Chemoprophylaxis Strategies in High-Risk Groups
With an Emphasis on Lung Cancer

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The incidence of lung cancer in the United States has stabilized in recent years, but it remains a major cause of death in the United States. Whereas the single most effective primary prevention of this disease would be to eliminate tobacco use from society, this is currently an unrealistic goal. Secondary prevention, however—that is, chemoprophylactic treatment of smokers, exsmokers, and others at risk—represents a viable option. Agents proven effective in both laboratory models and humans include vitamin A and its synthetic derivatives, the retinoids and the carotenoids. It is fairly easy to identify patients at risk of lung cancer compared with other cancers. Yet aside from patients who are under a physician's care and aware of their risk, it can be difficult to target individuals for chemoprophylactic treatment, especially those who are healthy but at high risk and not seeing a physician or other health care provider. Screening for the presence of predictive cellular and molecular changes may facilitate more accurate selection of individuals for chemoprophylactic treatment.

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Lung cancer is a major cause of cancer death in the United States. An estimated 130,000 people died of this disease in 1991. Although the incidence of lung cancer appears to have stabilized, it remains a major health hazard.

Findings over the past decade have rapidly expanded our understanding of the complex process of carcinogenesis. It is now believed that cancer develops as a multistep phenomenon encompassing gene deletion, mutation, activation, and inactivation. Although the original concept dividing carcinogenesis into initiation, promotion, and progression appears to have been simplistic, it can illustrate useful concepts of prevention. Primary prevention can be defined as avoiding initiation by minimizing exposure to a causative, environmental agent. For lung cancer, this means avoiding tobacco smoke. Secondary prevention consists of using an intervention that effectively prevents or delays carcinogenesis during the promotional phase. In the area of lung cancer, this would comprise treating smokers with cancer prevention agents. Tertiary prevention would include the treatment of patients who have bronchial metaplasia/dysplasia. Strictly speaking, screening studies do not constitute tertiary prevention, since their goal is to diagnose disease already present but still localized and of low tumor burden.

The optimal scenario for primary prevention of lung cancer is to eliminate tobacco use from our society. This remains a difficult goal. Moreover, even if it were achieved, a large population would continue to be at risk for developing lung cancer. The relative risk of lung cancer for continued smokers vs those who stop falls to 0.3 after 20 years. However, the risk for a smoker who has stopped smoking for 20 years remains seven times that of someone who never smoked. We have estimated that approximately 9 million Americans have a history of 20 pack-years of cigarette smoking as of 1990, are current smokers or recent exsmokers, and are at risk for developing lung cancer.

Chemoprophylaxis of lung cancer entails using agents, usually antipromotional agents, that can inhibit or reverse the process of carcinogenesis. The agents most tested in both laboratory models and humans are vitamin A and its family of compounds, the retinoids, and the carotenoids. Bollag and Matter first showed that a number of retinoids can decrease the incidence of skin carcinomas in mice given known carcinogens. Using the Syrian hamster lung cancer model, Saffiotti et al demonstrated that retinyl palmitate can decrease the incidence of both benign and malignant respiratory tract tumors after inhalation of benzpyrene and ferric oxide. More recently, Hong and coworkers at M.D. Anderson Cancer Center in Houston, Texas, have extended these findings to humans. This group treated 100 patients with potentially cured head and neck cancer with 13-cis-retinoic acid to determine its effect on second primary cancers and recurrence. While this agent had no effect on recurrence, it did reduce second primary cancers in the treatment group compared to the placebo group (4 percent vs 24 percent incidence, respectively, p<0.005). These trials suggest that even when the process of carcinogenesis is well advanced, chemoprophylaxis may be effective in decreasing the incidence of cancer.

HIGH-RISK GROUPS

Chemoprophylaxis presents a unique challenge to health care professionals. By definition, chemoprophylaxis must be considered a health maintenance rather than a treatment issue. Since our role as health care providers usually involves the treatment of diagnosed disease, the scope of medical practice will have to be expanded.

To better target populations in whom chemoprophylaxis can be potentially useful, populations can be divided into different risk groups. There are groups at very high risk of developing cancer, such as families with familial polyposis who have a 100 percent chance of developing colon cancer. Other very high-risk groups consist of patients with cured lung or head and neck cancers, in whom the incidence of second malignancy can be as high as 5 percent per year. Lower but still high-risk groups include cigarette smokers and women with multiple relatives diagnosed as having breast cancer.

To prevent a specific cancer, one must be able to define a population at high risk for that cancer. An agent effective in preventing a rare cancer, for example, would have little

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value unless a specific high-risk group could be targeted. This is currently true for many cancers since risk factors have not been elucidated.

Defining the side effects of a given chemoprophylactic agent is also important and requires careful clinical investigation. Such agents are often administered to large populations for prolonged periods of time. The incidence and severity of side effects of a specific agent must be justified by its efficacy and the statistical risk of the target population.

Perception of Risk

Perception of risk for developing cancer among the target population greatly influences the success of any chemoprophylactic strategy. Perceived risk is usually not an issue that medical care practitioners consider. In the clinical setting, the patient is typically the initiator of the interaction. He or she approaches the medical community with a problem and seeks a diagnosis. Once a diagnosis is made, it is understood treatment will follow. On the other hand, those patients at risk for cancer who may be appropriate candidates for chemoprophylaxis may not be seeing a physician. The willingness of individuals to take a chemoprophylactic agent and tolerate potential side effects will directly relate to their perception of cancer risk. Those who perceive they are at risk and wish to take action will most likely adhere to a preventive regimen. Those who perceive little risk, regardless of their actual statistical risk, are unlikely to comply.

“Participants” vs “Patients”

Many clinical trials evaluating chemoprophylactic agents enroll individuals, or “participants,” who are healthy but at high risk of developing cancer. Such individuals, however, can be difficult to locate, since they often are not seeing a physician or health care provider. On the other hand, there are groups of “patients” who could potentially benefit from chemoprophylaxis. As opposed to participants, patients frequently see a physician and are well educated as to their risk. Those include patients with cured primary cancers such as acute leukemias, lymphomas, and small-cell and non-small-cell lung cancer. Many of these individuals are at high risk for developing a second malignancy because of prior treatment and/or underlying risk factors responsible for the original cancer. For these reasons, and because patients are relatively easy to recruit, initial trials of a chemoprophylactic agent will most likely enroll patients rather than participants. If the agent is found to be useful or active in a selected patient group, its application to a wider population may be indicated.

Carotene and Retinol Efficacy Trial

As opposed to patient trials, participant trials have major disadvantages. The Carotene and Retinol Efficacy Trial (CARET) illustrates some of the major problems of participant trials. This trial will evaluate the efficacy of oral beta-carotene 30 mg/day, and retinol, 25,000 U/day, in two groups at high risk for lung cancer: (1) men and women aged 50 to 69 years with a history of more than 20 pack-years and who are current smokers or exsmokers (quit less than 6 years ago); and (2) male asbestos workers aged 45 to 69 years who currently smoke or have stopped smoking within the past 15 years. The latter participants must have an occupational history of asbestos exposure (more than 15 years since first exposure) or have a chest x-ray compatible with asbestosis.

This trial will accrue 17,000 participants from six study centers nationwide. Accrual began in 1988, and the analysis of end points (lung cancer and death) is expected in 1998. As of April 1992, 11,000 participants have been randomly assigned to treatment. The disadvantages of participant trials like CARET are apparent. They require a very large number of participants. The planning, organization, and conduct of these trials frequently take more than 15 years. When one considers that lung cancer is a prevalent and rapidly fatal disease with clearly defined high-risk groups, it is apparent that conducting participant trials with other tumor types would be even more difficult.

Intermediate End Points

Short of treating only “patient” populations, it becomes important to better identify high-risk groups by means other than carcinogenic exposure or family history. To accomplish this, investigators have been looking more closely at the carcinogenic process. Genetic and cellular antigenic changes have been identified that may predate the histologic identification of a tumor cell. It is hoped that these intermediate end points can be used as surrogate end points for prevention trials and ultimately have clinical utility in identifying high-risk groups. Tockman et al. reported the accuracy of predicting lung cancer using immunostaining of cell surface antigens in the sputum of individuals in the Johns Hopkins Early Cancer Screening Trial. This study showed that cells expressing tumor-associated antigens could be identified in expectorated sputum up to 40 months before the clinical diagnosis of cancer. Investigators have identified other markers that may predate and predict the development of cancer.

The development of intermediate end points could change our approach to chemoprophylaxis. Screening high-risk groups would identify those individuals who have had molecular transformations known to predate cancer. These individuals could then be treated chemoprophylactically. Those patients who failed to show reversal of the abnormal markers could be switched to a different chemoprophylactic agent. Use of agents with higher efficacy but also high toxicity may be justified in patients having multiple transformations or in those not responding to less toxic agents. Molecular markers may enable us to more accurately select high-risk groups and chemoprophylactic groups of varying efficacy and side effect potential.

Conclusion

The elimination of tobacco use in our environment would greatly decrease the incidence of lung cancer. Barring achievement of this laudable goal, secondary prevention can be used to prevent lung cancer in individuals who have successfully quit smoking, as well as in those who are unable to stop. Screening for the presence of predictive cellular and molecular changes will enable us to select those individuals who truly require intervention with a chemoprophylactic agent.

REFERENCES

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