for lung cancer or have a history of lung cancer, the use of oltipraz as a primary, secondary, or tertiary chemopreventive agent of lung cancer is not recommended. Grade of recommendation, 1B

5. For individuals at risk for lung cancer or...
have a history of lung cancer, the use of selenium and ADT for primary, secondary, or tertiary lung cancer chemoprevention is not recommended outside the setting of a well-designed clinical trial. Grade of recommendation, 1B

Looking Forward, New Targets

Many other targeted therapeutic agents have potential as chemopreventive agents. Table 1 lists potential targets for lung cancer chemoprevention.

Protein kinase C (PKC) is involved in cellular proliferation, apoptosis, and mobility. Enzastaurin, a PKC-β inhibitor, is being studied in patients with glioblastoma, lung cancer, and non-Hodgkin lymphoma. The role of PKC in carcinogenesis is complex. Since there are 12 known isoforms with distinct and at times opposing effects. The β isoform is activated by growth factors. Enzastaurin competes with the adenosine triphosphate-binding site of PKC-β. More specific, in lung cancer cells, enzastaurin demonstrates inhibitory activity on intracellular signaling proteins. Because of its molecular mechanism of action and low adverse effect profile, this drug is a possible candidate for chemoprevention in high-risk individuals. As demonstrated by the COX-2 inhibitor experience, extensive data on safety and efficacy are needed before novel agents can be applied to the realm of chemoprevention.

Ras is an oncogene that is important for cancer cell survival. Farnesyltransferase inhibitors block ras farnesylation. They have been tested extensively in A/J mice and transgenic mice and are strong chemopreventive agents. This prompted further investigation in patients with lung cancer. The adverse effects experienced by participants in these trials included myelosuppression, nausea, diarrhea, abdominal pain, and fatigue. The clinical toxicity limits this drug as a candidate for chemoprevention despite the impressive preclinical data.

Table 1—Potential Target Molecules for Lung Cancer Chemoprevention Trials

<table>
<thead>
<tr>
<th>COX-2</th>
<th>PGI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histone deacetylase</td>
<td>Insulin-like growth factor binding protein 3</td>
</tr>
<tr>
<td>Mammalian target of rapamycin</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>PKC</td>
<td>Signal transduction and activator of transcription-3</td>
</tr>
<tr>
<td>5-, 12-LOX</td>
<td>VEGF</td>
</tr>
<tr>
<td>Farnesyltransferase</td>
<td>Protein kinase B</td>
</tr>
</tbody>
</table>

Recommendation

6. For individuals at risk for lung cancer or have a history of lung cancer, there are not yet sufficient data to recommend the use of any agent either alone or in combination for primary, secondary, or tertiary lung cancer chemoprevention outside a clinical trial. Grade of recommendation, 1B

Conclusion

Chemoprevention is a developing area of research. The main goal of lung cancer chemoprevention is to find an effective agent with a favorable toxicity profile for patients who are at high risk for primary or secondary lung cancer. A number of compounds have been tested, but results of trials to date have been either negative or, in the case of those evaluating beta carotene and retinoids in active smokers, deleterious. Table 2 summarizes the large phase III trials that have been conducted. In addition, several smaller, phase II chemoprevention trials have been performed that used morphologic parameters, such as metaplasia and dysplasia in bronchoepithelial biopsy specimens or cellular atypia in cytologic sputum specimens, as intermediate end points. Agents that have been investigated include various retinoids, folate and vitamin B12, and budesonide, but none has demonstrated improvement.

Some of the phase III trials, although largely disappointing, nonetheless provided useful lessons that continue to shape the design of ongoing chemoprevention trials, including the importance of taking into consideration environmental as well as host factors when conducting chemoprevention trials in lung cancer. These large trials have underscored that small increases in adverse effects cannot be appreciated without large and lengthy clinical trials; however, small increases may have a large public health impact given the number of people at risk. Finally, these trials have reinforced the lesson that nutritional supplements, just like other pharmacologic interventions, can have significant adverse effects; therefore, these agents must also be tested in rigorous clinical trials.

With the understanding of important cellular signaling pathways, various inhibitors that may prevent or reverse lung carcinogenesis are being developed. Many trials are under way to evaluate agents such as selenium and COX-2 inhibitors. For helping to lessen the need for a large sample size, extensive time commitment, and expense, focus has turned toward assessment of SEBs for lung
carcinogenesis. By integrating biological knowledge, more pilot trials can be performed in a shorter time frame. For individuals who are at high risk for lung cancer or have a history of lung cancer, it is strongly recommended to encourage them to participate in lung cancer chemoprevention trials.

The future of lung cancer chemoprevention should entail the evaluation of single or drug combinations that will target multiple pathways while working toward identification and validation of intermediate end points. Despite this promising future, no one agent is recommended for use in the chemoprevention of lung cancer.

### Summary of Recommendations

1. **For individuals with a smoking history >20 pack-years or with a history of lung cancer, the use of beta carotene supplementation is not recommended for primary, secondary, or tertiary chemoprevention of lung cancer.** Grade of recommendation, 1A

2. **For individuals at risk for lung cancer and for patients with a history of lung cancer, the use of vitamin E, retinoids, N-acetylcysteine, and aspirin is not recommended for primary, secondary, or tertiary prevention of lung cancer.** Grade of recommendation, 1A

3. **For individuals at risk for lung cancer or have a history of lung cancer, budesonide, COX-2 inhibitors, 5-LOX inhibitors, and PGI analogs are not recommended for primary, secondary, or tertiary lung cancer chemoprevention outside the setting of a well-designed clinical trial.** Grade of recommendation, 2C

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