Chemoprevention and Screening for Lung Cancer: Changing Our Focus to Former Smokers

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Abstract

Clinical trials of chemoprevention for lung cancer have yielded negative results, with suggested worsening of cancer incidence in those who continue to smoke. Continued smoking over age 55 is associated with decreased longevity and multiple comorbidities. It is possible that clinical trials focusing on former smokers in both prevention and screening trials will yield significant benefit, now masked by the population of continued smokers.

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Introduction

In view of the high mortality and suffering resulting from from lung cancer, efforts have been made over the past 50 years to try to find a way of preventing lung cancer. In 1962, Auerbach et al[1] demonstrated in autopsy studies that atypia in the bronchial epithelium in former smokers was present in about 6% of subjects, compared with 93% of smokers at the time of death and 1.2% in never smokers. Saffiotti et al[2] developed an animal model of lung cancer using 10 intratracheal instillations of 3 mg of benzopyrene on hematite. One group of animals received no further treatment, and 13 of 53 animals had a squamous cell cancer. A second group provided with vitamin A palmitate after the benzopyrene installation was complete had only 1 squamous cell cancer in 46 animals. These trials raised hope that healing was possible in the tracheobronchial epithelium and that perhaps compounds could be provided to facilitate this process. Epidemiologic evidence suggested that people with the lowest levels of vitamin A/carotene or the lowest oral intake of retinoids had a higher risk of lung cancer.[3]

The concept of preventing cancer with low-toxicity agents was suggested as chemoprevention by Peto et al.[3] In addition to preclinical data, epidemiologic evidence also suggested that providing carotenoids may reduce the risk of cancer. This thorough 1981 review led to large clinical trials in patients at high risk for lung cancer. However, 2 trials of carotene in subjects at risk for lung cancer due to at least heavy smoking histories failed to show benefit in preventing lung cancer.[4,5] Other randomized trials have failed to establish any agent as being effective in preventing or reducing lung cancer in populations of both smokers and former smokers. The history of this research was reviewed by Hecht and Szabo.[6] Szabo et al[7] reviewed the lack of any effective chemopreventive agents that could be provided as part of clinical practice guidelines. In addition to lack of benefit, prevention trials which included β-carotene have shown harm in those who were current smokers.

In view of the multiple comorbidities associated with smoking, the question is whether preventing lung cancer in heavy smokers who continue to smoke can make an impact on survival. Although chemoprevention in lung cancer has been studied for about the last 40 years and certainly has seemed a worthwhile goal, no agent has emerged as effective in those at high risk for lung cancer. Those highest at risk for lung cancer due to heavy smoking are also those at great risk of death from myocardial infarction, stroke, chronic obstructive lung disease, and other types of cancer, including bladder, renal cell, and pancreatic cancers as well as acute leukemia. Eliminating lung cancer in such patients may not add significantly to their projected life span in those who continue to smoke. In former smokers, prolongation of life may occur with the greatest gains experienced by those who quit the earliest. In continued smokers, lung cancer prevention may delay death, but death from other smoking-related causes may still lead to short survival.

Preclinical Models of Chemoprevention

After the trial of Saffiotti et al[2] showing a reduction in lung cancer in hamsters treated with vitamin A, numerous studies were performed in small animals. Preclinical animal trials were reviewed in 2012.[8] Animal models of lung cancer now exist for adenocarcinoma, squamous cell carcinoma, and small-cell lung carcinoma.[8] One feature of almost all of the trials of chemopreventive agents is the administration of a carcinogen, then the introduction of a

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chemopreventive agent to reduce the number of cancers that develop. This model resembles the use of chemoprevention in former smokers, but it does not model prevention in ongoing smokers for whom carcinogenic exposure continues. The rather short duration of administration of chemopreventive agents in animals may not lead us to understand the potential toxicities of any chemopreventive agent, which would need to be administered much longer in humans. These models also cannot address the global health risks, including cardiovascular disease in smokers who are at risk for both lung cancer and vascular disease.

Models of lung cancer suggest that there is a progression in the tracheobronchial epithelium from normal, to metaplasia, to dysplasia, to in-situ cancer, and then to invasive cancer. Szabo et al[7] have pointed out that there are multiple DNA adducts in the lungs of smokers. More than 1000 mutations were found in cancer-related genes in DNA isolated from 188 primary adenocarcinomas of the lung. Other studies have shown multiple single-nucleotide variants in lung tumor and multiple mutations in adjacent noncancerous lung in smokers. Dragnev et al[9] reviewed potential ways to alter this progression. Interruption of this process might be possible with (1) anti-inflammatory agents such as budesonide or COX-2 inhibitors; (2) differentiating agents such as cell cycle inhibitors, retinoids, tripterpenoids, rexinoids, or epidermal growth factor receptor (EGFR) inhibitors; (3) antiangiogenesis agents; and (4) cell-cycle inhibitors such as demethylating agents, histone deacetylase inhibitors, PPAR agonists, RAS inhibitors, and proteasome inhibitors.[9]

It is unclear which of these agents might work best in former smokers versus current smokers. Oral iloprost was tried in a phase II trial of both former and continued smokers. The hypothesis was that prostacyclin levels are lower in lung cancer and that supplementation prevents lung cancer in preclinical models. Histologic improvement occurred in former smokers with iloprost but did not in ongoing smokers.[10] The animal models had not predicted the increase in lung cancer incidence observed in human clinical trials, where the chemopreventive agent actually increased the incidence of lung cancer. Even supplemental therapy with common vitamins has been associated with increased risk of lung cancer and mortality.[11]

Randomized Trials of Chemoprevention in Humans

The Alpha Tocopherol, Beta Carotene, Cancer Prevention (ATBC) trial was a prevention trial sponsored by the US National Cancer Institute and the National Public Health Institute of Finland.[12] The study enrolled 29,133 male smokers in Finland aged 50 to 69 years. All were current smokers. Patients were randomized to 50 mg of α-tocopherol (vitamin E), 20 mg of β-carotene (precursor of vitamin A), both tocopherol and carotene, or placebo. The study was initiated as a result of epidemiologic and preclinical trials that suggested that these interventions might prevent lung cancer. Patients received therapy for 5 to 8 years. When the study closed and was reported in 1994,[4] α-tocopherol had not effected any change in the incidence of lung cancer, but there was an 18% increase in the risk of lung cancer in those receiving carotene or both carotene and tocopherol. This was further evaluated in 1996.[13] The increased risk of carotene supplementation appeared to be greatest in those smoking at least 20 cigarettes (1 pack) daily. There was also an increased incidence of lung cancer in those with a higher intake of alcohol. Further follow-up of the ATBC trial was carried out about 5 years from the end of therapy.[14] The 18% increased incidence of lung cancer in those receiving carotene remained the same, but with cessation of the carotene supplementation, the incidence of lung cancers was no longer as high in the carotene group 4 years later. During the years receiving therapy, men receiving carotene had 8% higher mortality overall. This was due to excess deaths due to lung cancer and coronary artery disease. However, during the posttreatment follow-up period, the increased mortality was due to coronary heart disease, cardiomyopathy, hypertensive heart disease, stroke, and cardiac rupture.[14] There was an increase in hemorrhagic stroke in those receiving α-tocopherol, both during the trial's treatment period and in the follow-up period. In the posttreatment follow-up, deaths reported were due to coronary artery disease (28.8%), lung cancer (17.1%), other cancers (17.1), respiratory failure (8.2), nonhemorrhagic stroke (4.9%), hemorrhagic stroke (2.6%), and other cardiovascular disease (7.0%).

The Beta Carotene and Retinol Efficacy Trial (CARET) study, carried out in the United States about the same time as the ATBC study, examined the potential for supplementation with β-carotene and retinol to reduce the incidence of lung cancer.[5,14,15] This study was planned in 1983 before the results of the ATBC study had been reported. In contrast to the ATBC study, the CARET study enrolled both men and women at risk of lung cancer, including men with asbestos exposure. Participants with heavy asbestos exposure were randomized to carotene 15 mg plus retinol 25,000 units daily versus placebo. Men and woman with history of heavy smoking were randomized to carotene 30 mg per day, retinol 25,000 IU per day, carotene plus retinol, or placebo. There were 18,314 participants registered, and of the nonasbestos population of smokers, 44% were women. Only 1% of the participants had been receiving vitamin A supplements, and after 5 years on the study protocol, the serum carotene level for those receiving therapy was a median of 2100 ng/mL, versus 170 ng/mL in the placebo group. At the end of about 4 years of therapy, this study was stopped early as a result of concerns about an increase in mortality due to carotene/retinol. There was a 28% increase in lung cancer and an increase in the rate of cardiovascular disease of 26%.[14] A later analysis suggested that there was an increase in the risk of lung cancer except in the group of former smokers.[5] Similar to the ATBC trial, there was an association of increased risk of lung cancer in those in the highest quartile of alcohol consumption. Follow-up 6 years after the completion of the carotene/retinol therapy has been reported.[15] For the overall population of participants, the relative risk of lung cancer remained elevated through the posttherapy period, but the relative risk of cardiovascular disease returned to 1.0. However, although the intervention was stopped, female participants continued in the posttherapy period to have a larger risk of lung cancer, a larger risk for cardiovascular disease, and a larger risk of all-cause mortality.

In contrast, 3 years of carotene 50 mg every other day compared with placebo did not increase the risk of lung cancer or cardiovascular disease in 22,071 physicians.[16] Only 11% of the participants in this trial were smokers. There was originally a 4-group randomization to aspirin (ASA) 325 mg every other day, carotene 50 mg every other day, carotene and ASA, or placebo. The randomization to ASA was stopped on January 25, 1988, when a