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# REVIEW ARTICLE

## Chemoprevention of head and neck cancer

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**Increasing emphasis has been placed on chemoprevention as understanding of the genetic and molecular events of carcinogenesis has evolved. More than 1000 compounds that inhibit cancer development in vitro or in animal models have been identified, and active research is under way to determine which of these agents will be both effective and nontoxic in human beings. Currently, 13-cis-retinoic acid is the most studied chemopreventive agent against head and neck cancers. Unfortunately, this vitamin A derivative has significant clinical toxicity, which limits its utility in a practice setting. The efficacy of the retinoids, however, has stimulated efforts to find other chemopreventive compounds that are both effective and nontoxic. This review discusses head and neck premalignancy, chemoprevention strategies, retinoids, and several other classes of chemopreventive agents with potential efficacy against head and neck premalignancy.** (Otolaryngol Head Neck Surg 2000;122:728-35.)

Except for the effects of combined chemotherapy and radiation therapy in increasing the survival of patients with nasopharyngeal cancer,[1] extensive efforts to improve cure rates for head and neck cancers have resulted in only modest improvement in overall survival in the last 20 years. Current treatment modalities of surgery, radiation therapy, and chemotherapy are limited in their success, and improvement in long-term cure rates with these modalities has reached a plateau. The major successes in treatment of head and neck cancer have been improved surgical reconstruction after radical resections and preservation of function by use of combined-modality treatments with elimination of radical surgical resection, such as with the organ-preservation protocols for laryngeal cancer.[2] Patients with early-stage head and neck cancers are often cured of their original tumor but have at least a 2% to 4% per year risk of developing a second malignancy of the aerodigestive tract and are more likely to die of it than of the original malignancy.[3-6] Clearly, if significant improvement in cure rates of head and neck cancer is to occur, new modalities must be explored.

Carcinogenesis is a multistep accumulation of genetic damage, for which the phenotypic end result is development of cancer.[7,8] Arrest or reversal of carcinogenesis in its infancy offers the opportunity to make a meaningful impact on cancer in the premalignant disease state or before development of a second tumor.[9,10] Chemoprevention of cancer is an expanding area of both clinical and basic science research, and head and neck cancer is an excellent model for study of chemoprevention because there are precursor lesions that can be identified and the response to interventions directly observed. This article will outline chemoprevention strategies and discuss the current status of and future directions for chemoprevention of head and neck cancer.

### EPIDEMIOLOGY OF HEAD AND NECK CANCER

Worldwide about 500,000 new head and neck cancers are diagnosed annually. In the United States, approximately 41,000 new cases of head and neck aerodigestive cancers and 12,500 deaths occur each year, roughly 4% of all cancers.[11,12] Tobacco use is the number one risk factor, and approximately 75% to 85% of patients with head and neck cancer have histories of significant alcohol and tobacco consumption.[11,13] Alcohol consumption is also a significant contributor to risk. Although by itself alcohol use roughly doubles the likelihood of cancer developing, it acts synergistically with tobacco. A person who consumes more than 20 cigarettes per day and ingests more than 2 drinks per day has between a 10- and 15-fold increased incidence of head and neck squamous cell carcinoma than a nondrinker and nonsmoker.[13]

The role of host susceptibility in cancer development is an area of active study. The mutagen sensitivity assay

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developed by Hsu et al[14] to measure host DNA repair capacity has been shown to provide a rough estimate of susceptibility to cancer development. Case-control studies and meta-analyses have demonstrated an association of increased cancer risk with elevated mutagen sensitivity, independent of age and tobacco or alcohol use.[15-18] Study of genetic polymorphisms of enzymes affecting uptake, processing, and removal of carcinogens is also providing information about cancer susceptibility.[17] Cytochrome P450, glutathione S transferase, and *N*-acetyltransferase are examples of enzymes under active investigation to determine their usefulness as predictors of the likelihood of malignancy developing in an individual.[19,20] The goal of research in this area is to better identify those persons likely to eventually have cancer and to more precisely direct screening and prevention efforts in the future. Several other identified risk factors are listed in Table 1.

**Table 1.** Risk and protective factors for head and neck cancer

| |
|---|
| Risk factors |
| Tobacco, smokeless tobacco |
| Alcohol |
| Betel nuts |
| Human papilloma virus |
| Marijuana |
| Nickel refining |
| Woodworking |
| Textile fibers |
| Asbestos (larynx) |
| Mutagen sensitivity |
| Genetic susceptibility markers |
| Cytochrome P450-1A1 |
| Glutathione S transferase |
| *N*-acetyltransferase |
| Epoxide hydrolase |
| Protective factors |
| Dietary carotenoids |
| Fruit and vegetable consumption |

## ORAL PREMALIGNANT LESIONS

The most common premalignant lesion seen is leukoplakia, defined simply as a white patch that cannot be wiped away and does not represent other known processes.[21] Histologically, leukoplakia is represented by a number of findings, ranging in severity from hyperkeratosis to full-thickness epithelial dysplasia. Because the clinical appearance does not reliably predict the histologic appearance, biopsy of these lesions is mandatory to detect dysplasia, carcinoma in situ, or invasive carcinoma. The second, less common and more ominous lesion is erythroplakia, a red (often velvety-appearing) lesion that often contains leukoplakic areas in and/or around the erythroplastic component. Silverman et al[22] studied a large number of patients with leukoplakia and erythroplakia in the dental clinics at the University of California, San Francisco, and reported long-term follow-up in 257 patients evaluated for an average of 7.2 years. In this population, squamous cell carcinoma developed in 17.5% of patients with oral leukoplakia/erythroplakia during a mean follow-up period of 8.1 years. The two most significant risk factors for malignant transformation were cellular dysplasia and erythroplakia. During an 8-year mean follow-up period, the presence of dysplasia was associated with a 36% risk of malignant transformation, and the presence of erythroplakia was associated with a 23% risk factor for malignant transformation. Erythroplakia and dysplasia were highly correlated, with the great majority of patients with erythroplastic changes having coexistent dysplasia. Evaluation of smoking status revealed that nonsmokers with oral leukoplakia/erythroplakia had a higher incidence of malignant transformation than smokers in their population.[22,23]

## SECOND PRIMARY TUMORS

The single greatest risk factor for development of head and neck squamous cell carcinoma is a history of a previous head and neck cancer. The incidence of second primary tumors is at least 2% to 4% per year, and this risk persists for at least 10 years.[3-5,24] Patients with stage I and II cancer of the head and neck are more likely to die of a second primary tumor than of recurrence of the original cancer. Slaughter et al[25] studied clinically normal tissue adjacent to histologically proven head and neck cancers and identified many of the histologic changes seen in the malignant cells in the adjacent "normal" tissue, leading him to propose the concept of "field cancerization." Subsequent study of the molecular genetics of head and neck carcinogenesis has provided a molecular explanation for Slaughter's observations.[7,26] Bedi et al[26] studied female patients with multiple primary head and neck cancers. They examined X-chromosome inactivation and performed microsatellite analysis to evaluate allelic loss at chromosomes 3p and 9p, two sites damaged early in the course of progression to malignancy. Their work confirmed that both the original cancer and the second malignancy arose from a single clone. Califano et al[7] similarly observed that tissues adjacent to malignant and premalignant lesions shared common genetic changes. It appears that multiple tumors do not arise from multiple transforming events, but instead a single transforming event produces a cell with growth advantage over its neighbors and spreads throughout the mucosal surface. The tumor may accumulate further genetic damage, developing into malig-

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**Table 2.** Agents with potential chemopreventive activity against head and neck cancer

| |
|---|
| Carotenoids |
| Retinoids |
| Nonsteroidal anti-inflammatory agents |
| Vitamin E (α-tocopherol) |
| α-Interferon |
| Polyphenols (green tea) |
| Protease inhibitors (soy) |

nancies that are geographically distinct in location but are genetically related.[26]

Prevention of second primary tumors is an excellent area for chemoprevention research and has the potential to make a major impact on long-term survival. Several large-scale studies of chemopreventive agents for second primary tumors have been conducted and are discussed below.

## CHEMOPREVENTION

Chemoprevention can be defined as "the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy."[27] Epidemiologic evidence supports the concept that dietary compounds in nature have a protective effect against a number of cancers.[28,29] In numerous studies increased consumption of fruits and vegetables, maintenance of a low-fat diet, and increased fiber consumption were associated with a protective effect.[28,29] Proceeding from the recognition that dietary habits are correlated with lowering the incidence of cancer to the identification of specific compounds causing the effect has been a difficult task. More than 1000 potential chemopreventive agents have been identified in dietary sources, and many are being tested in in vitro and in vivo systems with a variety of cancers.[30] Some of the most thoroughly studied agents with potential or demonstrated activity against head and neck premalignancy are listed in Table 2.

Identification and testing of a successful chemopreventive agent is a long process, requiring in vitro studies, animal efficacy and toxicity studies, and eventually, lengthy human clinical trials. The process parallels that of treatment drug development, with the added requirement that the toxicity of the compound be minimal because the agent is being used to prevent occurrence of a potential future event or to regress a preneoplasia. Study of these compounds is complicated in that the ultimate end point is prevention of cancer development. Progression from normal tissue to invasive cancer is a multistep process occurring over many years.[9,10,31] Promising agents are first evaluated in phase I toxicity studies. Once safety is demonstrated, short-term (weeks) and intermediate-term (months) phase II efficacy studies are conducted. Successful agents can then be tested in long-term phase III efficacy trials. These studies are multiyear in length, and generally multi-institutional studies with long-term follow-up designed to determine whether there is a statistically significant change in incidence (and survival) of the cancer of interest.[32]

In an effort to better focus precious resources in the study of chemoprevention, surrogate end points for the development of cancer have been used in prevention studies to identify potential agents for further study. These markers represent a broad variety of changes in cells and tissues that are believed to correlate with the development of cancer. Examples of surrogate end points include clinical response of premalignant lesions, histologic regression, genomic markers such as the presence of micronuclei in cells, alteration or change of genetic markers such as the products of oncogenes and tumor-suppressor genes, presence of markers of cellular differentiation, and markers of apoptosis. Measurement of these biomarkers and changes in their levels are used to screen for effective compounds.[33,34] Although the relationship of these markers to cancer has not been proved conclusively, there are currently no better methods to screen potential agents.[4] If a compound is shown to have favorable effects on a marker, with an acceptable toxicity profile, the agent should be tested clinically to determine efficacy.

## CLASSES OF CHEMOPREVENTIVE AGENTS

Of the numerous potential chemopreventive agents, only a relative few have been studied in head and neck premalignancies. Classes of agents that have undergone testing for head and neck premalignancy in animal and or human studies are summarized below.

### Carotenoids

Carotenoids are a class of plant-derived compounds that are precursor molecules to vitamin A and are found in high quantities in green and yellow leafy vegetables. β-Carotene is the most plentiful of the carotenoids and is cleaved to form 2 molecules of retinol (vitamin A). Carotenoids have a number of activities that may underlie potential chemopreventive activity, including antioxidant activity, an immunoenhancing effect, and retinoid properties (by conversion to retinol).[35] The carotenoids are relatively nontoxic, with the most common side effect being the yellow discoloration of the skin. A number of trials of β-carotene for oral leukoplakia have been published, but only 2 were randomized.[36,37] Stich et al[36] studied 130 betel nut quid chewers in India and

compared cancer rates in groups of patients administered β-carotene plus retinol (vitamin A), β-carotene alone, or placebo 2 times per week for 6 months. They found a 27.5% complete remission rate with the combination of β-carotene and retinol, 14.8% with beta-carotene alone, and 3% with placebo. It is not clear how much of the effect was due to replenishment of vitamin A and β-carotene in a population with deficiency of these nutrients and whether these findings would be applicable to Western populations. Zaridze et al[37] found that the combination of retinol, β-carotene, and vitamin E decreased the prevalence of oral leukoplakia by approximately 40% compared with placebo in a 6-month trial conducted in Uzbekistan (odds ratio = 0.62).

Promising early results with β-carotene for chemoprevention of tumors at other body sites have not been confirmed in a number of larger randomized trials. In the 12-year Physicians Health Study of 22,071 male physicians randomly assigned to receive either β-carotene or placebo, β-carotene failed to alter the incidence of lung cancer or the number of deaths from cancer, cardiovascular disease, or any other causes.[38] Unfortunately, β-carotene, thought to be an innocuous compound, recently has been viewed with concern because of 2 studies showing an increased incidence of lung cancer in populations of smokers receiving pharmacologic doses of the compound.[39-41] The reason for the increase in lung cancers in smokers in these trials is not known but does highlight the fact that seemingly safe dietary substances administered in pharmacologic doses must be regarded as potentially toxic. Enthusiasm for β-carotene has also been tempered by the negative results of several other randomized trials for other types of cancer, including skin cancer,[42] colon polyps,[43] and cervical intraepithelial neoplasia,[44] in which β-carotene had no effect. To date, β-carotene has not been tested in a large randomized trial using either changes in premalignant lesions or appearance of second aerodigestive malignancies as end points.

### Retinoids

Vitamin A and its natural counterparts play a critical role in differentiation, development, and growth of epithelial cells, and they may have chemopreventive effects in both animal and human trials.[45,46] The effects of vitamin A are mediated through a family of nuclear retinoic acid receptors, which are members of the steroid receptor superfamily. Retinoids bind to these retinoic acid receptors and mediate gene expression. In oral premalignant lesions, expression of retinoic acid receptors is markedly decreased.[47,48] Furthermore, oral administration of 13-cis-retinoic acid (13-cRA; Isotretinoin, Accutane) restored expression of these receptors, which correlated with clinical regression of the oral leukoplakia lesions.[47]

13-cRA has been studied extensively in oral leukoplakia.[4,49] In randomized placebo-controlled clinical trials, 13-cRA has shown encouraging results against oral premalignant lesions. Hong et al[49] completed the first major human trial of 13-cRA in 1986. This group conducted a 3-month placebo-controlled randomized trial of 13-cRA and demonstrated a 67% response rate of oral leukoplakia in the treatment arm versus 10% response for the placebo group. Unfortunately, the drug had significant side effects, including dry skin and conjunctivitis, that limited patient tolerability. Also, 3 months after discontinuation of study medication, the mucosal lesions returned in half of the patients receiving 13-cRA. Natural vitamin A (retinol) has also been studied and has been shown to have significant effects in oral leukoplakia. Stich et al[36] studied β-carotene and vitamin A in a prospective clinical trial and demonstrated a 27.5% complete regression after twice weekly administration of β-carotene and vitamin A for 6 months compared with 3% for the placebo group. These trials demonstrated improvement of premalignant lesions, but to date, no trial has demonstrated the prevention of invasive head and neck cancer or improved survival.

In patients with prior head and neck cancer, 13-cRA has been shown to prevent second primary tumors in patients with prior head and neck cancers.[50] Hong's group found that patients treated with 13-cRA for 12 months had a decrease in second primary tumors in the lung and upper aerodigestive tract (24% in the control group, 4% in the treated group) after 32 months ($P$ = 0.005).[50,51] After 55 months of follow-up, the results were still favorable for the treatment arm (7% vs 33%, p = 0.008). Because the study included mostly patients with advanced stage III or IV disease, they were unable to demonstrate a survival benefit. However, toxicity of the dose of 13-cRA used was severe in this study. Hong's group is now conducting a long-term, low-dose study of 13-cRA for prevention of second primary tumors. Their current study design has been modified to include only stage I and II cancers, the drug dose has been lowered from 50-100 mg/day to 30 mg/day, and the treatment duration has been increased to 3 years.

Although retinoids have shown significant effects, they have several major drawbacks. First, available compounds are toxic at therapeutic levels, causing dry skin, mucositis, conjunctivitis, appetite loss, malaise, and hypertriglyceridemia.[46,49] 13-cRA is also highly teratogenic and cannot be used safely in women of child-bearing age. Furthermore, lesions frequently recur after the drug is stopped, implying that the user will require lifetime treatment for protection.[46,49] These

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properties make retinoids less than ideal chemopreventive agents. Nevertheless, in the head and neck region, retinoids are the most studied agents so far and are currently the gold standard to which other agents should be compared. Numerous synthetic retinoic acid derivatives are under development, and the hope is that these derivatives may be able to provide similar efficacy to 13-cRA with fewer side effects. Chiesa et al[52] evaluated 4-hydroxyphenyl retinamide (fenretinide) in 153 randomly grouped patients with oral leukoplakia who were treated after surgical excision of their leukoplakia lesions. Six percent of the patients in the treatment arm had a return of leukoplakia at the site of excision or development of new lesions, whereas the failure rate in the control arm was 30%.[52,53] Another synthetic retinoid, retinamide, also produced similar outcomes in a randomized trial involving 61 subjects.[54]

Another strategy to lower side effects is to combine other agents with lower doses of retinoids without affecting efficacy. An example of such combination therapy is the ongoing EUROSCAN phase III clinical trial of retinyl palmitate and *N*-acetylcysteine to prevent second primary head and neck cancers.[55] Another example is the investigation currently under way at MD Anderson Cancer Center of vitamin E and α-interferon with isotretinoin as adjuvant therapy to prevent tumor recurrence and second primary tumors in stage III and IV head and neck squamous cell carcinoma.[56] Nevertheless, there is active interest in finding alternative agents that are effective and have fewer side effects than retinoids.

### Other Chemopreventive Agents

A number of other chemopreventive agents have potential for use in preventing head and neck cancer; however, most of these agents have not been studied in detail. Many of these agents are in the preclinical testing stage; however, epigallocatechin from green tea, vitamin E, α-interferon, nonsteroidal anti-inflammatory agents, and protease inhibitors is either in or ready for human clinical trials.

**Green tea.** Recently, there has been interest in studying compounds found in green and black tea for their potential chemopreventive effects against premalignant lesions.[57,58] Green tea contains polyphenols, which have demonstrated chemopreventive effects in animal studies.[57,59-62] The Indian-US Head and Neck Cancer Cooperative Group conducted a feasibility study of green tea for chemoprevention of oral premalignant lesions in India.[58] The investigators reported good compliance during the 6-month trial, leading the group to propose a long-term population-based collaborative study of green tea for head and neck premalignant lesions.

**Vitamin E.** Several clinical trials incorporating vitamin E (α-tocopherol) either alone, or more commonly with other agents such as β-carotene and vitamin A derivatives, have shown clinical activity against leukoplakia.[36,37,63] Although these encouraging preliminary results suggest a possible role for vitamin E in chemoprevention, most of the studies to date used other chemopreventive agents, and the relative contribution from vitamin E to observed preventive effect is not well defined. However, one prospective phase II study of 400 IU of α-tocopherol administered twice daily demonstrated a 46% clinical response and a 21% histologic response after 24 weeks of treatment.[63] Further studies of vitamin E alone would be necessary to better define its effectiveness as a sole chemopreventive agent.

**Nonsteroidal anti-inflammatory agents.** Nonsteroidal anti-inflammatory drugs (NSAIDs) have recently received revived interest for their possible anticarcinogenic potential.[64,65] Prostaglandins and leukotrienes, products of arachidonic acid metabolism, influence a number of cellular processes, and administration of prostaglandins has been shown to promote tumor growth in animal models.[66,67] Conversely, administration of indomethacin has been associated with clinically observed tumor regression in head and neck squamous cell carcinoma,[65,68] cutaneous squamous cell carcinoma,[69] and breast cancer.[70] In several studies including the Nurse's Health Study, aspirin and other NSAIDs have been associated with a decreased risk for colon cancer.[71-74] Observations of head and neck cancer regression after administration of NSAIDs and a better understanding of arachidonic acid metabolic pathways have stimulated interest in the potential for NSAIDs.

Early in vitro studies of NSAIDs for the prevention of head and neck cancer demonstrate the potential utility of these agents. Recent work by Michaluart et al[75] has shown that tumor promoters can induce the cyclooxygenase pathway at least in part at the transcriptional level, and this correlates with increased levels of the COX II enzyme and PGE 2 in oral mucosal cells. Because the side effects of NSAIDs may in part reflect effects of COX I, inhibition by specific COX II inhibitors may be a useful chemoprevention strategy. Spingarn et al[67] have recently shown synergy between 13-cRA and arachidonic acid inhibitors on in vitro head and neck cancer cell growth. Although these studies are encouraging, much more work needs to be done, and these agents need further testing in animal models to further demonstrate their potential.

**Protease inhibitors.** Protease inhibitors are a group

of serine proteases with demonstrated cancer chemopreventive activity in a number of in vitro and in vivo models. These proteins are found in high quantities in legumes, especially soybeans.[76,77] Evidence for protease inhibitors as chemopreventive agents arose from epidemiologic observation of decreased incidence of colon, breast, and prostate cancers in populations with high soybean intake.[77,78] Several agents present in soybeans have been found to have anticarcinogenic potential, including isoflavones (genestein and daidzein), saponins, inositol hexaphosphate (phytic acid), and the protease inhibitor Bowman-Birk inhibitor (BBI).[79,80] Although the soybean isoflavones have received the most study, Kennedy and Manzone[79,81] have demonstrated that on a molar basis, BBI is more potent than any of the other anticarcinogenic compounds identified in soybeans. This has led them to hypothesize that BBI may be responsible for a significant proportion of the anticarcinogenic effects of soybeans in the diet.

BBI has been studied in 3 different animal models (mice, rats, and hamsters) and has anticarcinogenic effects against colon, liver, lung, esophageal, oral epithelial, and hematopoietic cancers.[81] An extract of soybeans, BBI concentrate (BBIC), which contains active BBI, has been developed for human trials and has the same activity spectrum and side effects as purified BBI. A phase I chemoprevention trial has shown that BBIC, when administered as a mouthwash, had no toxicity.[82] Currently, a phase II trial is evaluating the clinical effect, toxicity, and effects on biomarkers of BBIC on patients with oral leukoplakia (Armstrong W, unpublished data, 1999).

## SUMMARY

Interest in chemoprevention has increased in recent years in parallel with an increased understanding of oncogenesis. Traditional treatments for cancer (surgery, radiation therapy, and chemotherapy) have reached a plateau in their effectiveness against epithelial cancers of the head and neck. An improved understanding of the process of oncogenesis has led to strategies that take advantage of the mechanisms involved in the development of cancer. Oncogenesis is a multistep process occurring over a number of years, and in the head and neck the entire mucosal surface is exposed to carcinogenic agents (field cancerization). Chemoprevention provides an opportunity to arrest and reverse neoplastic progression before invasive carcinoma develops. In the head and neck region, retinoids have shown promise as chemopreventive agents, but they produce significant side effects, making them less than ideal chemopreventive agents. Several other agents have a significant potential to become safe, effective alternatives to the retinoids and are under active investigation.

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