Chemoprevention of Lung Cancer
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Current Oncology Reports 2002, 4:341–346
Current Science Inc. ISSN 1523-3790
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Introduction
Lung cancer is the leading cause of death worldwide. Its overall survival rate has improved only slightly, and surgery, radiotherapy, and chemotherapy remain the mainstays of current treatment. Therapies with novel targeted agents are currently under active investigation in all settings of treatment including chemoprevention, defined as the use of natural or synthetic agents to interrupt the process of carcinogenesis and to prevent or delay tumor occurrence. Thus, chemoprevention describes the collaborative efforts of researchers in basic science and clinical settings who study the biology of lung cancer with the hope of uncovering new mechanisms of treatment. Lung cancer prevention efforts have focused on prevention of tobacco use, secondary prevention with cessation efforts, and chemoprevention, targeting reversal of premalignant lesions and prevention of second primary tumors (SPTs) in patients with prior history of cancer. This article reviews the biology of carcinogenesis and previous clinical trials and explores future efforts to prevent lung cancer.

Historic Background and Biologic Rationale
In 1912, researchers first noted the potential role of tobacco in bronchogenic carcinoma and the possibility that cessation of smoking could prevent lung carcinoma [2]. Additionally, in the 1930s, Ochsner and DeBakey [3] observed that the increase in cigarette sales might be related to the simultaneous rising incidence of lung cancer. The carcinogenic link between smoking and lung cancer development is explained through two concepts: “field cancerization” and the model of multistep carcinogenesis. In the 1950s, Auerbach et al. [4] introduced the concept of field cancerization, which applies to cancers of the aerodigestive tract and holds that carcinogen exposure results in diffuse injury to the epithelium throughout the aerodigestive tract. Genetic changes and premalignant and malignant lesions in one region of the field translate into an increased risk of cancer development in the entire field. Areas of carcinoma in situ and of metaplasia have been found to occur in the bronchial epithelium after prolonged exposure to inhaled carcinogenic agents, specifically cigarette smoke [5,6]. There is increasing molecular evidence that these areas of histologic change are causally related to the development of lung cancer.

The multistep model of carcinogenesis holds that the development of cancer is a process with multiple steps in which exposure to a carcinogen (eg, in lung cancer, any of the multiple carcinogens identified in cigarette smoke) results in repeated damage and repair until the accumulated exposure triggers a transformation from normal to premalignant cells (from normal cells to metaplasia and dysplasia) and eventually to frank carcinoma.
Lung Chemoprevention Trials

The rationale for prevention of lung cancer is similar to that for head and neck cancer. In both diseases, chronic exposure to tobacco is the major risk factor and dysplastic epithelial lesions are thought to represent a premalignant stage. Preclinical data indicate that retinoids reverse dysplastic bronchial epithelial lesions. Despite these data, placebo-controlled, randomized trials in smokers have revealed that retinoid treatment adds no significant benefit to the effects of smoking cessation and reversal of bronchial metaplasia. In light of results demonstrating that retinoids reduce SPTs in patients who have had a lung cancer resected, bronchial metaplasia may not accurately reflect the chemopreventive effects of retinoids on bronchial epithelium. Research is underway to identify intermediate markers that predict retinoid chemopreventive effects on bronchial epithelial cells.

Reversal of Premalignant Lesions

Early detection by chest radiography has not yet significantly changed the outcome for patients with lung cancer. However, premalignant markers detectable by sputum cytology studies or found in bronchial metaplasia have been investigated as early predictors of lung cancer. Reversal of these premalignant lesions through various treatment modalities may prevent progression to lung cancer. Studies have included various agents to treat sputum atypia [4–7] or bronchial squamous metaplasia [8–11]. One study even showed improvement of bronchial epithelium metaplasia in smokers with administration of folate and vitamin B12 [12]. However, because of problems with the consistency of the endpoints in this study, positive results must be viewed with temperance. Larger trials of biologic endpoints are needed to confirm treatment efficacy. Attempts to reverse premalignant lesions in the head and neck using retinoids have met with some success. It is possible that lessons learned in the aerodigestive tract can be transplanted into the arena of lung cancer [13]. Low-dose isotretinoin (13-cRA) was shown to decrease oral premalignancy when employed as a maintenance regimen [14]. Trials targeting intermediate biologic markers, including molecular indicators of genetic damage, may well be the most promising element in control of lung cancer.

The alpha-tocopherol, beta-carotene (ATBC) cancer prevention study was a randomized, double-blind, placebo-controlled, primary-prevention trial in which 29,133 Finnish male smokers received either alpha-tocopherol (50 mg/d) alone, beta-carotene (20 mg/d) alone, both alphatocopherol and beta-carotene, or placebo [15]. Male participants were aged between 50 and 69 years, and all smoked five or more cigarettes a day. Patients received follow-up observations for 5 to 8 years. Lung cancer incidence, the primary endpoint, did not change with the addition of alpha-tocopherol alone, nor did the overall mortality rate. However, both groups who received beta-carotene supplementation (alone or with alpha-tocopherol) had an 18% increase in the incidence of lung cancer. A stronger adverse effect from beta-carotene was apparent in the men who smoked more than 20 cigarettes a day. This trial raised the serious issue that pharmacologic doses of beta-carotene could be harmful in active smokers.

The Beta-Carotene and Retinol Efficacy Trial (CARET) confirmed the results of the Finnish trial. This randomized, double-blind, placebo-controlled trial tested the combination of 30 mg of beta-carotene and 25,000 IU of retinyl palmitate (vitamin A) against placebo in 18,314 men and women aged 50 to 69 years who were at high risk for lung cancer [16]. A majority of the participants had a smoking history of at least 20 pack-years and were either current smokers or recent exsmokers [17]. Extensive occupational exposure to asbestos was noted in 4060 men. This trial was stopped after 21 months because there was evidence of no benefit or of possible harm. Lung cancer incidence, the primary endpoint, increased 28% in the active intervention group. The overall mortality rate also increased 17% in this group. Given these results, in addition to those of the ATBC trial, high-dose beta-carotene is not recommended for patients at high risk who continue to smoke.

The Physicians’ Health Study, a randomized, double-blind, placebo-controlled trial, evaluated 22,071 healthy male physicians. Half of the participants (11,036) received 50 mg of beta-carotene on alternate days, and the other half (11,035) received placebo. The use of supplemental beta-carotene showed virtually no adverse or beneficial effects on cancer incidence or overall mortality rate during a 12-year follow-up period [18].

Analysis of subgroups of the previously mentioned trials, especially the ATBC and CARET studies, has provided few explanations for the increase in lung cancer incidence. It seems that beta-carotene has a harmful effect only in heavy smokers at high risk or in people who have been exposed to asbestos. Current recommendations are for these people to avoid beta-carotene in large doses [19].

Chemoprevention and treatment trials of the aerodigestive tract will continue because these cancers remain a challenge. Use of natural and synthetic agents may indeed reduce the risk of cancer in high-risk individuals. The optimal dosage and maintenance schedules still need further clarification. Through this approach we hope to identify accurate biomarkers and to establish effective treatment regimens for carcinogenesis in the aerodigestive tract.

Much work is needed before chemoprevention agents can be instituted in lung cancer. Current efforts include the EUROSCAN study, described in the following section. In addition, an Eastern Cooperative Oncology Group trial in patients with stage 1 lung cancer is studying the effect of daily selenium supplementation.