Lung Cancer Chemoprevention*

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

Jhanelle Gray, MD; Jenny T. Mao, MD, FCCP; Eva Szabo, MD; Michael Kelley, MD; Jonathan Kurie, MD; and Gerold Bepler, MD, PhD

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, α-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.** ***(CHEST 2007; 132:56S–68S)***

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 = α Tocopherol β-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

*From the H. Lee Moffitt Cancer Center and Research Institute (Drs. Gray and Bepler), Program and Division of Thoracic Oncology, Tampa, FL; Jonsson Comprehensive Cancer Center (Dr. Mao), University of California, Los Angeles, CA; National Cancer Institute (Dr. Szabo), Bethesda, MD; Duke Comprehensive Cancer Center (Dr. Kelley), Duke University Medical Center, Durham, NC; and MD Anderson Cancer Center (Dr. Kurie), Houston, TX.

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Correspondence to: Gerold Bepler, MD, PhD, Division of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr, MRC-4W, Room 4046, Tampa, FL 33612; e-mail: gerold.bepler@moffitt.org

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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.[2] 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.[3] 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.[4] 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.[5] 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.[6,7] 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.[8] By providing mutual support, behavior modifications, and coping skills, group therapy has been found to be an effective method.[9] The use of pharmacologic interventions such as all forms of nicotine replacement (including nicotine spray, gum, and patches), bupropion, and varenicline (partial agonists of nicotinic acetylcholine receptors) have been effective in increasing smoking cessation rates.[10–16] Other techniques, such as acupuncture and hypnosis, to date, have not been effective.[17]

Smoking cessation results in a decrease in precancerous lesions from 27 to 7%.[18] 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.[3,18]

Many options are available to help with smoking cessation. Physicians are strongly encouraged to