

UC Irvine

UC Irvine Previously Published Works

Title

Retinoids and carotenoids in the prevention of oral cancer: a critical appraisal.

Permalink

<https://escholarship.org/uc/item/5kh5d5p0>

Journal

Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 1(2)

ISSN

1055-9965

Authors

Garewal, H S
Meyskens, F, Jr

Publication Date

2014-12-23

Peer reviewed

Review

Retinoids and Carotenoids in the Prevention of Oral Cancer: A Critical Appraisal¹

Harinder S. Garewal² and Frank Meyskens, Jr.³

Section of Hematology-Oncology, Tucson VA Medical Center, Tucson, Arizona 85723

Introduction

The term "oral cancer" refers to malignant tumors arising in the oral and oropharyngeal mucosa, including those of the tongue and lips. Squamous cancers account for over 90% of oral cancer. Internationally, oral and pharyngeal cancers constitute the sixth commonest site in both sexes combined (1). The highest reported incidences occur in parts of South and Southeast Asia, Brazil, and other developing countries, where up to 25% of all cancers are found in the oral cavity (2, 3). Recently, increases in some types of oral cancer have been noted in Scandinavia, the United States, and Scotland, especially among younger males (4-6). In the United States approximately 30,000 new cases occur annually, resulting in about 9,000 deaths (7). This variation in regional incidence has been related to known etiological agents, the most important of which are tobacco and alcohol. In developing countries, tobacco and betel nut chewing, often mixed with other substances such as slaked lime, are responsible for most cases of this disease (8).

Although management of oral cavity cancers has improved, there is little to no evidence that treatment has resulted in an increased survival rate. Patients who present with advanced disease and local metastases have a 5-year survival of about 30%. Unfortunately, most patients are diagnosed late, even with easily detectable lesions such as those of the lip or tongue. Early tumors have a high cure rate by radiotherapy and/or surgery. More advanced cancers have traditionally been treated by radiation, neoadjuvant chemotherapy, and/or surgery. Although producing rather dramatic responses in the range of 50-85%, neoadjuvant chemotherapy has not changed overall patient survival. The major causes of death of advanced-disease patients include local recurrence (about 50-60%), distant metastasis usually accompanying local recurrence (20-30%), and, especially for early-stage patients cured of their initial lesion, development of second primary tumors (10-40%) (9, 10). The latter has been attributed to the concept of "field cancerization," presumably by exposure to carcinogens lead-

ing to tumor formation in the epithelium of the upper aerodigestive tract (11).

As stated in a recent editorial in *Lancet*, "Prevention is likely to prove the most fruitful avenue in reducing the morbidity and mortality from oral cancer" (12). This statement is based on the rather well-defined etiological associations with respect to tobacco use, betel quid chewing, and alcohol consumption. Furthermore, considerable recent evidence suggests a role for nutritional agents, particularly those related to vitamin A (retinoids and carotenoids), in the inhibition of oral carcinogenesis. In fact, intervention trials with these compounds in subjects at risk for oral cancer have produced some of the most promising data on the potential for cancer chemoprevention.

The epidemiological and biological evidence of a role for these agents in the inhibition of upper aerodigestive tract carcinogenesis has been the subject of recent reviews (13, 14). Similarly, experiments using animal models also have shown a marked inhibitory effect on oral carcinogenesis, especially in the hamster cheek pouch model system (15-17). In this review we will concentrate mainly on human intervention trials conducted in individuals at high risk for oral cancer. A number of such studies describing improvement in putative "intermediate markers" of cancer development or reversal or inhibition of premalignant lesions have been reported over the past several years. The results indicate that vitamin A-related compounds may indeed have a role in the prevention of this malignancy.

Intermediate Marker Studies. A number of intermediate markers of potential use in defining high-risk populations are under study. These include micronucleated exfoliated cells, specific cytokeratin expression, proliferation indices, growth factor expression, transglutaminase, involucrin, and oncogene expression. Of all these, only the frequency of micronucleated exfoliated cells has so far been reported in published intervention trials. Micronucleated oral mucosal cells are considered to be indicative of genotoxic damage induced by carcinogens (18). Their frequency has been increased in individuals at increased risk of cancer, particularly in studies conducted in India and Southeast Asia, where betel nut, tobacco, and lime chewing are prevalent (18). Orally administered β -carotene, especially when given in conjunction with vitamin A, reduced the proportion of micronucleated cells from mucosa containing premalignant lesions (18, 19). This reduction can be demonstrated within a few weeks of beginning therapy and was sustained during the course of treatment. At present, however, there are no studies clearly linking the reduction in frequency of micronuclei to the reversal of premalignant lesions or prevention of cancer.

Received 4/16/91.

¹ Supported in part by USPHS Grant CA27502 and a Career Development Award from the American Cancer Society (H. S. G.).

² To whom requests for reprints should be addressed, at Section of Hematology-Oncology (111D), Tucson VA Medical Center, 3601 S. 6th Avenue, Tucson, AZ 85723.

³ Present address: UCI Cancer Center, 101 The City Drive, Building 44, Route 81, Orange, CA 92668.

Studies in Premalignant Lesions. The development of cancer occurs through several steps involving initiation, promotion, and progression to malignancy. Premalignant lesions are the first clinically identifiable lesions along this pathway. Therefore, the search for interventions causing reversal or suppression of premalignant lesions constitutes an important strategy for cancer prevention, e.g., reduction in incidence or removal of colonic polyps as a preventive approach for colon cancer.

We should emphasize at this point that the ultimate goal of this strategy is to develop interventions applicable to the prevention of cancer and not merely to eradicate premalignant lesions. In general, the latter are not lethal or even morbid by themselves and are associated with rather low rates of transformation to cancer. Therefore, it is imperative that any agents selected on the basis of trials in premalignant lesions that are likely to prove worthwhile for cancer prevention have minimal, or preferably no toxicity, since a large number of subjects whose lesions are unlikely to progress to cancer will necessarily be exposed to the intervention. Clearly, the types and amount of side effects considered acceptable for any therapy depend on the severity of the condition being treated. High levels of toxicity are quite acceptable in treatments for overt malignancy. Similarly, a moderate degree of toxicity can be tolerated for some premalignant diseases such as familial polyposis of the colon which are associated with a very high cancer risk. However, for the majority of the more common premalignant lesions, the cancer risk is often very low, and almost any side effects produced by a drug will generally be unacceptable.

The majority of oral cavity premalignant lesions come under the category of leukoplakia, i.e., a white patch or plaque on the mucosa that cannot be rubbed off and is not attributable to a specific disease entity. In general, they have a rather low malignant potential (20). Oral erythroplakia and speckled leukoplakia have a higher transformation rate but are relatively rare lesions. Similarly, the presence of severe dysplasia demands a more aggressive treatment strategy (20).

The ultimate objectives of intervention trials involving leukoplakia must therefore be kept in mind when designing chemoprevention studies. If the objective is to develop a treatment applicable to a small minority of patients with erythroplakia and/or high-grade dysplasia that are not amenable to standard treatments such as reduction in local irritants, surgical excision, or cryosurgery, then some degree of toxicity in the therapy may be acceptable. In this category would be the use of agents such as topical bleomycin and 5-fluorouracil, which have

been shown to be effective (21). However, if the objective is to develop agents for generalized, population-based use for the primary prevention of oral cancer, then clearly such agents are not practical.

Retinoid and Carotenoid Trials in Leukoplakia

Several trials have been conducted demonstrating the efficacy of various retinoids, both natural and synthetic, in reversing leukoplakia. In earlier studies Koch (22, 23) showed that 13-*cis*-retinoic acid, *trans*-retinoic acid, and etretinate each could produce objective responses in 60–90% of patients. The treatment was associated with considerable (particularly mucocutaneous) toxicity, with frequent relapses after therapy was discontinued. Results of more recent trials are summarized in Table 1. Shah *et al.* (24) also reported a high response rate (82%) in 11 patients treated with 13-*cis*-retinoic acid lozenges. It is of interest that 16 patients were entered on this trial, but five could not complete the treatment, with three stopping because of toxicity. (One of five showed carcinoma *in situ* of the lip along with leukoplakia of the tongue and was considered inevaluable. No change in the tongue lesion was noted during 7 weeks of treatment in this patient.) Therefore, the total response rate based on 16 entered patients was nine of 11 evaluable (82%) or perhaps more correctly nine of 16 treated (56%). Of the three patients with complete response, a follow-up biopsy showed normal epithelium with residual leukoplakic changes in a single microscopic focus in one patient, another showed improvement of leukoplakia to normal epithelium, while the remaining case showed hyperkeratosis only. Varying histological findings in the six patients with partial responses were also reported.

In a randomized, double-blind, controlled trial of 13-*cis*-retinoic acid in 44 patients, a response rate of 67% (8% complete, 59% partial response) was reported in 24 patients in the treatment arm versus two partial responses in 20 patients (10%) in the placebo arm (25). Mucocutaneous toxicity including cheilitis, facial erythema, and dryness and peeling of the skin occurred in 79% and conjunctivitis in 54% of patients in the treatment arm. These results compared with 20% or less reported side effects in the placebo arm, emphasizing the problems and futility of “blinded” randomized trials of toxic drugs versus placebo or other nontoxic agents.

“Histological responses” were reported in 39 of the 44 patients entered in whom pretreatment and posttreatment biopsy specimens had been obtained. Dysplasia was “reversed” in 13 of 24 (54%) of patients in the 13-

Table 1 Recent retinoid/carotenoid trials in oral leukoplakia

Investigator (Ref.)	Agent	No. of patients	CR ^a %	PR %	OR %	Country
Shah <i>et al.</i> (24)	13-cRA (lozenges)	11 (16) ^b	27 (19)	55 (37)	82 (56)	United States
Hong <i>et al.</i> (25)	13-cRA	24	8	59	67	United States
Stich <i>et al.</i> (19) ^c	BC	27	15	NS	NS	India
	BC + Vit A	51	27	NS	NS	
Stich <i>et al.</i> (26) ^c	Vit A	21	57	NS	NS	India
Garewal <i>et al.</i> (27)	BC	24	8	63	71	United States

^a CR, complete remission; NS, not stated; PR, partial response; OR, overall response; 13-cRA, 13-*cis*-retinoic acid; BC, β -carotene.

^b Numbers in parentheses are results based on patients entered (see text).

^c Only complete remission rate reported.

cis-retinoic acid group, as compared with 10% (2 of 20) in the placebo group. However, close scrutiny of the reported histological change data (Ref. 25, Fig. 3) shows that in the placebo arm the majority of patients with pretreatment and posttreatment biopsies were in the atypical hyperplasia (*i.e.*, free of dysplasia) category and remained so at the end of treatment. Only five patients had dysplasia on their pretreatment biopsy, with three remaining in the same severity category, two showing improvement (including one severely dysplastic becoming nondysplastic), and one showing worsening. In addition, two patients without dysplasia on pretreatment biopsy reportedly had dysplasia on their posttreatment biopsy. Also, a larger number of patients in the treatment group (15) had dysplasia compared with the placebo group (8). As discussed further below, one must be cautious in interpreting "improvement" in histology because this may merely reflect sampling error, especially in the partial responders, which constituted the vast majority of responding patients in this trial.

Stich *et al.* (19, 26) have conducted a series of trials in India using vitamin A alone or in combination with β -carotene. It should be emphasized that this study population is different from that enrolled in other trials, since the majority of lesions here result from tobacco and betel quid chewing. Nevertheless, from a worldwide perspective, these studies are particularly relevant, since they are being conducted in countries where the disease is a major health problem. In one trial treatment consisted of β -carotene (180 mg/week) (group I), β -carotene (180 mg/week) plus vitamin A (100,000 IU/week) (group II), and placebo (group III) given twice weekly for 6 months (19). After 6 months of treatment complete remission of leukoplakias was observed in 15% of patients in group I, 27% in group II, and only 3% in group III. Similarly, development of new leukoplakias during the 6-month period was strongly inhibited in group II (8%) and inhibited to a lesser degree in group I (15%) in comparison with group III (21%). In a second trial by the same investigators, subjects were randomly divided into two groups, one receiving 200,000 IU of vitamin A/week for 6 months and the other receiving placebo (26). A 57% complete remission rate was observed in the vitamin A group with total suppression of the development of new leukoplakias. In contrast a 3% complete remission and 21% new lesion rate in the placebo group were observed. Biopsies were performed at the beginning and the end of treatment in this second trial. Improvement in various histological criteria such as number of layers of spinous cells, loss of polarity of basal cells, and subepidermal lymphocytic infiltration was significant in the vitamin A-treated but not in the placebo group.

In a pilot study conducted by our group, a response rate of approximately 70% (8% complete, 63% partial response) was observed in 24 patients treated with β -carotene at a dose of 30 mg/day (27). A majority of the patients used tobacco and/or alcohol. Biopsies of all lesions were done at entry, with dysplasia present in 11 of the 24 subjects. Follow-up biopsies were not performed in this preliminary trial.

In interpreting the above trials as well as developing a strategy for the chemoprevention of oral cancer several issues need to be kept in proper perspective. Some of the more important ones are briefly discussed below.

Clinical Response Criteria. Leukoplakia is a lesion that can be directly visualized. Therefore, marked improvement and thinning of the lesion are often apparent on visual examination but are difficult to quantitate in a manner similar to that usually used in therapeutic trials of anticancer agents, where often the responding lesion is visualized and measured on a radiograph or other scanning modality. Therefore, although we and others (*e.g.*, Ref. 25) have tried to apply the standard 50% reduction in the product of the two longest diameters of lesions to define so-called partial responses, this is by no means easy to do with any degree of precision in a disease such as leukoplakia in which a response may clearly be evident but difficult to measure.

One approach is to consider only complete responses in the evaluation of leukoplakia trials. This approach has been taken in the studies reported by Stich *et al.* (19, 26) with β -carotene and vitamin A. If this is done, then the response rates of β -carotene in our trial (8%), 13-*cis*-retinoic acid in the trial by Hong *et al.* (8%), and β -carotene alone observed by Stich *et al.* (15%) are quite similar. Higher complete response rates of 27% with β -carotene in combination with 100,000 IU/week of vitamin A and 57% using 200,000 IU of vitamin A were reported by Stich *et al.* (19, 26). Adopting this approach of estimating complete response only does have the risk of discarding potentially valuable modalities in short-duration trials since, even though they are difficult to quantitate, many lesions do improve dramatically, and this may signify considerable activity by the agent being tested.

Histological Response. The interpretation of so-called histological responses deserves considerable scrutiny. It is known that dysplasia or other histological abnormalities are not evenly distributed throughout premalignant or other lesions, including those of the oral cavity. In other precancerous conditions such as ulcerative colitis, Barrett's esophagus, esophageal dysplasia, and cervical dysplasia, it is well established that the distribution of dysplastic changes is patchy, with respect not only to their presence or absence but also to their degree (28, 29). In addition, there is considerable intra- and interobserver variability in quantitating the degree of such change in an individual biopsy (28). Therefore, comparing two biopsies often taken weeks to months apart, with the objective of comparing the degree of dysplasia, is an approach potentially subject to serious error. This is not to say that follow-up biopsies are of no utility at all. Their greatest usefulness lies in the setting of complete clinical response where it would be important to show that epithelial maturation has also normalized at the histological level. Patients with partial or no clinical response to treatment that are alleged to have improved histologically in their degree of dysplasia may perhaps be acceptable if this improvement is demonstrated in a series of follow-up biopsies that show few to no "oscillations" of dysplasia grades from biopsy to biopsy. Otherwise, changes from a single pretreatment biopsy to a single follow-up post-treatment biopsy will most probably reflect sampling and interpretation error rather than a true change in the grade of dysplasia.

Recognizing these difficulties with quantitating changes in hyperplasia and dysplasia, Stich *et al.* (26) in their recent publications have attempted to develop other histological and cytological criteria. These too need

to be validated before they can be accepted as response criteria on their own. Another approach that has been applied to some organs, such as the stomach or the colon, would involve doing multiple biopsies at each evaluation visit and comparing the composite scores of several biopsy readings to try and reduce the effect of sampling. However, because of the nature and location of oral cavity lesions, this is not generally feasible for most patients entered into oral leukoplakia trials.

Suitability of Agents for Chemoprevention. Prevention and treatment are two different goals in the control of cancer. Potential chemopreventive agents must have properties that are not necessarily required for drugs used in advanced cancer. They must be essentially nontoxic to be acceptable for widespread use. Availability of a chemopreventive agent as a nutrient has a definite advantage, since it allows consideration of supplementation by dietary adjustments. Finally, the cost of the agent should not be totally prohibitive for use in underdeveloped countries, which face the most serious problems with oral cancer.

With the above considerations in mind, it is evident that toxic agents such as bleomycin, 13-*cis*-retinoic acid, and *trans*-retinoic acid, even if active, are not suitable for use except in the rare case with severe dysplasia that is not amenable to treatment by presently available techniques. At the doses used, these retinoids produce dermatological, hepatic, and other side effects too severe for general population use. Their teratogenicity, even at lower doses, is also a serious problem. Perhaps similar considerations apply to higher doses of vitamin A. Although Stich *et al.* report no toxicity at the 200,000 IU/day dose that has produced the highest complete response rate (57%) reported to date, it should be emphasized that only a small number of patients were treated and no results of liver function tests, serum lipids, and other biochemical measurements were reported. In addition, these trials were conducted in a population that is probably deficient in vitamin A. β -Carotene, on the other hand, does fulfill all the criteria for a suitable chemopreventive agent in that it is nontoxic, it is relatively inexpensive, and it is a nutrient.

Future Directions

From currently available data, both vitamin A and β -carotene appear to have some activity in reducing the frequency of micronucleated exfoliated oral cells and in the reversal and suppression of leukoplakia. Although β -carotene appears to have some activity on its own, the trials conducted by Stich *et al.* suggest that the combination of this agent with low doses of vitamin A may result in a greater complete response rate. It should be noted, however, that a biweekly dosing schedule was used in these trials because of practical considerations rather than the usual daily doses used in trials conducted by other groups. Owing to the known toxicities of vitamin A, especially when used over a prolonged period of time at doses in excess of about 25,000 IU/day, caution must be exercised when selecting a dose for use in chemoprevention trials. Vitamin E is another relatively nontoxic agent that is effective in animal models (17, 30). No clinical trials with vitamin E have been reported to date.

Target populations suitable for screening trials include not only those subjects with leukoplakia but also

patients who have been cured of their primary head and neck cancer. Most patients with early cancer are cured by current treatment modalities but are at a high risk for second primary neoplasms. Agents active in reversing preneoplastic lesions might indeed prove to be effective in reversing the "field cancerization" defect thought to underlie the increased incidence of second malignancies of the aerodigestive tract. Nontoxic combinations are to be preferred in this setting also, since prolonged treatment is anticipated and many of these patients have received radiation treatment resulting in mucosal injury. Therefore, they may be unable to tolerate the mucocutaneous toxicity associated with the currently available synthetic retinoids. Nevertheless, a somewhat greater degree of toxicity may be acceptable in this group, since cancer risk appears to be higher than in the usual patient with leukoplakia.

A recent report of an adjuvant trial using high-dose 13-*cis*-retinoic acid in patients with all stages (I to IV) of cancer showed a remarkable reduction in the incidence of second primary tumors, although it failed to show a significant adjuvant effect, *i.e.*, reduction in recurrence (31). Toxicity was a major problem, leading to premature discontinuation of therapy in one-third of the study patients. Trials using lower doses of 13-*cis*-retinoic acid or β -carotene (\pm retinol) in early-stage patients have recently been initiated.

Finally, the role of maintenance or long-term therapy needs to be studied. In most leukoplakia trials reported so far, the lesions tend to recur once treatment is discontinued. In fact, in the study by Hong *et al.*, the reported time course of response data suggests that some patients began to relapse while still receiving 13-*cis*-retinoic acid at 1–2 mg/kg/day, *i.e.*, within the 3-month treatment period. It is not yet clear whether continued treatment with lower doses of vitamin A or β -carotene, alone or in combination, will indeed be effective for this purpose in the trials of Stich *et al.*, after an initial response has been obtained with higher doses of vitamin A.

Nevertheless, in view of these early exciting results, which do establish the ability of these agents to affect established precancerous lesions, the time is appropriate to begin planning strategies to test whether oral cancer can actually be reduced in a targeted population by supplementation with chemoprevention agents. The identification of a suitable population and the training of personnel to conduct such a trial over a prolonged period of intervention will clearly be an immense undertaking. However, the ultimate objective is prevention of oral cancer and not merely treatment of leukoplakia. It appears likely from current trials that a promising nontoxic agent or combination of agents will be identified from ongoing studies in patients with oral premalignant lesions. But will their supplementation actually prevent oral cancer? This can be definitively answered only by conducting randomized controlled phase III intervention trials in suitable populations, *i.e.*, high-risk populations in endemic areas, for prevention of "primary" cancers, and early-stage head and neck cancer patients, cured of their primary tumor, for prevention of second malignancy. In the United States, a number of trials in the latter category have recently begun or are being planned, reflecting the increasing interest in this field of cancer research. These include interventions with β -carotene alone (Yale), β -carotene plus low-dose vitamin A (Southwest Oncology

Group), and 13-*cis*-retinoic acid (Northern California Oncology Group).

References

- Parkin, S. M., Laara, E., and Muir, C. S. Estimates of the worldwide frequency of sixteen major cancers. *Int. J. Cancer*, 41: 184-197, 1988.
- Dunham, L. J. A geographic study of a relationship between oral cancer and plants. *Cancer Res.*, 28: 2369-2371, 1968.
- Baden, E. Tabac et cancers de la region oropharyngée et des bronches. Données actuelles. *Rev. Med. Toulouse*, 14: 549-560, 1978.
- Davis, S., and Severson, R. K. Increasing incidence of cancer of the tongue in the US among young adults. *Lancet*, 2: 910-911, 1987.
- Hakulinen, T., Anderson, A. A., Malker, B., et al. Trends in cancer incidence in the Nordic countries. *Acta Pathol. Scand.*, 288(Suppl): 94, 1986.
- McFarlane, G. J., Boyle, P., and Scully, C. Rising mortality from cancer of the tongue in young Scottish males. *Lancet*, 2: 912, 1987.
- Silverberg, E., Boring, C. C., and Squires, T. S. Cancer statistics. *CA Cancer J. Clin.*, 40: 9-26, 1990.
- Muir, C. S., and Kirk, R. Betel, tobacco and cancer of the mouth. *Br. J. Cancer*, 14: 597-608, 1960.
- McGuirt, W. F., Mathews, B., and Kaufman, J. A. Multiple simultaneous tumors in patients with head and neck cancer. *Cancer (Phila.)*, 50: 1195-1199, 1982.
- Kotwall, C., Razack, M. S., Sako, K., et al. Multiple primary cancers in squamous cell cancers of the head and neck. *J. Surg. Oncol.*, 40: 97-99, 1990.
- Slaughter, D. P., et al. Field cancerization in oral stratified squamous epithelium, clinical implications of multicentric origin. *Cancer (Phila.)*, 5: 963-968, 1953.
- Oral cancer (Editorial). *Lancet*, 2: 311-312, 1989.
- Lippman, S. M., Kessler, J. F., and Meyskens, F. L. Retinoids as preventive and therapeutic anticancer agents. Part I. *Cancer Treat. Rep.*, 71: 391-405, 1987.
- Ziegler, R. G. A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J. Nutr.*, 119: 116-122, 1989.
- Burge-Bottenbley, A., and Shklar, G. Retardation of experimental oral cancer development by retinyl acetate. *Nutr. Cancer*, 5: 121-129, 1983.
- Schwartz, J., Suda, D., and Light, C. β -Carotene is associated with the regression of hamster buccal pouch carcinoma and induction of tumor necrosis factor in macrophages. *Biochem. Biophys. Res. Commun.*, 136: 1130-1135, 1986.
- Shklar, G., Schwartz, J., Trickler, D., et al. Regression of experimental cancer by oral administration of combined α -tocopherol and β -carotene. *Nutr. Cancer*, 12: 321-325, 1989.
- Stich, H. F. Micronucleated exfoliated cells as indicators for genotoxic damage and markers in chemoprevention trials. *J. Nutr. Growth Cancer*, 4: 9-18, 1989.
- Stich, H. F., Rosin, M. P., Hornby, A. P., et al. Remission of oral leukoplakias and micronuclei in tobacco/betel quid chewers treated with β -carotene and with β -carotene plus vitamin A. *Int. J. Cancer*, 42: 195-199, 1988.
- Silverman, S., and Shillitoe, E. J. In: S. Silverman (ed.) *Etiology and Predisposing Factors in Oral Cancer*, Ed. 2, pp. 7-36, New York: American Cancer Society, 1985.
- Wong, F., Epstein, J., and Millner, A. Treatment of oral leukoplakia with topical bleomycin. *Cancer (Phila.)*, 64: 361-365, 1989.
- Koch, H. F. Biochemical treatment of precancerous oral lesions: the effectiveness of various analogues of retinoic acid. *J. Maxillofac. Surg.*, 6: 59-63, 1988.
- Koch, H. F. Effect of retinoids on precancerous lesions of oral mucosa. In: C. E. Orfanos, O. Braun-Falco, E. M. Farber, et al. (eds.), *Retinoids: Advances in Basic Research and Therapy*, pp. 307-312. Berlin: Springer-Verlag, 1981.
- Shah, J. P., Strong, E. W., DeCosse, J. J., et al. Effect of retinoids on oral leukoplakia. *Am. J. Surg.*, 146: 466-470, 1983.
- Hong, W. K., Endicott, J., Itri, L. M., et al. 13-*cis*-Retinoic acid in the treatment of oral leukoplakia. *N. Engl. J. Med.*, 315: 1501-1505, 1986.
- Stich, H. F., Hornby, A. P., Mathew, B., et al. Response of oral leukoplakias to the administration of vitamin A. *Cancer Lett.*, 40: 93-101, 1988.
- Garewal, H. S., Meyskens, F. L., Killen, D., et al. Response of oral leukoplakia to β -carotene. *J. Clin. Oncol.*, 8: 1715-1720, 1990.
- Reid, B. J., Haggitt, R. C., Rubin, C. E., et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. *Hum. Pathol.*, 19: 166-178, 1988.
- Crissman, J. D. Upper aerodigestive tract. In: E. D. Henson and J. Albores-Saavedra (eds.), *The Pathology of Incipient Neoplasia*, pp. 39-55. Philadelphia: W. B. Saunders Co., 1986.
- Odukoya, O., Hawach, F., and Shklar, G. Retardation of experimental oral cancer by topical vitamin E. *Nutr. Cancer*, 6: 98-104, 1984.
- Hong, W. K., Lippman, S. M., Itri, L. M., et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.*, 323: 795-801, 1990.

Cancer Epidemiology, Biomarkers & Prevention



Retinoids and carotenoids in the prevention of oral cancer: a critical appraisal.

H S Garewal and F Meyskens, Jr

Cancer Epidemiol Biomarkers Prev 1992;1:155-159.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/1/2/155.citation>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.