

Chemopreventive Agents in Oral Premalignancy: A Medical Management Review

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ABSTRACT **Aims and Objective:** The term chemoprevention denotes the use of specific natural or synthetic chemical agents to prevent carcinogenesis. Chemoprevention may help delay the process of carcinogen activation and prevent the conversion of preneoplastic cells. These agents play an active role in the secondary level of prevention and reduce malignancy-associated morbidity and mortality. A new term, “prophylactic antioxidant therapy,” was coined and proposed. This review has assessed all major chemopreventive agents used for oral premalignancy and malignant conditions, which will reduce the economic burden on the patients. **Materials and Methods:** A systematic literature search was performed using PubMed, Medline, Embase, Cochrane Library, and EBSCO search, with language restriction to English. The search incorporated published literature from 1990 to 2018 using the medical subject heading terms. Literature search was performed using the following keywords: Chemoprevention, Premalignancy, and Oral Malignancy. **Results:** Of 99 publications related to the search strategy, 45 full articles relevant to the chemopreventive agents in premalignancy and oral malignancy were acquired for further inspection. Of the 45 articles, 30 met the inclusion criteria. Data were collected, and a brief summary of the studies regarding different chemopreventive agents that were most commonly used in oral premalignancy and malignancies was written. **Conclusion:** This review suggests administration of major chemopreventive agents for superior prognosis in individuals with an elevated risk of premalignancy and malignancy.

KEYWORDS: Antioxidant treatment, chemoprevention, oral malignancy, premalignancy, prophylaxis

INTRODUCTION

Oral premalignancy predominantly affects individuals exposed to tobacco, betel nut chewing, unhealthy diet, physical inactivity, and infections.^[1,2] To reduce the incidence of malignant transformation, early diagnosis and prompt treatment of potentially malignant disorders are necessary. Therefore, chemopreventive agents play a crucial role in reversal, suppression, and prevention of carcinogenesis.^[3] This is directed toward a secondary preventive stage where appropriate action can be directed toward early

precursor lesions. Intervention at this stage will reduce the morbidity and mortality associated with the lesion prognosis toward oral cancer and thus will add less financial burden on the patients.^[4]

In 1976, Michael B. Sporn coined the term chemoprevention and defined it as the use of specific

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natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy. The word chemoprevention includes prevention of initiation, promotion, and progression of carcinogenesis to cancer.^[3] A term “Prophylactic Antioxidant Therapy” for premalignancies was thus coined and proposed by Chaitanya Nallan C and Suvarna C, which implies the administration of antioxidants eliminating the chances of occurrence of any premalignancies.

In the past decades, several studies have been conducted to assess the efficacy of chemopreventive agents used for the management of oral premalignancies and malignancies. The usage of chemopreventive agents in oral premalignancies has been a common practice. Various medications have been used for a single entity with varying dosages and vice versa. The exhaustive list is rather more elaborative and not a comprehensive one for any clinician. Several chemopreventive agents still do not have clinically established outcomes. Therefore, compilation of evidence from published studies quoted in medical databases in a single systematic review focusing on different chemopreventive agents was needed for the management of oral premalignancies and malignancies.

MATERIALS AND METHODS

SEARCH STRATEGY, PROTOCOL, AND ELIGIBILITY CRITERIA

An extensive literature search was performed using databases, namely PubMed, EBSCO, Cochrane, Medline, ScienceDirect, and ResearchGate. The keywords used for the search were Chemoprevention, Premalignancy, and Oral Malignancy. The search was carried out incorporating the published literature from 1990 to 2018 using the aforementioned medical subject heading terms.

Only randomized controlled trials were included in the study. Exclusion criteria included non-English language articles, articles with only abstracts, case reports, cohort studies, poorly designed studies, and review articles. There were no similar reviews registered or performed under PROSPERO.

DATA COLLECTION PROCESS AND ITEMS

Of 99 publications related to the search strategy, 45 full articles, which were relevant to the chemopreventive agents in premalignancy and oral malignancy, were acquired for further investigation. Of the 45 articles, 30 met the inclusion criteria. The data were collected and a brief summary of the studies regarding the different chemopreventive agents that were most commonly used in oral premalignancy and malignancies was

explained. A meta-analysis was not attempted because of the presence of heterogeneity in the selected studies. Because the study designs and results varied in various trials, only a systematic review was warranted.

This review also describes the agents that were under clinical trials [Figure 1].

MAJOR CHEMOPREVENTIVE AGENTS USED FOR PREMALIGNANCY

- (1) Aspirin: Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), which causes an irreversible inactivation of cyclooxygenase-1 (COX-1) and COX-2. A randomized controlled trial revealed that dosage of aspirin 81–325 mg reduces the risk of head and neck cancer by 22% through inhibition of COX-2 and downstream biological pathways, such as NF- κ B signaling in carcinogenesis.^[5]
- (2) Indomethacin: Indomethacin presents antineoplastic activity at low doses. A study by Lundholm *et al.*^[6] has stated that indomethacin 50 mg twice daily can significantly extend survival of patients with metastatic disease due to its inhibition activity on prostaglandin E₂ levels, which in turn inhibit cell growth.
- (3) Lovastatin: Lovastatin reduces cellular proliferation and induces apoptosis in cancer cells. A study by Knox *et al.*^[7] has found that oral administration of lovastatin 7.5 mg/kg daily for 21 days and repeat therapy for every 28 days is effective against squamous cell carcinoma of head and neck and cervix with no adverse effects on renal function.
- (4) Atorvastatin: Atorvastatin exhibits anti-tumorigenic activity in cancer cells through induction of apoptosis, cell-cycle G₁ arrest, and autophagy, resulting in reduced cell proliferation. In a phase II ongoing randomized controlled trial, oral administration of atorvastatin 20 mg/night for 2 years during radiotherapy was found to be effective in nasopharyngeal carcinoma with no reported side effects.^[8]
- (5) Metformin: Metformin exhibits an indirect antineoplastic effect through an insulin-dependent pathway. A study by Curry *et al.*^[9] has found that oral administration of metformin 500–2500 mg daily in patients with diabetes is effective in head and neck squamous cell carcinoma (HNSCC) by inducing the apoptosis of carcinoma cells. Metformin is associated with adverse effects, such as diarrhea, nausea, fatigue, weakness, and dizziness.^[9]
- (6) Human papillomavirus vaccine: Approximately 12%–63% of oropharyngeal cancer cases are

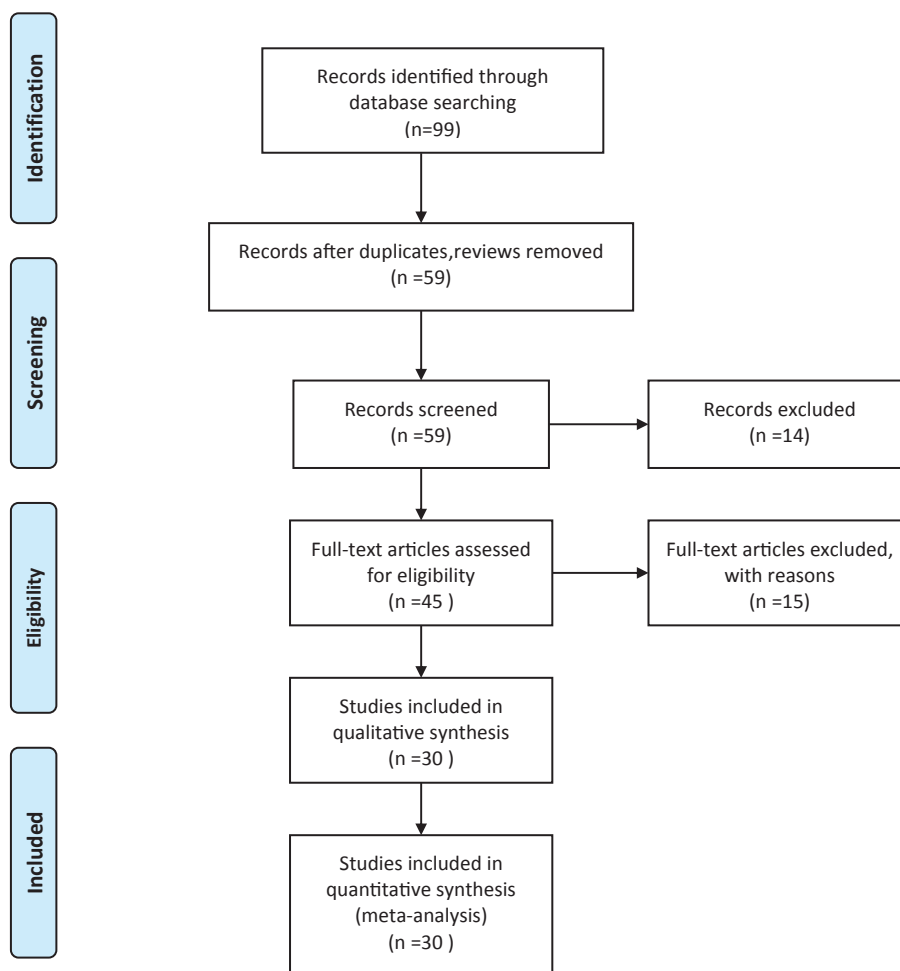


Figure 1: PRISMA flow diagram

associated with human papillomavirus (HPV). A phase III randomized study showed that an HPV bivalent (types 16 and 18) vaccine conjugated with AS04 and an HPV quadrivalent (types 6, 11, 16, and 18) vaccine conjugated with amorphous aluminum salts have both shown to be highly effective and may reduce the burden of HPV-associated HNSCC.^[10]

- (7) Adenovirus Onyx-15 vaccine: Chemoprevention of HNSCC by modified adenovirus Onyx-15 replicates selectively only in cells with mutated gene p53, eventually destroying them. Rudin *et al.*^[11] administered Onyx-015 mouthwash in 10^[10] plaque-forming units daily for 5 days, with cycles repeated every 4 weeks for a maximum of 12 cycles, in 22 patients with grossly evident dysplasia on biopsy. The study found that application of adenovirus Onyx-15 in patients with dysplasia of the oral cavity resulted in resolution of dysplasia.^[11] Intraepithelial injection of the recombinant human adenovirus P53, 0.5 mL for 15 days, was effective in

dysplastic oral leukoplakia after 24 months of follow-up.^[12]

- (8) Bacille Calmette–Guérin vaccine: Bacille Calmette–Guérin immunotherapy was found to be effective against HNSCC through increase in the CD4+ and CD8+ lymphocyte count with an elevation in the levels of the antitumor cytokines, namely interleukin-6, tumor necrosis factor alpha, and interferon gamma.^[13]
- (9) Vitamin A: Vitamin A is a lipid-soluble micronutrient, which acts during the promotion and progression stages of carcinogenesis, causes cell-cycle arrest in the G₁ phase, and allows repair of genomic damage caused by carcinogens. It also acts as an immune modulator and an inducer of apoptosis. Physiologic doses of retinoids also stimulate killer T-cell production and cell-mediated cytotoxicity, which may be crucial in the treatment of cancer.^[14,15] The teratogenic action of retinoids has been the most serious adverse effect.^[16]
- (10) Vitamin C: Vitamin C is the most prevalent antioxidant component of fruits and vegetables,

which could exert chemopreventive effects and can prevent oxidative stress-mediated chronic diseases without apparent toxicity at doses higher than the current recommended dietary allowance of 100–120 mg/day for adults. It protects cells from oxidative DNA damage, thereby blocking the initiation of carcinogenesis. Combination of vitamin C with other antioxidants, such as beta-carotene, vitamin E, and vitamin A, has been used as adjunctive supplemental therapy to correct the nutritional status of the patient.^[17]

- (11) Vitamin E: Vitamin E is a key lipid-soluble antioxidant found in several foods, such as corn oil, peanuts, vegetable oils, fruits, and vegetables, consumed through diet. In addition to its antioxidant mechanism, it may act as an anti-inflammatory agent and as an inhibitor of cancer-cell proliferation and growth, apoptosis, and angiogenesis.^[18] Combination of vitamin E with lycopene and selenium with different formulations and dosages has been found to be an effective management strategy for oral premalignant lesions. This combination may also reduce the incidence of second primary cancers, with yellowing of the skin as a side effect.^[19]
- (12) Vitamin B9: Folic acid is a water-soluble vitamin that is distributed widely in green leafy vegetables, beans, whole grains, citrus fruits, and animal products. A study by Mesolella *et al.*^[20] has stated that oral dosage of folic acid 15 mg every 8 hours for 6 months is effective for 80% clinical improvement in mild and moderate laryngeal dysplasia and 58% with clinically evident regression of the laryngeal leukoplakia.
- (13) Zinc: Zinc is an essential mineral that helps regulate key cellular functions, such as response to oxidative stress, DNA damage repair, cell-cycle progression, and apoptosis. A case series by Chaitanya *et al.*,^[21] Mehdi-pour *et al.*,^[22] and Thomas *et al.*^[23] suggested that different formulations of zinc with different dosages were effective in reducing the severity of lesions in subacute and chronic eczema, oral lichen planus, and psoriasis.
- (14) Selenium: Selenium is an essential nutritional element. It inhibits initiation and promotion phases of carcinogenesis. Combination of selenium with vitamin A, C, and E is effective in managing ulcerative lesions of oral lichen planus.^[24] A study by Agha-Hosseini *et al.*^[25] has suggested that an immunomodulatory drug with herbal origin, which has selenium as one of the components administered 400 mg/day for 3 months, is effective in the management of signs and symptoms of oral lichen planus.
- (15) Curcumin: Curcumin is the active component of turmeric extracted from the dried rhizome of *Curcuma longa*. A phase IIB trial has suggested that oral dosage of curcumin 3.6 g twice daily for 6 months is well tolerated and demonstrates significant and durable clinical response for 6 months in oral leukoplakia.^[26] Another trial has suggested that curcumin 400 mg lozenges for 3 months and oral curcumin 500 mg with topical application of turmeric oil 12 drops (600 mg) for 6 months was effective in oral submucous fibrosis through its antioxidant and anti-inflammatory properties, which enhance the neoangiogenic and antifibrotic potential in oral submucous fibrosis.^[27]
- (16) Green tea polyphenols: Tea is obtained from the dried leaves of the plant *Camellia sinensis*. Oral administration of green tea extracts 350 mg thrice daily for 12 weeks showed that high-dose green tea extract (750 and 1000 mg/m²) had a significant clinical and histological outcome in oral premalignant lesions, although these were not associated with long-term oral cancer prevention.^[28]
- (17) Beta-carotene: Beta-carotene is a vitamin A precursor commonly found in dark green, orange, or yellowish fruits and vegetables, such as spinach, sweet potato, carrots, papaya, mango, and oranges. A randomized controlled trial suggested that oral dosage of beta-carotene 30–90 mg/day for 6 months showed a complete clinical response of 8.3% and partial clinical response of 62.5% in oral leukoplakia,^[29] whereas the dosage of 15 mg/day 4 times a day for 4 months reduces the multinucleated exfoliated cells frequency in atrophic and erosive oral lichen planus.^[30]
- (18) Lycopene: Lycopene is a natural pigment and a fat-soluble carotenoid synthesized by photosynthetic plants and microorganisms. A study by Singh *et al.*^[31] has suggested that oral supplementation of lycopene 4–8 mg per day for 3 months showed reduction in hyperkeratosis in 80% of cases, and complete remission of the lesion was noted in 55% of cases at 8 mg/day doses, and in 25% of cases at 4 mg/day doses.
- (19) Resveratrol: Resveratrol is a component of grape skin, red wine, berries, peanuts, and many other plants. Resveratrol at 0.5, 1.0, 2.5, and 5 g/day for 29 days significantly reduced the levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 in plasma, which would support the use of resveratrol as a chemopreventive agent in humans.^[32]
- (20) Capsaicin: Capsaicin possesses analgesic, antioxidant, anti-inflammatory, anti-obesity,

anti-invasive, and anti-migratory properties. It induces apoptosis in many types of cancer cell lines while leaving normal cells unharmed.^[33]

- (21) Omega-3 fatty acids: “Omega-3 fatty acids” (*n*-3 polyunsaturated fatty acids [PUFA]) and “omega-6 fatty acids” (*n*-6 PUFA) influence multiple targets implicated in various stages of cancer development, including cell proliferation, cell survival, angiogenesis, inflammation, and metastasis against various cancers.^[34]
- (22) Miscellaneous agents: Agents such as ferulic acid, emodin, ursolic acid, celastrol, ellagic acid, genistein, polydatin, caffeic acid, and phenethyl ester, and many plant extracts, such as *Allium sativum*, *Azadirachta indica*, aloe vera, and ginseng extract, were evaluated for chemopreventive properties against several premalignancies; however, their efficacy is yet to be established through long-term trials.

DISCUSSION

Chemopreventive agents can operate at different levels of carcinogenesis. In the initiation phase, they block or delay the process of carcinogen activation. Scavenging the activated carcinogens reduces DNA damage and the agents used in this phase are known as blocking agents. In the promotion phase, the initiated cells are actively converted into preneoplastic cells, which are more prone for malignancy, and the agents used are ideally described as suppressing agents.^[35]

These chemopreventive agents also present the anti-initiation activity through inhibition of metabolic activation of carcinogens. Therefore, their action at the root level could be used for eliminating the chance of occurrence of any premalignancies.

An ideal chemopreventive agent must possess the characteristics of negligible or no toxicity, high efficacy at multiple sites, and availability of oral consumption with a wide range of therapeutic actions, low cost, and human acceptance. It should have excellent bioavailability at the targeted site.^[36]

These chemopreventive agents were broadly classified into four categories: hormonal chemopreventive agents, medications, diet-related agents, and vaccines.

- (1) Hormonal chemopreventive agents: They include antiestrogens, which include two inhibitors such as selective estrogen receptor modulators and aromatase inhibitors, and antiandrogens. Antiestrogen agents, such as tamoxifen and raloxifene, and aromatase inhibitors, such as exemestane and anastrozole, were effective for reduction of the risk of invasive breast

cancer in postmenopausal women. Antiandrogen agents, such as finasteride and dutasteride, were most commonly used for the treatment of prostate cancer.^[37]

- (2) Medications: Medications include NSAIDs, such as aspirin and indomethacin; statins, such as lovastatin and atorvastatin; and antidiabetic medications, such as metformin.^[37]
- (3) Diet-related agents: Diet-derived compounds include polyphenols (green tea polyphenols, soy flavonoids, quercetin, resveratrol, and curcumin), polyunsaturated fatty acids, carotenoids (beta-carotene and lycopene), vitamins (E, C, or folic acid) and minerals (Se and Zn), and dietary fiber.^[37]
- (4) Vaccines: Several infections have been linked to increased cancer risk. However, only the vaccines against hepatitis B virus and HPV are currently used in clinical practice for the prevention of cancer.^[37]

These agents induce their action at the molecular level to inhibit cancer-cell proliferation, inhibit growth factor signaling pathways, induce apoptosis, inhibit angiogenesis, suppress the expression of antiapoptotic proteins, inhibit COX-2, and reverse chemo-radio resistance, which may have untapped therapeutic value.^[38]

These agents have undergone several preclinical, clinical, and human trials to demonstrate their efficacy in various premalignant diseases and conditions. Few studies have reported adverse effects during their use in various premalignant diseases and conditions. A new model “prophylactic antioxidant therapy” which was proposed by Chaitanya Nallan C and Suvarna C., was used as a chemopreventive agent right before the initiation of carcinogenesis.

RISK OF BIAS

Risk of bias could not be established due to various confounding factors as well as presence of heterogeneity. Therefore, a meta-analysis was not possible considering the nonhomogeneous variables in the included studies. Therefore, a systematic review was carried out, which focused on the demonstration of various agents as chemopreventive agents in a broader perspective.

CONCLUSION

An ideal chemopreventive agent mediates the beginning stage of carcinogenesis to remove premalignant cells so that malignancy can be prevented. They do so by impeding or interfering the promotion or progression of premalignant or malignant cells by modulating cell proliferation or differentiation. Furthermore, they could also be used in blocking the initiation of premalignant pathologies. More studies should be

directed toward such preventive strategies in individuals with an elevated risk of cancer development for more accurate prognosis.

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CONFLICTS OF INTEREST

No conflict of interest.

AUTHOR CONTRIBUTIONS

Suvarna: Substantially contributed to conception and designing the study, done the literature search and contributed in the clinical study, acquisition and analysis of the data, statistical analysis, prepared, edited and reviewed the manuscript and is the guarantor.

Nallan CSK Chaitanya: Contributed to the intellectual content of study, searched the literature, contributed to clinical study, acquisition and analysis of data, statistical analysis and also worked for manuscript preparation, editing and review.

Sheik Ameer: Contributed for the designing the content of study, literature search, data acquisition, statistical analysis and in the writing and reviewing the manuscript.

Pavitra Inamdar: worked for the content of the study, searched the literature, clinical material, analyzed the data, manuscript preparation and review.

Swetha Alugubelli: Contributed to the literature search and clinical study, data acquisition, statistical analysis and review.

Alakananda Bhagyanagar: Accounted for the content of the study, searched the literature, contributed in clinical study, analyzed the data, statistical analysis, manuscript preparation and editing.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

All the procedures have been performed as per the ethical guidelines laid down by Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

All the data is available in the article.

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