Oral Cavity Cancer
Theoretical Discussion: Evidence for localized folate deficiencies in aerodigestive tissues includes lower folate levels in scrapings of the buccal mucosa in smokers than non-smokers. This observation, as well as animal and in vitro studies, also suggests that folate deficiency may be co-carcinogenic (Heimberger DC. Localized deficiencies of folic acid in aerodigestive tissues. Ann N Y Acad Sci 669:87-96, 1992).

Niacin
May protect against carcinogenesis.
Review Article: NAD, the principal form of niacin, is consumed as a substrate in ADP-ribose transfer reactions. Also, one of the 4 unique classes of ADP-ribose transferases that are responsible for the turnover of NAD, poly (ADP-ribose) polymerase, is activated by DNA strand breaks and functions in the repair of DNA. Limiting niacin intake in humans results in a decrease of up to 70% of intracellular NAD, and evidence is accumulating that maintenance of intracellular NAD is a critical factor in responses to DNA damage (Jacobson EL, Jacobson MK. A biomarker for the assessment of niacin nutriture as a potential preventive factor in carcinogenesis. J Intern Med 233:59-62, 1993; Jacobson EL. Niacin deficiency and cancer in women. J Am Coll Nutr 12(4):412-16, 1993).

Negative Review Article: Dietary excesses and deficiencies of niacin or nicotinamide do not appear to exert any influence on in vivo carcinogenesis in animals, while epidemiologic studies have not investigated the relationship between niacin deficiency or excess and carcinogenesis in humans (Bryan GT. The influence of niacin and nicotinamide on in vivo carcinogenesis. Adv Exp Med Biol 206:331-38, 1986).
Supplementation may reduce the cardiotoxicity of adriamycin.

Animal Experimental Study: Niacin reduced the cardiotoxicity of adriamycin in mice without interfering with its antitumor activity


- and aspirin
  Combined administration may reduce thrombogenic complications.

**Experimental Controlled Study:** 106 pts. with bladder carcinoma (stage T3NxMo) were followed for 3 yrs. after treatment with surgery along with pre- and post-operative gamma-beam radiation therapy. 51/106 also received nicotinic acid and aspirin at common doses to prevent thrombogenic complications, while the other 55 pts. served as controls. Relapses were noted in 33.3% of the experimental gp. compared to 72.5% of the controls. The 5-yr. survival in the treatment gp. was 72.5% compared to 27.4% in the control gp. (Popov AI. [Effect of the nonspecific prevention of thrombogenic complications on late results in the combined treatment of bladder cancer.] Med Radiol (Mosk) 32(2):42-5, 1987).

**Riboflavin**
Intake may be inversely correlated with the risk of prostate cancer.

**Observational Study:** Dietary records of 55 black pts. with prostate cancer were compared to those of matched controls. An inverse relationship was noted between dietary intake of riboflavin and risk for developing prostate cancer for the more than 50-years-old group (p<0.03) (Kaul L et al. The role of diet in prostate cancer. Nutr Cancer 9:123-8, 1987).

Blood riboflavin level may inversely correlate with the risk of esophageal cancer.

Thiamine
Intake may be inversely correlated with the risk of prostate cancer.
**Observational Study:** Dietary records of 55 black pts. with prostate cancer were compared to those of matched controls. An significant inverse relationship was noted between dietary intake of thiamine and risk for developing prostate cancer for the 30 to 49-year-old group (p<0.05) (*Kaul L et al. The role of diet in prostate cancer. Nutr Cancer 9:123-8, 1987*).

Vitamin A
Intake may be inversely correlated with cancer risk (*see also ‘Vitamin A and Beta-Carotene’ below*).
**Review Article:** The association of high retinoid intake with decreased cancer risk may be due to immunosuppression during vitamin A deficiency or immunoenhancement during extremely high intakes. High dietary vitamin A enhances macrophage functioning, while retinol suppresses T-lymphocyte function *in vitro* (*Watson R et al. Cancer prevention by retinoids: Role of immunological modification. Nutr Res 5:663-75, 1985*).

Oral and Pharyngeal Cancer
**Observational Study:** In a study of 34,691 postmenopausal American women, after adjustment for age, smoking, and total energy intake, higher vitamin E intakes were associated with lower risk of oral/pharyngeal/esophageal cancers (*Zheng W, Sellers TA, Doyle TJ, et al. Retinol, antioxidant vitamins, and cancer of the upper digestive tract in a prospective cohort study of postmenopausal women. Am J Epidemiol 142:955-60, 1995*).

**Observational Study:** 24 newly-diagnosed oral cancer pts. were compared to age- and sex-matched normals and to age- and sex-matched controls with lifestyle habits such as tobacco chewing or smoking and alcohol consumption similar to those of the patients. Plasma vitamin E concentrations were significantly lower in the pts. than in the normal or control groups. Plasma vitamin E concentrations were also reduced in controls compared to normals (*Monoharan S, Nagini S. Lipid peroxidation and antioxidant status in oral cancer patients. Med Sci Res 22:291-2, 1994*).
Observational Study: In a population-based study of the relationship between the risk of oral and pharyngeal cancer and vitamin supplementation, after controlling for the effects of tobacco, alcohol and other risk factors, only vitamin E supplementation was significantly associated with a reduced cancer risk. The adjusted odds ratio for vitamin E supplementation ‘ever regularly used’ was 0.5 (Gridley G, McLaughlin JK, Block G, et al. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. Am J Epidemiol 135(10):1083-92, 1992).

Oral Cancer
Observational Study: The use of vitamin and mineral supplements in 4 areas of the U.S. was investigated and compared to oral and pharyngeal cancer incidence. Only vitamin E supplementation was found to exert a significant protective effect; the odds ratio for developing those cancers in people who “ever regularly used” vitamin E supplements was half the normal risk. Past studies that found no association were looking simply at dietary vitamin E intake which is much lower than the common doses found in supplements (Gridley G, McLaughlin J, Block G, et al. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. Am J Epidemiol 135:1083-92, 1992).

Observational Study: In a case-control study of 290 oral cancer cases, vitamin E supplementation was found to be associated with a lower cancer risk (Barone J, Taioli E, Hebert J, et al. Vitamin supplement use and risk for oral and esophageal cancer. Nutr Cancer 18:31-41, 1992).

Oral Cavity Cancers
Observational Study: Mean selenium levels were 77 ng/ml in 19 pts. with malignant oral cavity lesions, while levels in 22 pts. with precancerous oral cavity lesions were 105 ng/ml and levels in 13 healthy controls were 101 ng/ml. The difference between the neoplastic gp. and both of the other gps. was significant (p<0.005) (Toma S et al. Selenium therapy in patients with precancerous and malignant oral cavity lesions: preliminary
Oral Cavity Cancers

Experimental Study: 18 pts. with leukoplakia or other precancerous dysplastic lesions of the oral cavity received three 4-wk. cycles of either inorganic or organic selenium 300 mcg/d. After treatment, there were 2 complete responses, 5 partial responses and 6 minor responses. Progression after cessation of treatment occurred in 7 pts., suggesting that pts. may need a longer treatment period (Toma S et al. Selenium therapy in patients with precancerous and malignant oral cavity lesions: preliminary results. Cancer Detect Prev 15(6):491-4, 1991).

ORAL CANCER

Beta-carotene

Experimental Double-blind Study: In Uzbekistan, in an area with a high incidence of oral and esophageal cancer, 532 men aged 50-69 with chronic esophagitis and/or oral leukoplakia, considered to be precancerous conditions, randomly received a combination of retinol 100,000 IU/wk., retinol with betacarotene 40 mg daily and vitamin E 80 mg/wk., or both. After 20 months of treatment, a secondary analysis not based on the randomized design revealed a decrease in the prevalence of oral leukoplakia in men with medium (OR = 0.45) and high (OR = 0.59) blood concentrations of beta-carotene (Zaridze D, Evstifeeva T, Boyle P. Chemoprevention of oral leukoplakia and chronic esophagitis in an area of high incidence of oral and esophageal cancer. Ann Epidemiol 3(3):225-34, 1993).

Review Article: Beta-carotene suppresses micronuclei in exfoliated oral mucosa cells from subjects at risk for oral cancer and is active in reversing leukoplakia; it is possible that it may prevent second primary tumors in pts. cured of their initial cancer who have an increased risk of developing new cancers of the upper aerodigestive tract (Garewal HS. Potential role of bcarotene in prevention of oral cancer. Am J Clin Nutr 53:294S-7S, 1991).
Experimental Study: Natives of Guam, Taiwan, the Philippines, India, Peru and Canada who chew tobacco mixtures were studied. Beta-carotene 180 mg/wk produced a substantial reduction in frequency of micronucleated mucosal cells and remission of leukoplakias within 3-6 mo. of treatment; it also reduced the frequency of new leukoplakias. Micronucleated mucosal cells and leukoplakia returned when the supplements were discontinued. Beta-carotene 60 mg/wk. was less effective than vitamin A 50,000 IU/wk. in maintaining the protective effect for the 12-mo. post-treatment period (Stich H et al. Remission of oral precancerous lesions of tobacco/areca nut chewers following administration of beta carotene or vitamin A, and maintenance of the protective effect. Cancer Det 15:93-8, 1991).

Experimental Double-blind Study: Fishermen in Kerala, India who chewed tobacco-containing betel quids were administered beta-carotene 2.2 mmol/wk for 6 mo. Leukoplakia remitted in 14.8% and micronucleated cells were reduced by 98%; formation of new leukoplakia was suppressed by 50%. The protective effect could be maintained for at least 8 additional mo. by lower doses (Stich HF, Mathew B, Sankaranarayanan R, Nair Krishnan M. Remission of precancerous lesions in the oral cavity of tobacco chewers and maintenance of the protective effect of b-carotene or vitamin A. Am J Clin Nutr 53:298S-304S, 1991).

Experimental Study: In a phase II study, 24 pts. with oral leukoplakia received beta-carotene 30 mg daily for 3 mo., and responding pts. were continued on treatment for another 3 months. Based on bidimensional measurements and photography, 2 pts. had complete responses, and 15 pts. had partial responses, a response rate of 71%. There was no significant toxicity (Garewal HS, Meyskens FL Jr, Killen D, et al. Response of oral leukoplakia to beta-carotene. J Clin Oncol 8(10):1715-20, 1990).

Experimental Placebo-controlled Study: Inuits using smokeless tobacco eat a diet rich in meat including liver, but low in vegetables, leading to normal serum vitamin A levels but low
beta-carotene levels. Supplementation with beta-carotene 90 mg twice weekly for 10 wks. significantly decreased the frequency of exfoliated cells from the oral mucosa with micronuclei, while placebo and untreated controls showed no change (Stich HF et al. A pilot beta-carotene intervention trial with Inuits using smokeless tobacco. Int J Cancer 36(3):321-7, 1985).