Chemoprevention of Lung Cancer

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Chemoprevention is defined as the use of specific natural or pharmacologic agents to reverse, suppress, or prevent the carcinogenic process to the development of invasive cancer. The basic idea behind lung cancer

Introduction

Lung cancer is the most common and deadly malignancy in the United States and throughout the world. It is the leading cancer killer of both men and women in the United States, and is expected to be responsible for approximately 31% of all cancer deaths in men and 25% of cancer deaths in women in 1999. Overall, the 5-year survival rate for lung cancer is only 15%. [1]

Since 90% of lung cancers are tobacco related, primary prevention of lung cancer by smoking prevention and cessation is one of the highest priorities for United States health policy. In the United States today, 50 million individuals are current smokers, and another 50 million are former smokers. In fact, 50% of newly diagnosed lung cancers occur in former smokers, perhaps due to persistent genetic changes in the bronchial epithelium from tobacco carcinogens. [2,3] Chemoprevention is defined as the use of specific natural or pharmacologic agents to reverse, suppress, or prevent the carcinogenic process to the development of invasive cancer. [4]

Biologic Concepts

The basic idea behind lung cancer chemoprevention is the concept that diffuse injury of the respiratory epithelium results from chronic carcinogen exposure. This is known as the field cancerization, which describes the diffuse mucosal changes observed in patients with head and neck cancers. These changes, identified from resected surgical specimens of carcinoma of the oral cavity, were of three primary histologic abnormalities surrounding the primary tumor: Hyperplasia (an increase in the number of rows in the epithelium), hyperkeratinization, and dyskariosis (atypia). When the entire surgical specimen was further sectioned, separate foci of in situ and invasive carcinoma were frequent findings. Basically, the entire upper aerodigestive tract is exposed to long-term carcinogenic insult (in this instance, cigarette smoke), and is therefore at increased risk of developing cancer. [1-4]

The evidence for multistep carcinogenesis in this setting also includes genetic damage to lung tissue, demonstrated by the linear relationship between genetic instability (eg, polysomy of chromosomes 3, 9, and 17) in human lung tissue and cigarette smoking, and the increased frequency of proliferative markers in high-risk tissues and premalignant lesions (Figure 1). [5-9] Auerbach et al sectioned the entire tracheobronchial trees of chronic smokers and patients who died of lung cancer. They recorded three major types of epithelial changes: an increase in the number of cell rows, loss of cilia, and the presence of atypical cells. The most striking finding was the frequency of carcinoma in situ, a lesion composed entirely of atypical cells without cilia in an average thickness of 5 or more cell rows; this finding was observed in 15% of the sections from those who died of lung cancer. These lesions were found in 4.3% of sections from men who smoked one to two packs of cigarettes per day, and 11.4% of sections from those who smoked two or more packs per day. [5,6,10,11] These lesions were never found in pathologic specimens of nonsmokers, and few were found in the bronchial trees of light smokers.

Rationale for Chemoprevention

The field of chemoprevention grew in large part out of the epidemiologic data demonstrating the existence of dietary inhibitors of carcinogenesis. The rationale for chemoprevention arose from a combination of sources: epidemiologic data demonstrating the existence of dietary inhibitors of
carcinogenesis, basic studies of epithelial carcinogenesis, and laboratory evidence from animal models.[5,12-15] Despite these data, difficulty has persisted in determining which specific compounds within complex foods provide anticarcinogenic (or carcinogenic) effects. The term “chemoprevention” was coined by Michael B. Sporn to define the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer.[3,4] In 1981, Peto et al examined the impact of dietary b-carotene on the reduction of human cancer rates. Several groups had previously demonstrated an inverse correlation between human cancer risk, blood retinol, and dietary b-carotene.[16] They reviewed the literature on whether supplemental b-carotene or vitamin A could materially retard the carcinogenic process. The cancer-preventive data from epidemiologic studies led to in vitro and in vivo (animal) laboratory studies evaluating the specific components of complex foods. Whereas these studies discovered many agents with laboratory anticarcinogenic activity and suggested potential toxicity profiles of these agents, translational clinical chemopreventive trials to substantiate their efficacy in humans were lacking at the time.[6,17,18]

Much of this work has been conducted by investigators from M. D. Anderson Cancer Center (Houston) in carefully designed, double-blind, placebo-controlled clinical chemoprevention trials.[3,17,18] These studies focused on vitamin A and its synthetic analogs, collectively referred to as retinoids. The retinoids appear to act by binding to a specific set of retinoic acid receptors (RAR) and retinoid-X-receptors (RXR). The binding of retinoids to these receptors results in binding to specific nuclear sites and the transcriptional activation of multiple downstream genes. Retinoids function by inducing differentiation in cells that have lost normal regulatory mechanisms. Whereas retinol and the synthetic retinoids produce significant toxic effects if given in high doses, different synthetic retinoids with different receptor-specific ties are being developed, several of which have undergone extensive clinical testing. Synthetic retinoids that have demonstrated activity in various clinical trials to date include 13-cis-retinoic acid (13cRA) in head and neck cancers, myelodysplasia, childhood neuroblastoma, and juvenile chronic myelogenous leukemia; all-trans-retinoic acid (ATRA) in acute promyelocytic leukemia (APL); etretinate in cervical and skin cancers; and retinyl palmitate in lung cancer. Also, 9-cis-retinoic acid (9cRA), an RXR-specific ligand, 4-N-(4-hydroxyphenyl) retinamide (4-HPR), and other new vitamin A derivatives are under active clinical investigation.[2,3,9,12]

The ability of retinoids to suppress lung carcinogenesis in animal models was believed to result from changes in the expression of their nuclear retinoid receptors, because these receptors play a proximal role in the retinoid signaling pathway. Retinoids exert their actions through activation of the nuclear retinoid receptors that act as transcription factors for genes that influence cell growth and differentiation. Therefore, changes in their expression may cause aberrations in cells’ response to retinoids and alterations in growth and differentiation regulation. It was found that RAR-β expression is suppressed in many lung cancer cell lines, a finding that implies a selective suppression of RAR-β in malignant transformation. Selective suppression of RAR-β in the early stages of carcinogenesis in the oral cavity and marked upregulation of RAR-β after retinoid treatment associated with clinical response have been confirmed, thus giving RAR-β excellent potential as an intermediate biomarker.[2-4,19] A pilot study of RAR-β expression in specimens from a previous chemoprevention trial in bronchial metaplasia revealed that only 55% of patients expressed RAR-β before treatment, with some upregulation of RAR-β expression taking place after retinoid treatment.

Retinoid receptor expression was compared in specimens from normal and malignant lung tissues. All receptors were expressed in at least 89% of control normal bronchial tissue specimens from patients without a primary lung cancer and in distant normal bronchus specimens from patients with non–small-cell lung cancer. RAR-α, RXR-α, and RAR-γ were expressed in more than 95% of the 79 non–small-cell lung cancer specimens, in contrast to RAR-β, RXR-γ, and RXR-β expression, which were detected in only 42%, 72%, and 76% of non–small-cell lung cancer specimens, respectively. These findings provide further evidence for implication of RAR-β, and possibly RAR-g and RXR-β, in lung carcinogenesis.[19]

**Chemoprevention Trials in Bronchial Premalignant Lesions**

Bronchial metaplasia, dysplasia, and sputum atypia are associated with lung cancer and a history of smoking. Sputum atypia was examined in a multi-center lung cancer screening, and was not found to predict lung cancer development. Chemoprevention trials have investigated the effect of different agents on bronchial metaplasia and dysplasia and sputum atypia (Table 1). In a small uncontrolled pilot trial of participants with at least a 15-pack-year smoking history, Mathe et al observed a reduction in bronchial metaplasia following treatment with etretinate, a synthetic retinoid.[28] In smokers with at least a 15-pack-year history, Arnold et al examined the effect of 6 months of...
treatment with etretinate or placebo on sputum atypia and found no effect.[21] In a population with a heavier smoking history and exposure to asbestos, McLarty et al observed no effect of β-carotene and retinol on sputum atypia.[22] In participants with at least a 20-pack-year smoking history, Lee et al found no effect on 13cRA on bronchial metaplasia, but bronchial metaplasia was reduced by smoking cessation, suggesting that bronchial metaplasia is an acute reaction to cigarette smoke exposure in active smokers.[17]

The previously mentioned trials have relied on white-light bronchoscopy for the detection of bronchial metaplasia and dysplasia. A new technique using a laser incorporated into a bronchoscope was reported to be 50% more sensitive in the detection of bronchial dysplasia than standard white-light bronchoscopy. This technique is based on the principle that light of specific wavelengths can stimulate intrinsic cellular florophors, such as flavins, riboflavins, nucleic acids, and proteins, to fluoresce, thereby emitting a spectral pattern of light typical of that particular tissue. Epithelial carcinogenesis is associated with altered levels of these floroflors; by using fluorescence spectroscopy, normal, dysplastic, and neoplastic tissues can be distinguished on the basis of their spectral patterns. This new bronchoscopic technique is under evaluation in chemoprevention trials as a method of enhancing the detection of bronchial premalignancy in smokers and former smokers.[29-31]

Prevention of Second Primary Lung Tumors
Non–small-cell lung cancer patients who have been rendered free of disease develop second primary tumors at a rate of 2% to 4% per year.[4,32] The role of vitamin A and its metabolites in preventing second primary tumors in patients with a previous lung cancer diagnosis was explored by Pastorino et al from the Istituto Nazionale Tumori (Milan, Italy).[23] These investigators randomized 307 patients who had been surgically cured of stage I non–small-cell lung cancer to receive either retinyl palmitate (300,000 IU/day for 12 months) or placebo. Retinyl palmitate treatment was generally well tolerated, with a compliance rate of greater than 80%. Retinyl palmitate treatment was also associated with an overall reduction in second primary tumors (18 patients in the retinyl palmitate arm vs 29 patients in the control arm). When only tobacco-related tumors were considered, 13 patients in the retinyl palmitate arm developed tobacco-associated second primary tumors vs 25 patients in the control arm. Tobacco-related second primary tumors took statistically significantly (P = .045) longer to develop in patients treated with retinoid.[23] Currently, several ongoing multi-institutional trials in both North America and Europe are evaluating chemoprevention regimens for aerodigestive tract cancers. The North American Intergroup Lung Study to prevent second primary tumors is a National Cancer Institute-sponsored, randomized, placebo-controlled trial to assess whether long-term, low-dose 13cRA can significantly retard the development of second primary tumors following the resection of stage I (T1, N0, M0 or T2, N0, M0) non–small-cell lung cancer. In this study, which has accrued more than 1,350 patients (target accrual = 1,402), those with successfully resected stage I non–small-cell lung cancer are randomized to receive either 13cRA (30 mg/day) or placebo. Patients are eligible for up to 36 months after curative resection and are treated for 3 years, with a subsequent follow-up of 4 years.[4]

Similarly, the Euroscan study is evaluating the efficacy of retinyl palmitate (300,000 IU/day) and the antioxidant N-acetylcysteine (600 mg/day) in the prevention of second primary tumors following the definitive therapy of early-stage squamous cell carcinoma of the head and neck or fully resected stage I (T1-2, N0), stage II (T1-2, N1), or stage IIIA (T3, N0 only) non–small-cell lung cancer. This study has a 2 × 2 factorial design, in which study participants receive either retinyl palmitate or N-acetylcysteine alone, both drugs, or placebo for 4 years, and then undergo 4 years of follow-up. This study has met its accrual target, and results show neither harm nor benefit.[33]

Primary Prevention Trials to Prevent Lung Cancer
The results of three large well-designed, phase III chemoprevention trials using incidence of lung cancer as the definitive end point were recently reported (Table 1). All three trials included arms to study the effect of β-carotene on lung cancer risk. The findings were sobering to the medical community, and underscore the complex mechanisms underlying chemoprevention and our need to understand them better. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) randomized 29,133 male Finnish smokers to receive either supplemental β-carotene, α-tocopherol (vitamin E), a combination of the two, or placebo using a 2 × 2 factorial design. Unexpectedly, the β-carotene arm showed a statistically significant (P = .02) 18% increased risk of lung cancer, whereas the α-tocopherol arm showed no difference. Further, β-carotene did not appear to affect the incidence of other cancers in this population.[24] A similarly designed large randomized US trial, the Beta-Carotene and Retinol Efficacy Trial (CARET Study), examined the effects of supplemental β-carotene and retinol in smokers and
asbestos-exposed workers. The trial was terminated 2 years early due to a 28% increase in lung cancer incidence among smokers treated with β-carotene.[27] The third randomized trial, the Physicians’ Health Study, tested supplemental β-carotene in a predominantly nonsmoking population and found no difference in lung cancer risk associated with β-carotene use.[34]

The above studies thus negate the protective effects of β-carotene against lung cancer development postulated by prior epidemiologic studies. The most likely reason for this contradiction is that a single dietary supplement such as β-carotene cannot provide all the elements in yellow and green leafy vegetables that confer anticancer protection. It is also possible that the anticarcinogenic effect of β-carotene is too small to have been detected, even in large-scale trials such as those described above.

A disturbing finding was the increased incidence of lung cancer associated with β-carotene in smokers in the first two studies. This raises the possibility that b-carotene may have a carcinogenic effect in smokers. The reasons for this increased lung cancer risk are not clear, but postulated mechanisms include inhibition of the intestinal absorption of other nutrients by daily large doses of β-carotene, and a possible pro-oxidant effect of β-carotene in the damaged lungs of long-term heavy smokers.

Thus, given the above findings, there appears to be no justification for consuming supplemental β-carotene for cancer chemoprevention, and smokers should refrain from high doses of b-carotene altogether. As studies continue to unravel the mysteries behind lung cancer chemoprevention, progress in this field will have to rely on well-designed (randomized, double-blinded, placebo-controlled), large-scale, phase III trials that test preclinical and clinical hypotheses.[35]

**Molecular Biomarkers**

Chemoprevention trials are designed to prevent the development of cancer in cancer-naïve patients (primary prevention) or in patients cured of a prior cancer (second primary prevention). Among smokers, the risk of developing lung cancer is less than 1% per year. Because of the low prevalence of lung cancer in this population, primary lung cancer chemoprevention trials require 20,000 to 30,000 participants followed for 5 to 10 years to reach statistical significance. This sample size can be reduced in second primary lung cancer prevention trials because the participants have a higher incidence of lung cancer than cancer-naïve patients.

To reduce the cost and time commitment required for these studies, investigators have sought biomarkers that detect either the presence of increased cancer risk or a biologic response to chemopreventive treatment. Biomarkers of lung cancer risk can be divided into several categories, including those that reflect an inherited lung cancer susceptibility, damage associated with environmental exposure (eg, cigarette smoke, asbestos), and the presence of premalignant cells. Using biomarkers, the ultimate goal in chemoprevention research is to construct a risk model that can predict an individual’s risk of developing lung cancer.[3,4] In addition, sample size can be reduced through the use of biomarkers that reflect activation of signal transduction pathways associated with chemoprevention treatment. Because modulation of these biomarkers replaces cancer as an end point of the trial, they are considered intermediate end points of chemoprevention trials.

A molecular analysis of changes present in premalignant and histologically normal lung tissues may give insight into the risk of developing second lung cancers. In situ hybridization, which allows visualization of chromosomes in nondividing cells, demonstrated that chromosome polysomy (an expression of genetic instability) was associated with histologic progression. There was also a correlation between genetic instability and p53 status, with increased polysomy in p53 mutations.[4,36,37]

Another manifestation of genomic instability is the frequent loss of chromosomal segments that often harbor tumor suppressor genes. Such changes (particularly loss of chromosomes 3p, 9p, and 17p) have been demonstrated in premalignant lesions and second primary tumors distant from primary lung tumors. They are often distinct from changes seen in the primary tumor, supporting the concept of field cancerization. Loss of chromosomes 9p and 3p is thought to occur early in the lung carcinogenesis process and at an increasing rate as histology progresses from hyperplasia to dysplasia to invasive cancer. These genetic alterations are present even in the absence of squamous metaplasia in the bronchial mucosa of former smokers.[4,6-8,36-38] Candidate genes that might be important targets during the lung carcinogenesis process are present in these frequently deleted chromosomal regions (eg, the FMT gene at 3p and p16, a cell-cycle regulator at 9p).[38]

The frequency of the p53 gene mutation in lung cancer is estimated at approximately 50% to 60%,
and these mutations are thought to arise later in the process than 3p and 9p loss. Abnormalities in the p53 gene have been found in one third of mild-to-moderate bronchial dysplasia and in up to 60% of severe dysplasias and carcinomas in situ.[39]

Mutated K-ras has been detected in morphologically normal sputum cells predating the appearance of clinical cancer as well as in atypical alveolar hyperplasias. The exact role and timing of K-ras mutations, however, in the multistep lung carcinogenesis process is not yet well established. Other chromosome deletions and tumor-suppressor gene inactivations in lung cancer are 5q deletion and Rb inactivation, seen in the majority of small-cell lung cancers and in approximately 20% of non-small-cell lung cancers.[4,36,37]

Cyclin D1 gene amplification and protein overexpression are additional events linking disruption of the cell cycle with carcinogenesis, along with inactivation of p16 and Rb. Telomerase, an enzyme that halts the normal shortening of human chromosomes with successive cell divisions, has been found reactivated in 80% of primary lung cancers, but also in bronchial premalignant lesions (from 25% in hyperplasia to 100% in carcinomas in situ), suggesting implication in the early stages of carcinogenesis. As noted above, the detection of early molecular alterations might help in the selection of a population of patients that would benefit most from chemopreventive intervention or approaches such as gene therapy.[4,36,37]

**Markers of Genetic Susceptibility**

Lung cancer risk is defined by the balance between metabolic activation and metabolic detoxification of xenobiotic compounds, as well as the efficiency of DNA repair. That lung cancer is caused by a single explanatory gene-environmental interaction is unlikely; one marker may not have a strong effect, but in conjunction with other genes, one marker may shift the risk profile in an unfavorable direction. Multiple susceptibility factors must therefore be accounted for to represent the true dimensions of gene-environmental interactions. The number of cigarettes consumed before the onset of lung cancer might be lower in “susceptible” individuals than in “nonsusceptible” individuals (ie, individuals with a susceptible genotype have a high risk for lung cancer, even at a low cigarette dose level). The genetic component of risk tends to be lower at high-dose levels, when the environmental influence may overpower genetic predisposition.

The ability to identify smokers with the highest risk of developing cancer has substantial preventive implications. These subgroups could be targeted for the most intensive smoking-cessation interventions, could be enrolled into chemoprevention trials, and might be suitable for screening programs not appropriate for the general population. Finally, studying susceptibility to common cancers and widely prevalent exposures may provide further insights into the basic mechanisms of carcinogenesis.[19,39,40]

There is increasing interest in the use of biomarkers in cancer epidemiology to enhance exposure assessment, to gain insight into diverse mechanisms, to understand acquired or inherited susceptibility, and to refine risk-assessment markers of susceptibility to lung cancer. The fate of tobacco carcinogens is tightly controlled by specific genes involved in carcinogen metabolism. The three major pathways are activation (enzyme A–cytochrome p450[CYP]1A1, CYP2D6, CYP2A6, CYP2E1), detoxification (enzyme B–GSTM1, MSTT1, GSTM), and the DNA repair process (mutagen sensitivity). For example, individuals who lack a gene-controlling enzyme B, which regulates detoxification of tobacco carcinogens, have a higher risk of lung cancer development than individuals with the intact gene.[41]

**Future Directions**

All of the following developments are not only possible, but likely to be achieved within the next decade. Alone and in combination, they will lead to tremendous improvements in the treatment and prevention of this deadly disease.

- A growing body of molecular and epidemiologic evidence will be used to identify markers of genetic susceptibility for lung cancer.

- Discovery and validation of intermediate biomarkers (including genetic susceptibility; loss of heterozygosity at 3p, 9p, and 17p; RAR-β loss; p53; and ras) will provide a more precise molecular model of lung carcinogenesis.

- Correlations will be made between inherent genetic-susceptibility markers and molecular...
markers in target tissue.

- The mechanisms of retinoid-signaling pathways to restore retinoid anticarcinogenic activity will be elucidated.
- Refinement of aerosolized drug delivery to improve targeting of respiratory epithelium will be accomplished.[41]
- Chemoprevention will be used more extensively to target former smokers who remain at high risk for lung cancer development.[38,39]

References:


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