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Review Article

Therapeutic Role of Bioactive Micronutrients in Oral Squamous Cell Carcinoma: Pharmaceutical Perspectives on Metabolic Disorders and Cancer Prevention

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ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is one of the most common cancers worldwide, and despite advances in diagnosis and treatment, survival rates remain poor. This review critically evaluates the role of bioactive micronutrients, especially antioxidant Vitamins and essential trace elements, in the genesis, progression, prevention and management of OSCC. It also describes the effects of metabolic disorders on the homeostasis of micronutrients and their participation in the molecular mechanisms of oral carcinogenesis. A thorough literature review was performed in the main biomedical databases to identify relevant peer-reviewed studies. To evaluate the diagnostic, prognostic and therapeutic significance of micronutrients in oral cancer, critical analysis and systematic synthesis of evidence on micronutrient deficiencies, metabolic disorders, oxidative stress, inflammatory signaling, immune dysregulation, epigenetic alterations and their association with OSCC were performed. There is present evidence that deficiencies of antioxidant vitamins and essential trace elements impair cellular antioxidant defense mechanisms, leading to oxidative stress, chronic inflammation, immune dysfunction and activation of oncogenic pathways. Metabolic disorders further aggravate micronutrient imbalances thus accelerating disease progression. Targeted nutritional supplementation may improve therapeutic efficacy, slow disease progression and improve clinical outcome when used with conventional therapies. The role of micronutrient deficiencies and metabolic dysfunction in the pathogenesis of OSCC is critical through regulation of oxidative stress, inflammation, immune responses. The incorporation of nutritional assessment and specific micronutrient interventions into routine clinical management may offer a promising approach to improve OSCC prevention, therapy and patient outcomes.

Keywords: Antioxidant vitamins, Chronic inflammation, Malnutrition, Nutritional supplementation, OSCC.

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INTRODUCTION

In 2020, the World Health Organization (WHO) reported oral and lip carcinoma as the 16th most prevalent cancer with 377,713 new cases (Sarode *et al.*, 2020). In spite of the developed diagnostics and treatment, the five-year survival rate remains approximately 50 and many of the survivors have severe functional and aesthetic impairment that affects their quality of life (Schantz and Yu, 2002). The prevalence and incidence of OSCC are 11th most common, being more prevalent in South and Southeast Asia and some of the Southern Europe (Ghantous and Abu Elnaaj, 2017). Tobacco, alcohol intake, chewing betel nuts, and Human Papillomavirus (HPV) infection are some of the main risk factors (Yakin *et al.*, 2017; Khan, 2012). However, recent research highlights the contribution of the metabolic disorders, especially the abnormalities of glucose metabolism in the initiation and progression of oral cancer (Suba and Ujpal, 2007). Type 2 diabetes and insulin resistance promote tumor growth by hyperinsulinemia, enhanced Insulin-like Growth Factor (IGF) signalling and hyper-glycemia. Also, tobacco consumption interferes with the metabolism pathways-alterations of amino acids, carbohydrates, fatty acids, nucleotides, steroids, and vitamin metabolisms, which also manifest in OSCC (Rushing *et al.*, 2022). Such metabolic alterations, especially in the use of glucose, amino acid, and lipid are some of the basic differences in OSCC and may be used as potential biomarkers to enable early and accurate diagnosis (Wang *et al.*, 2022). Malnutrition, which includes undernutrition and overnutrition, is a worldwide healthcare issue which impacts development, physiological support, and health vulnerability (Meza-Valderrama *et al.*, 2021).

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The disproportion between oxidative stress and antioxidant protective mechanisms in oral cancer encourages the metastasis of tumors and chronic inflammation (Kundu and Surh, 2012; Gokul *et al.*, 2010; Katakwar *et al.*, 2016). Malnutrition negatively affects oral health, which leads to malformation of the developing organs, mucosal diseases of the mouth, and periodontal disease (Shaik and Pachava, 2017). Oral cancer patients have been reported to possess very low levels of antioxidant vitamins in serum by a number of case-control studies, which implies that they could be used as prognostic markers (Lawal *et al.*, 2012; Chippagiri *et al.*, 2014). Nonetheless, there is limited research on ubiquinone (coenzyme Q10), a major mitochondrial antioxidant in the generation of energy in the body. The ubiquinone deficiency of 5 head and neck cancer patients that was observed by Folkers *et al.* (1997) is the only available clinical study that can be cited in the context of biochemical dysfunction. The trace elements are also critical in keeping the mouth healthy and preventing a number of oral diseases. Other factors like fluoride, molybdenum, strontium, lithium and vanadium have been linked with lower risk of dental caries, and selenium, cadmium, lead and copper could increase the risk of caries formation (Pathak *et al.*, 2016). These trace elements, such as iron, copper, zinc, and selenium, play a critical role in metabolism and physiology, which impact the formation of the craniofacial structure and preservation of the oral tissues. However, an overdose of some elements, e.g. copper, has been found to cause some conditions like oral submucous fibrosis (Bhattacharya *et al.*, 2016). The effects of the lack and overdose of trace elements shows the necessity of a healthy diet in cancer prevention and oral health (Faber and Wenhold, 2009). This study will assess the importance of nutritional deficiencies in metabolic disorders and their effects on the risk of oral cancer with reference especially to antioxidant vitamins and trace elements. Knowledge about these associations could be used to identify possible biomarkers and therapeutic targets that could be used to enhance the prognosis of oral cancer.

Search Strategy

A comprehensive literature search was conducted to identify relevant peer-reviewed articles published until 2026 using electronic databases including PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar. Search terms included Oral Squamous Cell Carcinoma (OSCC), bioactive micronutrients, antioxidant vitamins, trace elements, metabolic disorders, oxidative stress, inflammation, immune dysregulation, nutritional supplementation and oral carcinogenesis. Only original research articles, clinical studies, experimental studies, systematic reviews and meta-analyses published in English were considered. A critical review of studies on the role of micronutrients in OSCC pathogenesis, prevention, prognosis and therapeutic management was done, excluding duplicate records, non-English articles, conference abstracts and studies lacking scientific relevancy.

Nutritional Deficiencies In Metabolic Disorders

The nutrition balance can be applied to general health and determines the metabolic pathways, the structure of enzymes and their physiological functions. The cofactors of the enzymes involved in the metabolic processes are also the micronutrients, whose deficiency can lead to several clinical outcomes (Petersen *et al.*, 2005). All the vitamins play a significant role in energy metabolism (Water-soluble B-complex, C, Fat-soluble A, D, E, K). The trace elements are tended to be extremely limited in number but very important in metabolic homeostasis and in case of deficiency, they fail to create any specific symptoms, instead, they trigger a general metabolic malfunction (Tummolo *et al.*, 2023; Ekpenyong, 2018; Kawicka *et al.*, 2015). These absorption changes, food restriction and chronic inflammation result in nutrient deficiency of nutrients that are significant to the health and complicate morbidity (Nompleggi *et al.*, 1989; Yang *et al.*, 1984). Diabetes mellitus is linked with the lack of vitamins A, B6, C, K, iron, potassium, and zinc, which is mainly caused by gastroparesis, malabsorption, and hyper oxidative stress (Parkman *et al.*, 2011; Ghishan and Kiela, 2014). Research shows that two out of three patients with gastroparesis intake calorie deficient diets and thus do not take nutrient deficient vitamins and minerals (Parkman *et al.*, 2011). The prevalence is so high, but only 19.4, 32% of such patients have a nutritional consultation, which is why dietary interventions are necessary (Amjad *et al.*, 2021; Ogorek *et al.*, 1991; Parrish and Pastors, 2007).

Nutritional deficiencies are also increased by obesity and bariatric surgery. Overweight is linked with impaired micronutrient metabolism causing the lack of Vitamins (D, B12, A, K, C, folate), and such essential minerals as iron, zinc, selenium, and copper (Xanthakos, 2009; Shankar *et al.*, 2010). Malabsorption induced by bariatric procedure is a serious complication associated with anemia, neurobiological complications and bone demineralization, which require permanent nutritional follow-up and supplementation (Folope *et al.*, 2007). The absorption of fat-soluble vitamins, especially Vitamins A and E is also altered by liver disease and pancreatic insufficiency that affects lipid metabolism, impairs fatty acid oxidation, and modifies the activity of the peroxisome (Kang *et al.*, 2007). On the same note, pancreatic failure is among the factors that cause deficiencies in the fat-soluble vitamins, including those undergoing enzyme therapies (Dutta *et al.*, 1982). The cholestatic liver diseases also worsen the absorption of vitamins and hence special supplementation of these vitamins is necessary so that the metabolism is not thrown off (Sokol, 1994). The glucose and amino acids metabolism are affected too, as do the absorption of nutrients and cellular activity, as a result of metabolic disorders. In the case of Alzheimer disease, there can be a temporary compensation of the loss of glucose by amino acid oxidation but the abnormality level of amino acid can cause toxicity (Griffin, 2017). In obesity, improved transport of glucose through

GLUT4 dependent mechanisms alters lipid and amino acid metabolism to offset metabolic stress and change mitochondrial activity of enzymes (Gurley *et al.*, 2016). There is also an effect of the branched chain amino acids on the glycemia through the stimulation of the insulin and GLP-1 secretion, which has an impact on the glucose tolerance and metabolic homeostasis (Pena *et al.*, 2015). Metabolic disorders are the disturbances of glucose metabolism, enzyme activity, and health caused by the nutritional deficiencies. These should be solved by means of diet examination and supplementation to achieve improved patient outcomes (Figure 1A).

Pathophysiological Mechanisms

OSCC is also affected by the genetic, epigenetic and molecular alterations that transform normal epithelium to invasive carcinoma. It was shown that the extent of lipid peroxidation and nitric oxide levels, and the quantity of antioxidants, is more elevated in the oral cancer patients and suggested that the oxidative stress is a significant factor in the progression of oral cancer (Beevi *et al.*, 2004). Major oncogenic changes comprise the overexpression of EGFR, K-ras, c-myc and PRAD-1 and loss of tumor suppressor genes such as p53, p16 and FHIT that result in unchecked cell growth and genomic instability (Kamb *et al.*, 1994; Brennan *et al.*, 1995). Progressive tumorigenesis involves regular genetic mutations that include Loss of Heterozygosity (LOH) of chromosomes 3p, 9p, and 17p and instability of the Microsatellites (MSI) (Boyle, 1933). Further and more extreme epigenetic modifications like hypermethylation of tumor suppressors like p16 and MGMT, are other factors that promote malignant transformation by inhibiting major factors of DNA repair (Spafford *et al.*, 2001). HPV infection, alcohol use, and tobacco are environmental factors that are highly risky of oral cancer because these factors lead to the occurrence of genetic mutations, facilitation of oncogenic signaling pathways (Spafford *et al.*, 2001). It has been identified that nutritional deficiencies play an essential role in the oral carcinogenesis because of the diminished cell repair, enhanced oxidative stress and disrupted immune responses. Deficiency of essential micronutrients such as Vitamins A, C, E, folate and iron has been associated with damage of the DNA, disruption of methylation processes, and inefficient antioxidant mechanisms resulting in genomic instability and tumor formation. To be more precise, the lack of the folate in question interferes with the process of methylation and repair of the DNA, predisposing it to the mutation of the oncogenes and tumor suppressor genes, and the iron deficiency activates the oxidative stress and damage of the DNA even further and contributes to the malignant transformation further (Williams, 2000). The role of nutrients in prevention of oral cancer has become the main topic of discussion and this means that more research would be required regarding dietary interventions.

Nutritional deficiencies lead to carcinogenesis on the molecular level through destabilization of the genome, alteration of the epigenetic homeostasis and cellular homeostasis. An increased risk of gastrointestinal cancers in iron deficiency has been linked to the significance of iron in DNA synthesis, repair and iron-based metabolism pathway, which is necessary in the maintenance of genomic integrity (Pra *et al.*, 2009). Similarly, the breakage of DNA methylations and repair disruption induced by folate deficiency leads to genomic instability, altered gene expression and increased mutation rates of critical regulation genes (Choi and Mason, 2000). Antioxidant micronutrients, such as Vitamins A, C, E, 8-carotene and selenium, play a vital role in the neutralization of Reactive Oxygen Species (ROS) and protection of the cells against oxidative DNA damage, a symptom of carcinogenesis (Borek, 1993). The effect of nutrients on DNA damage responses, signal transduction pathways, apoptosis and angiogenesis have also obtained more information through genomic technologies because it could serve as a potential biomarker and new dietary interventions in cancer prevention and treatment (Go *et al.*, 2003).

Oxidative stress is another critical predictor of oral mucosal disease particularly in the chronic inflammatory and carcinogenesis processes. The disequilibrium between the ROS production and antioxidant defense mechanism leads to lipid, protein and DNA peroxidation leading to cell death and tissue destruction (Das *et al.*, 2007; Sardaro *et al.*, 2019). This oxidative damage is further contributed by additional disorders of the oral mucositis induced by radiations where ROS triggers a cascade of biological reactions including epithelial destruction, inflammatory magnification and ulceration until the mucosa heals (Soni, 2021). Chronic oxidative stress sustains chronic inflammation, which provides a favourable environment to assist malignant transformation by increasing the mutation of DNA, disrupting the process of cell repair and resulting in genomic instability. The inflammatory cells, and also the cancer cells, promote oxidative damage by forming free radicals, cytokines and prostaglandins, leading to negligence of cellular signaling and amplified tumor growth (Figure 1B) (Federico *et al.*, 2007). Only through these complicated interactions of the molecules can we develop new therapy interventions like antioxidants and anti-inflammatory agents to minimize the oxidative damages and improve prevention and therapy of oral cancer (Das *et al.*, 2007).

Oral Cancer Risk and Nutritional Status

Nutritional deficiencies, especially of the vital vitamins and trace elements, have a lot of effects on oral health and could be a contributory factor to oral cancer. Vitamins and other antioxidant nutrients like Vitamins A, C, E, and carotene have protective effects by neutralizing the effects of free radicals and carcinogenesis. It has been indicated by research that diets that do not contain vegetables and fruits or the important micronutrients put individuals at a risk of having oral cancer (Prasad *et al.*, 1995; Warnakulasuriya *et al.*, 2009). Malnutrition is a common problem, especially in patients undergoing surgery

as an adjuvant therapy of oral squamous cell carcinoma, which adversely influences their nutritional condition and quality of life (Neralla *et al.*, 2019). A number of studies indicate the presence of certain antioxidant vitamin in cancer of the mouth. The reduced serum concentrations of carotenoids, especially 2-carotene and 1-tocopherol, are associated with an increased risk of oral and pharyngeal cancer (Zheng *et al.*, 1993). Equally, a deficiency of both Vitamins A and C is also related to a high risk of oral cancer (Marshall *et al.*, 1982), and lack of antioxidant Vitamins A, C, and E further increases the risk. Dietary determinants like high levels of fruits have been associated with lowered risks of oral cancer, but low nutrition and alcohol use are some of the causes that lead to oral cancer (Winn, 1995).

In addition to the risk of cancer, the vitamin deficiencies also have significant implications on oral health (Bloch, 1931; Day and Sedwick, 1934; Dinnerman, 1951; Boyle *et al.*, 1993). Vitamin A deficiency may result in enamel hypoplasia and a developmentally retarded periodontium. B-complex deficiencies (B1, B2, B3, B9, and B12) result in glossitis, cheilitis, gingivitis, mucosal atrophy and periodontal destruction (Newman *et al.*, 2011; Najeeb *et al.*, 2016). Vitamin C deficiency is the cause of scurvy, which causes bleeding gums, inability to heal wounds, and faulty collagen formation (Hodges *et al.*, 1971; Woolfe *et al.*, 1980; Nishida *et al.*, 2000). Deficiency in Vitamin D is one of the factors that lead to delayed tooth eruption, jawbone resorption and risk of periodontal diseases and its supplementation enhances bone and enamel health (Miley *et al.*, 2009; Garcia *et al.*, 2011). Even though the deficiency of Vitamin E is not strongly linked to oral complications, it could contribute to wound healing (Anand *et al.*, 2013). Deficiency of Vitamin K has been indicated to disrupt the inhibition of the acid of bacteria and the calcification of the teeth (Mellanby and Pattison, 1928; Nelson and Chaudhry, 1966).

Also, there has been specific association of insufficient intake of Vitamin D with the risk of developing oral cancer (Patini *et al.*, 2024). In case-control study of 150 individuals, beta-carotene, Vitamin C and zinc levels were significantly lower and there were high levels of copper and ceruloplasmin in the oral precancer and cancer patients (Singh *et al.*, 2015). That is an indication that disproportions in antioxidants and trace elements could contribute to the development of diseases.

Among trace elements, lack of fluorine makes enamel weak thereby making it more prone to dental caries, whereas excess consumption causes dental fluorosis. Deficiency of copper affects immune system, making people susceptible to oral infections (Harless *et al.*, 2006). Periodontal disease is worsened by high exposure to lead, antibacterial protection is lowered by iodine deficiency, and insufficient levels of beryllium may be the cause of calculus formation. Low levels of iron and zinc make the immune systems weak, slows down the healing process of the wounds and increases the risk of infections whereas low levels of selenium weaken the ability of the body to produce antibodies (Palmer, 2001; Boyd and Madden, 2003). It has also been indicated that Tin deficiency has been related with poor health and control of plaque and poor health of gums (Leverette *et al.*, 1984). The remedy of these shortcomings especially in the antioxidant vitamins and trace elements might be important in lowering the risk of oral cancer and enhancing periodontal well-being (Figure 2A and Table 1).

Nutritional Interventions For Prevention And Management

Micronutrient supplementation has a potential in lowering the risk of oral cancer which is the 6th most common cancer all over the world (Madiyal *et al.*, 2016). Consumption of fruits and vegetables

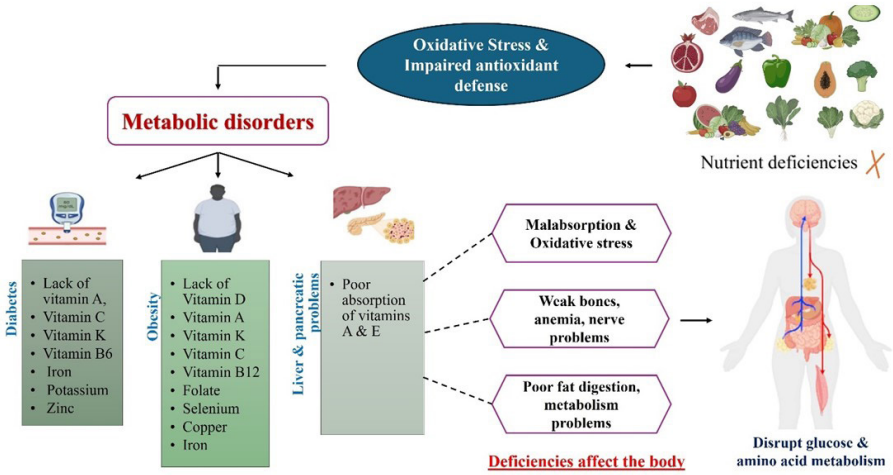


Figure 1A: Summarize metabolic disorders cause nutrient deficiencies, leading to oxidative stress, impaired metabolism, and related health complications.

Table 1: Summarizes the effects of Vitamin and trace element deficiencies on oral health, immunity, and their potential link to increased oral cancer risk.

Nutrients	Deficiency Effects	Results	References
Vitamin A	Enamel hypoplasia, impaired periodontium growth	Increased risk of oral cancer	(Boyle, 1933); Dinnerman, 1951)
Vitamin B-complex	Glossitis, cheilitis, gingivitis, mucosal atrophy, periodontal damage	Poor oral health may contribute to risk	(Najeeb *et al.*, 2016)
Vitamin C	Scurvy, bleeding gums, delayed wound healing, defective collagen formation	Increased risk due to weakened tissue defense	(Nishida *et al.*, 2000)
Vitamin D	Delayed tooth eruption, jawbone resorption, increased periodontal disease	Directly linked to increased oral cancer risk	(Miley *et al.*, 2009); (Anand *et al.*, 2013)
Beta-carotene & Carotenoids	Lower serum levels associated with increased oral cancer risk	Increased risk of oral & pharyngeal cancer	(Zheng *et al.*, 1993)
Copper	Weakened immunity, increased risk of oral infections	Imbalances (high copper, low zinc) found in oral cancer patients	(Singh *et al.*, 2015)
Zinc	Weakened immunity, delayed wound healing	Deficiency linked to higher oral cancer risk	(Chen *et al.*, 2019)

is highly advised as part of a diet in oral cancer prevention (Chainani-Wu *et al.*, 2011). Major antioxidants and trace elements such as zinc, copper, and selenium help in protecting DNA from the attack of free radicals (Madiyal *et al.*, 2016). Although dietary supplements cannot absolutely replace a healthy food, some of the micronutrients that can be used to prevent oral cancer include beta-carotene, Vitamins A, C, and E, lipoic acid, zinc, selenium, and *spirulina*, especially in premalignant lesions. These micronutrients have antitumor effects and work by modulating immunity, tumor suppressor gene activating, and angiogenesis inhibitory actions. Nevertheless, more research is required to determine their conclusive use in the prevention of oral cancer (Jawanda, 2010). Negri *et al.* (2000) indicated that an increased dietary oral carotene, Vitamin C, and Vitamin E intake had a lower risk of oral cancer. Also, the beta-carotene (180 mg/week) and Vitamin A (100,000 IU/week) supplements considerably reduced the number of oral leukoplakia and micro-nucleated cells in chronic betel-quid chewers despite tobacco consumption (Stich *et al.*, 1988). Similarly, Vitamin A (1 lakh IU twice weekly for 3 months) reduced mutant p53 (91.7%) and bcl2 expression (58.0%) in premalignant oral lesions, highlighting its preventive potential. However, its effectiveness was lower in chronic smokers and tobacco users (Varma *et al.*, 2007). Contrastingly, a randomized, double-blind controlled trial in 46 Japanese patients found that 10 mg/day of 10-carotene and 500 mg/day of Vitamin C did not have a significant effect on clinical remission of oral leukoplakia or prevention of malignant transformation as 5-year follow up showed no significant difference in cancer risk between experimental and placebo groups (Figure 2B) (Mayne *et al.*, 2001).

Later studies have revealed that supplement 2-carotene was not significant to reduce the secondary primary oral cancer and local recurrence. The results however indicated that there could be the decrease of the risk of head and neck cancer, and the rise of the susceptibility of lung cancers (Mayne *et al.*, 2001). It was also reported that Vitamin A and zinc acetate supplementation would help improve the symptoms of the Oral Submucous Fibrosis (OSF) patients to the level that they could open the mouth and allay the burning sensation. It was found that after the histological results re-epithelialization and epithelial thickening accompanied by a reduction of collagen (Dhariwal *et al.*, 2010). Vitamin D supplement was also reported to be effective in inhibiting the decrease of symptoms in oral lichen planus and the statistical significance was observed in the treated groups (Nazeer *et al.*, 2021). Besides, the combination of lycopene, selenium and Vitamin E was found to be helpful in reducing the diameter of oral lesion of leukoplakia as compared to placebo and this means it can be utilized in the treatment of the disease (Manas *et al.*, 2022). In patients with Oral Squamous Cell Carcinoma (OSCC) undergoing radiotherapy, Vitamin E supplementation significantly lowered elevated glycoconjugate levels (hexose, hexosamine, fucose, and sialic acid), indicating its potential to enhance treatment response and limit disease progression (Chitra and Shyamala devi, 2008). Nutritional deficiencies, particularly those affecting antioxidants and trace elements, are strongly associated with an increased risk of oral cancer and overall oral health deterioration. Adequate intake of essential Vitamins (A, C, and E) and trace elements like zinc and selenium may play a critical role in oral cancer prevention and periodontal health. Addressing dietary deficiencies in high-risk populations could be a practical strategy for reducing the incidence and progression of oral malignancies (Figure 3A and Table 2).

Table 2: Highlights the role of nutritional supplementation in reducing oxidative stress and impacting oral cancer progression.

Number of Patients	Study design	Micronutrients	Results	References
290 oral cancer cases, 133 esophageal cancer cases, matched controls	Retrospective study	Vitamins C, E, B, multivitamins	Vitamin E reduced oral cancer risk, while Vitamins C, E, and B lowered esophageal cancer risk, especially in smokers.	(Barone, 1992)
130 fishermen from Kerala, India	Randomized, placebo-controlled intervention trial; 3 groups: Group I (Beta-carotene 180 mg/week), Group II (Beta-carotene 180 mg/week + Vitamin A 100,000 IU/week), Group III (Placebo)	Beta-carotene (180 mg/week), Vitamin A (100,000 IU/week)	Supplementation significantly reduced micro-nucleated cells, promoted leukoplakia remission, and inhibited new leukoplakia formation compared to placebo.	(Stich *et al.* 1988)
24 patients with premalignant oral lesions	Pre-post intervention study; all patients received Vitamin A	Vitamin A (1 lakh IU twice weekly for 3 months)	Vitamin A reduced mutant p53 (12.5%) and bcl2 (50%) but was less effective in chronic smokers and tobacco chewers.	(Varma *et al.*, 2007)
46 participants (25 male, 21 female)	Multi-centre, randomized, double-blind controlled trial (RCT). Experimental arm: 23 patients (10 mg/day beta-carotene + 500 mg/day Vitamin C), Placebo arm: 23 patients (50 mg/day Vitamin C)	Beta-carotene (10 mg/day), Vitamin C (500 mg/day)	Beta-carotene and Vitamin C showed no significant effect on clinical remission or prevention of malignant transformation in oral leukoplakia.	(Nagao *et al.*, 2015)
264 patients	Randomized, placebo-controlled, double-blind clinical trial, β-carotene (50 mg/day) vs. placebo	β-carotene (50 mg/day)	β-Carotene supplementation showed no significant effect on preventing second primary oral cancers in treated patients.	(Mayne *et al.*, 2001)
7 (1 case report + 6 additional cases)	Case report and case series with follow-up for 4 months. Patients diagnosed with oral submucous fibrosis (OSF), treated with zinc acetate and Vitamin A.	Zinc acetate, Vitamin A	Zinc acetate and Vitamin A improved OSF symptoms.	Dhariwal *et al.* (2010)
450 patients	Clinical study; Group I: 150 patients (Vitamin D<15 ng/mL + history of stress), Group II: 150 patients (Vitamin D <15 ng/mL, no stress), Group III (Control): 150 patients (Vitamin D>30 ng/mL, no stress)	Vitamin D	Vitamin D supplementation significantly improved symptoms in oral lichen planus patients.	(Nazeer *et al.* 2020)

Number of Patients	Study design	Micronutrients	Results	References
52 patients	Cross-sectional observational prospective study, Group I: 26 patients (Lycopene, Selenium, Vitamin E) Group II: 26 patients (Placebo)	Lycopene (6 mg), Vitamin E (400 IU), Selenium (200 µg) - twice daily	Lycopene, selenium, and Vitamin E significantly reduced oral leukoplakia lesion size compared to the placebo (p<0.05).	(Manas *et al.*, 2022)
26 oral squamous cell carcinoma (OSCC) patients, 26 healthy controls (total: 52)	Observational study; Group 1: Radiotherapy alone (6000 cGy, 5 fractions/week for 6 weeks), Group 2: Radiotherapy + Vitamin E (400 IU/day for 6 weeks)	Vitamin E (400 IU/day)	Vitamin E reduced elevated glycoconjugate levels in OSCC patients.	(Chitra & Shyamala Devi, 2008)
In vitro study	*In vitro* experimental study using five SCCHN cell lines, Single agents (13-cRA, IFN-α2a, α-TF), 2-drug combinations, and 3-drug combination	13-cis-retinoic acid (13-cRA), Interferon-α2a (IFN-α2a), α-Tocopherol (α-TF)	3-drug combination (13-cRA, IFN-α2a, α-TF) significantly inhibited oral squamous cell carcinoma cell growth by inducing S-phase arrest and apoptosis.	(Zhang *et al.*, 2007)
200 patients (Age range: 20-60 years)	Case control study, Oral Leukoplakia (OL) - 50 patients (44 males, 6 females); Oral Submucous Fibrosis (OSMF) - 50 patients (47 males, 3 females); Oral Squamous Cell Carcinoma (OSCC) - 50 patients (40 males, 10 females); Healthy Controls (HC) - 50 age and gender-matched healthy subjects	Copper (Cu), Zinc (Zn), Iron (Fe)	Altered trace elements (elevated copper, reduced zinc, and iron) in oral cancer patients indicate their potential as biomarkers.	(Shetty *et al.* 2013)
41 hamsters (*In vivo*) + KB cell line (*In vitro*)	Experimental study using hamster oral cancer model and KB human oral cancer cells	β-Carotene, Lycopene, Lutein, Vitamin E (α-Tocopherol)	Carotenoids suppressed oral cancer progression by inhibiting PCNA and cyclin D1 expression, with lycopene showing the strongest effect	(Cheng *et al.*, 2007)

Clinical Guidelines And Barriers To Implementing Nutritional Interventions In Oral Cancer

The patients who have oral cancer need to consume a healthy nutritious diet to enhance their immunity system, have stable body weight and improve to recover. The healthcare members recommend intake of high-protein, high-energy food, vegetables, fruits, and healthy fats. Antioxidants can also be inflammatory and oxidative stress reducing such as Vitamin C and E, carotenoids, and omega-3 fatty acids. However, eating is a problem that is normally caused by side effects of treatment. Oral pain, mouth ulcers and swallowing can significantly reduce the consumption of food which can sometimes necessitate oral nutritional supplements or tube feeding. Moreover, chemotherapy and radiation may alter taste and appetite, which will also result in the loss of weight and malnutrition. Besides the physical obstacles, the barriers may also be the financial obstacles that may impede the specialized nutrition care and most patients and medical personnel lack complete knowledge of the relevance of nutrition in managing cancer. Patients have different nutrition requirements and responses to individualized diets are of great essence. Having managed to cope with these issues through the assistance of dietary counselling and special interventions, the medical workers will manage to reach better outcomes of the treatment process and enhance the quality of life of the people who have oral cancer (Figure 3B).

FUTURE DIRECTIONS

Future research should be focused on identifying sensitive and specific micronutrient-based biomarkers for early detection and risk stratification of oral squamous cell carcinoma. Long-term, multi-center randomized clinical trials are needed to determine the optimal dosages, bioavailability and safety

profiles of micronutrient supplementation in various patient populations. Nutrigenomics, metabolomics and systems biology may allow for customized dietary interventions based on an individual's metabolic signature. In addition, the development of nanoformulations and targeted delivery systems may improve the therapeutic efficacy and tissue bioavailabilty of bioactive micronutrients. Standardized clinical guidelines for nutritional screening and intervention in oncology practice will be critical to successful clinical translation.

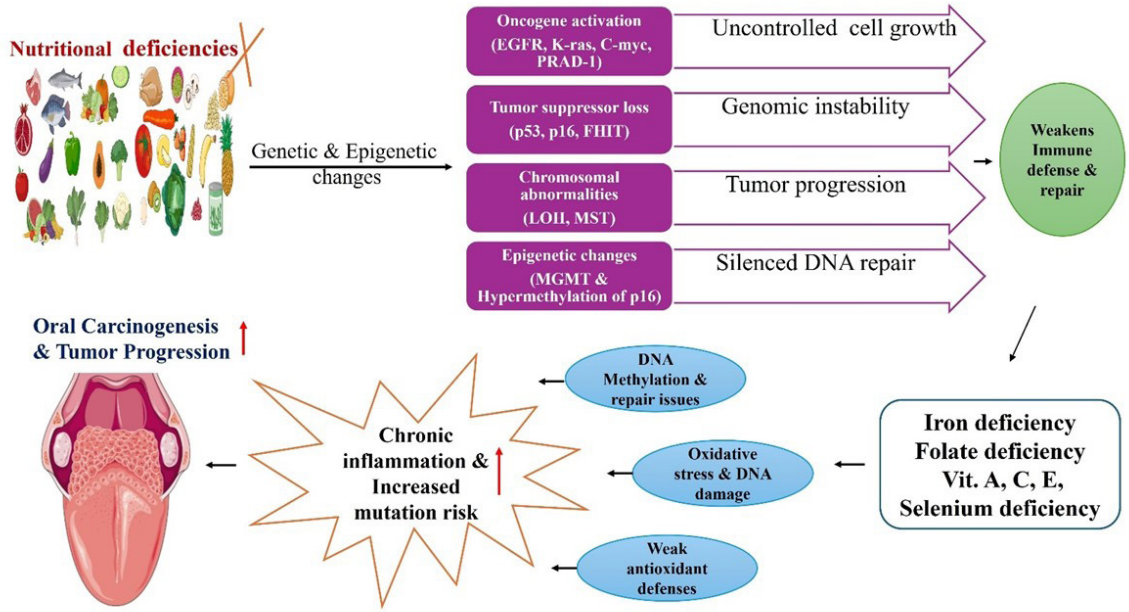


Figure 1B: Illustrates that nutrients prevent metabolic disorder-induced inflammation, DNA damage, and oral cancer progression by enhancing antioxidant, anti-inflammatory, and apoptotic responses.

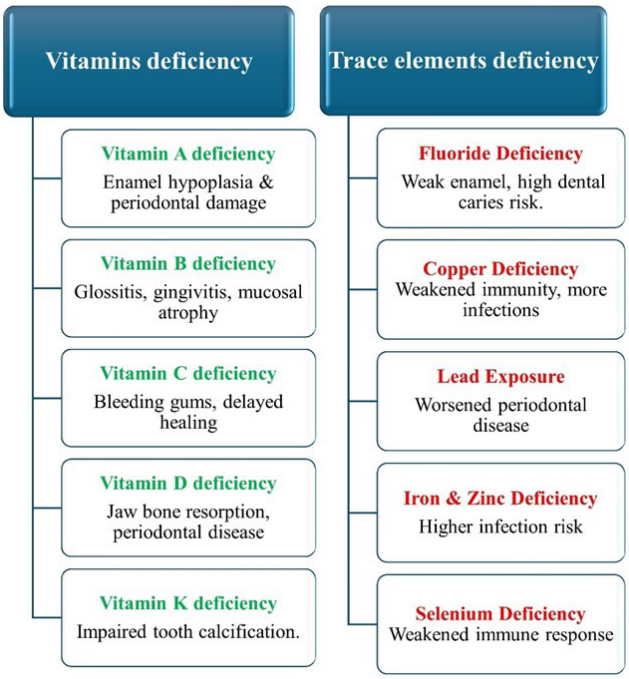


Figure 2A: It outlines how vitamin and trace element deficiencies contribute to dental problems, immune weakness, and higher infection risk.

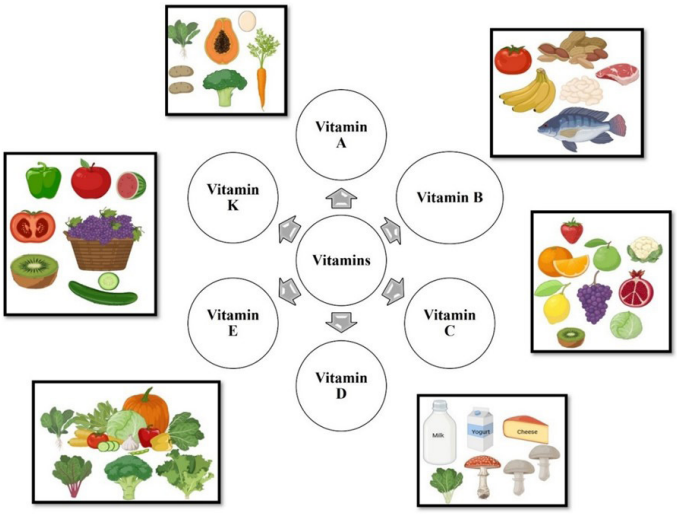


Figure 2B: Illustrates the various types of fruits and vegetables enriched with water-soluble and lipid-soluble vitamins.

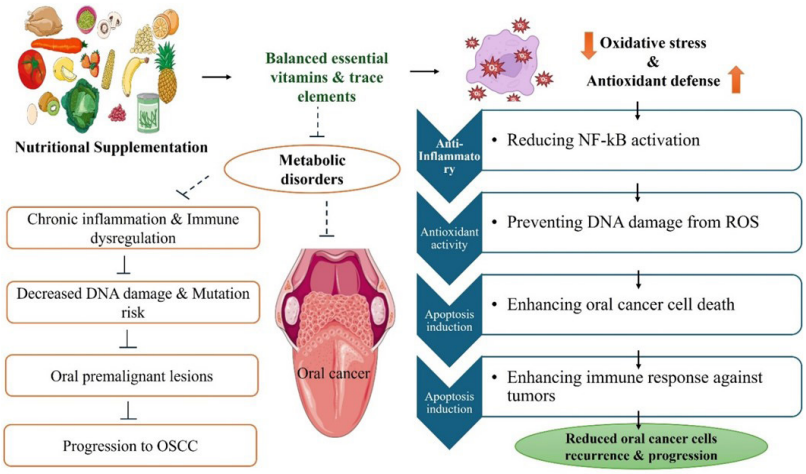


Figure 3A: This indicates that nutritional supplementation reduces oxidative stress, inhibits metabolic disorders, and influences oral cancer progression.



Figure 3B: Represents the various strategies for preventing oral cancer recurrence.

CONCLUSION

Bioactive micronutrients participate in the maintenance of cellular homeostasis and in the modulation of biological processes related to oral squamous cell carcinoma. Growing evidence indicates that micronutrient disturbances in metabolic disorders are involved in disease susceptibility and progression through multiple interconnected mechanisms. The results of this review highlight the clinical significance of nutritional status in the overall management of oral cancer. The incorporation of micronutrient assessment in the routine of patient care could complement existing treatments and improve clinical outcomes, emphasizing the growing role of nutrition in the practice of precision oncology.

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ABBREVIATIONS

OSCC: Oral Squamous Cell Carcinoma; **ROS:** Reactive Oxygen Species; **DNA:** Deoxyribonucleic Acid; **HPV:** Human Papillomavirus; **LOH:** Loss of Heterozygosity; **MSI:** Microsatellite Instability; **IGF:** Insulin-like growth Factor; **GLUT-4:** Glucose Transporter type 4; **RCT:** Randomized controlled Trial; **OSF:** Oral Submucous Fibrosis; **ROS:** Reactive Oxygen Species; **OL:** Oral Leukoplakia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Amjad, W., Qureshi, W., Singh, R. R., and Richter, S. (2021). Nutritional deficiencies and predictors of mortality in diabetic and nondiabetic gastroparesis. *Annals of Gastroenterology*, *34*(6), 788.

Anand, N., Chandrasekaran, S. C., and Rajput, N. S. (2013). Vitamin D and periodontal health: Current concepts. *Journal of Indian Society of Periodontology*, *17*(3), 302-308.

Barone, J., Taioli, E., Hebert, J. R., and Wynder, E. L. (1992). Vitamin supplement use and risk for oral and esophageal cancer. Nutrition and cancer, 18(1), 31–41. https://doi.org/10.1080/01635589209514202

Beevi, S. S. S., Rasheed, A. M. H., and Geetha, A. (2004). Evaluation of oxidative stress and nitric oxide levels in patients with oral cavity cancer. *Japanese Journal of Clinical Oncology*, *34*(7), 379-385.

Bhattacharya, P. T., Misra, S. R., and Hussain, M. (2016). Nutritional aspects of essential trace elements in oral health and disease: An extensive review. *Scientifica*, *2016*(1), 5464373.

Bloch, C. E. (1931). Effects of deficiency in vitamins in infancy: Caries of the teeth and vitamins. *American Journal of Diseases of Children*, *42*(2), 263-278.

Borek, C. (1993). Molecular mechanisms in cancer induction and prevention. *Environmental Health Perspectives*, *101*(Suppl 3), 237.

Boyd, L. D., and Madden, T. E. (2003). Nutrition, infection, and periodontal disease. *Dental Clinics*, *47*(2), 337-354.

Boyle, J. O., Hakim, J., Koch, W., Riet, P. V. D., Hruban, R. H., Roa, R. A., ... and Sidransky, D. (1993). The incidence of p53 mutations increases with progression of head and neck cancer. *Cancer Research*, *53*(19), 4477-4480.

Boyle, P. E. (1933). Manifestations of vitamin A deficiency in a human tooth-germ: Case report. *Journal of Dental Research*, *13*(1), 39-50.

Brennan, J. A., Boyle, J. O., Koch, W. M., Goodman, S. N., Hruban, R. H., *et al.* (1995). Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. *New England Journal of Medicine*, *332*(11), 712-717.

Chainani-Wu, N., Epstein, J., and Touger-Decker, R. (2011). Diet and prevention of oral cancer: Strategies for clinical practice. *The Journal of the American Dental Association*, *142*(2), 166-169.

Chen, F., Wang, J., Chen, J., Yan, L., Hu, Z., *et al.* (2019). Serum copper and zinc levels and the risk of oral cancer: A new insight based on large-scale case-control study. *Oral Diseases*, *25*(1), 80-86.

Cheng, H. C., Chien, H., Liao, C. H., Yang, Y. Y., and Huang, S. Y. (2007). Carotenoids suppress proliferating cell nuclear antigen and cyclin D1 expression in oral carcinogenic models. *The Journal of Nutritional Biochemistry*, *18*(10), 667-675.

Chippagiri, P., Ali, I. M., and Banavar, S. R. (2014). Role of serum β-carotene in the diagnosis and prevention of oral squamous cell carcinoma: A case-control study. *Journal of Clinical and Diagnostic Research*, *8*(4), ZC01.

Chitra, S., and Shyamala Devi, C. S. (2008). Effect of Vitamin E on protein-bound carbohydrate complexes in radiation-treated oral squamous cell carcinoma patients. *Indian Journal of Clinical Biochemistry*, *23*(1), 92-94.

Choi, S. W., and Mason, J. B. (2000). Folate and carcinogenesis: An integrated scheme. *The Journal of Nutrition*, *130*(2), 129-132.

Das, S., Kar Mahapatra, S., Gautam, N., Das, A., and Roy, S. (2007). Oxidative stress in lymphocytes, neutrophils, and serum of oral cavity cancer patients: Modulatory array of L-glutamine. *Supportive Care in Cancer*, *15*(12), 1399-1405.

Day, C. M., and Sedwick, H. J. (1934). The fat-soluble vitamins and dental caries in children. *The Journal of Nutrition*, *8*(3), 309-328.

Dhariwal, R., Mukherjee, S., Mohanty, S. P., Chakraborty, A., Ray, J. G., & Chaudhuri, K. (2010). Zinc and vitamin A can minimise the severity of oral submucous fibrosis. BMJ case reports, 2010, bcr10.2009.2348. https://doi.org/10.1136/bcr.10.2009.2348

Dinnerman, M. (1951). Vitamin A deficiency in unerupted teeth of infants. *Oral Surgery, Oral Medicine, Oral Pathology*, *4*(8), 1024-1038.

Dutta, S. K., Bustin, M. P., Russell, R. M., and Costa, B. S. (1982). Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. *Annals of Internal Medicine*, *97*(4), 549-552.

Ekpenyong, C. E. (2018). Micronutrient deficiency, a novel nutritional risk factor for insulin resistance and Syndrome X. *Archives of Food and Nutritional Science*, *2*(1), 16-30.

Faber, M., and Wenhold, F. A. M. (2009). Trace elements and oral health. In M. Wilson (Ed.), Food constituents and oral health: Current status and future prospects (pp. 331–349). Woodhead Publishing. https://doi.org/10.1533/9781845696290.2.331.

Federico, A., Morgillo, F., Tuccillo, C., Ciardiello, F., and Loguercio, C. (2007). Chronic inflammation and oxidative stress in human carcinogenesis. *International Journal of Cancer*, *121*(11), 2381-2386.

Folkers, K., Osterborg, A., Nylander, M., Morita, M., and Mellstedt, H. (1997). Activities of vitamin Q10 in animal models and a serious deficiency in patients with cancer. *Biochemical and Biophysical Research Communications*, *234*(2), 296-299.

Folope, V., Coeffier, M., and Dechelotte, P. (2007). Nutritional deficiencies associated with bariatric surgery. *Gastroentérologie Clinique et Biologique*, *31*(4), 369-377.

Garcia, M. N., Hildebolt, C. F., Miley, D. D., Dixon, D. A., Couture, R. A., *et al.* (2011). One-year effects of Vitamin D and calcium supplementation on chronic periodontitis. *Journal of Periodontology*, *82*(1), 25-32.

Ghantous, Y., and Elnaaj, A. (2017). Global incidence and risk factors of oral cancer. *Harefuah*, *156*(10), 645-649.

Ghishan, F. K., and Kiela, P. R. (2014). Epithelial transport in inflammatory bowel diseases. *Inflammatory Bowel Diseases*, *20*(6), 1099-1109.

Go, V. L. W., Butrum, R. R., and Wong, D. A. (2003). Diet, nutrition, and cancer prevention: The postgenomic era. *The Journal of Nutrition*, *133*(11), 3830S-3836S.

Gokul, S., Patil, V. S., Jailkhani, R., Hallikeri, K., and Kattappagari, K. K. (2010). Oxidant-antioxidant status in blood and tumor tissue of oral squamous cell carcinoma patients. *Oral Diseases*, *16*(1), 29-33.

Griffin, J. W., and Bradshaw, P. C. (2017). Amino acid catabolism in Alzheimer's disease brain: Friend or foe? *Oxidative Medicine and Cellular Longevity*, *2017*(1), 5472792.

Gurley, J. M., Ilkayeva, O., Jackson, R. M., Griesel, B. A., White, P., *et al.* (2016). Enhanced GLUT4-dependent glucose transport relieves nutrient stress in obese mice through changes in lipid and amino acid metabolism. *Diabetes*, *65*(12), 3585-3597.

Harless, W., Crowell, E., and Abraham, J. (2006). Anemia and neutropenia associated with copper deficiency of unclear etiology. *American Journal of Hematology*, *81*(7), 546-549.

Hodges, R. E., Hood, J., Canham, J. E., Sauberlich, H. E., and Baker, E. M. (1971). Clinical manifestations of ascorbic acid deficiency in man. *The American Journal of Clinical Nutrition*, *24*(4), 432-443.

Jawanda, M. K. (2010). Antitumor activity of antioxidants: An overview. *IJDC*, *1*(1), 3-6.

Kamb, A., Gruis, N. A., Weaver-Feldhaus, J., Liu, Q., Harshman, K., *et al.* (1994). A cell cycle regulator potentially involved in genesis of many tumor types. *Science*, *264*(5157), 436-440.

Kang, H. W., Bhimidi, G. R., Odom, D. P., Brun, P. J., Fernandez, M. L., and McGrane, M. M. (2007). Altered lipid catabolism in the Vitamin A-deficient liver. *Molecular and Cellular Endocrinology*, *271*(1-2), 18-27.

Katakwar, P., Metgud, R., Naik, S., and Mittal, R. (2016). Oxidative stress marker in oral cancer: A review. *Journal of Cancer Research and Therapeutics*, *12*(2), 438-446.

Kawicka, A., Regulska-Ilow, B., and Regulska-Ilow, B. J. P. H. M. D. (2015). Metabolic disorders and nutritional status in autoimmune thyroid diseases. *Postępy Higieny i Medycyny Doświadczalnej*, *69(803)*, 90.

Khan, Z. (2012). An overview of oral cancer in the Indian subcontinent and recommendations to decrease its incidence. *Webmed Central Cancer*, *3*(8), 1-29.

Kundu, J. K., and Surh, Y. J. (2012). Emerging avenues linking inflammation and cancer. *Free Radical Biology and Medicine*, *52*(9), 2013-2037.

Lawal, A. O., Kolude, B., and Adeyemi, B. F. (2013). Oral cancer: The Nigerian experience. *International Journal of Medicine and Medical Sciences*, *5*(4), 178-183.

Leverett, D. H., McHugh, W. D., and Jensen, Ø. E. (1984). Effect of daily rinsing with stannous fluoride on plaque and gingivitis. *Journal of Dental Research*, *63*(8), 1083-1086.

Madiyal, A., Shetty, S. R., and Babu, G. S. (2016). Micronutrients and their role in oral cancer: A review. *West Indian Medical Journal*, *65*(2), 383.

Manas, A., Venkateswararao, C. H., Vaid, S., Khanna, V. D., Muhaseena, M., and Alvi, S. (2022). Assessment of utility of lycopene, selenium, and Vitamin E in management of oral leukoplakia. *Journal of Pharmacy and Bioallied Sciences*, *14*(Suppl 1), S233-S235.

Marshall, J. R., Graham, S., Mettlin, C., Shedd, D., and Swanson, M. (1982). Diet in the epidemiology of oral cancer. Nutrition and Cancer, 3(3), 145–149. https://doi.org/10.1080/01635588109513716

Mayne, S. T., Cartmel, B., Baum, M., Shor-Posner, G., Fallon, B. G., Briskin, K., ... and Goodwin, W. J. Jr. (2001). Randomized trial of supplemental β-carotene to prevent second head and neck cancer. *Cancer Research*, *61*(4), 1457-1463.

Mellanby, M., and Pattison, C. L. (1928). The action of Vitamin D in preventing the spread and promoting the arrest of caries in children. *British Medical Journal*, *2*(3545), 1079.

Meza-Valderrama, D., Marco, E., Dávalos-Yerovi, V., Muns, M. D., Tejero-Sánchez, M., *et al.* (2021). Sarcopenia, malnutrition, and cachexia: Adapting definitions and terminology of nutritional disorders in older people with cancer. *Nutrients*, *13*(3), 761.

Miley, D. D., Garcia, M. N., Hildebolt, C. F., Shannon, W. D., Couture, R. A., *et al.* (2009). Cross-sectional study of Vitamin D and calcium supplementation effects on chronic periodontitis. *Journal of Periodontology*, *80*(9), 1433-1439.

Nagao, T., Warnakulasuriya, S., Nakamura, T., Kato, S., Yamamoto, K., *et al.* (2015). Treatment of oral leukoplakia with a low dose of beta-carotene and Vitamin C supplements: A randomized controlled trial. *International Journal of Cancer*, *136*(7), 1708-1717.

Najeeb, S., Zafar, M. S., Khurshid, Z., Zohaib, S., and Almas, K. (2016). The role of nutrition in periodontal health: An update. *Nutrients*, *8*(9), 530.

Nazeer, J., Singh, R., and Iqubal, M. A. (2012). Assessment of the role of Vitamin D in the treatment of oral lichen planus. *The Journal of Contemporary Dental Practice*, *21*(4), 390-395.

Negri, E., Franceschi, S., Bosetti, C., Levi, F., Conti, E., Parpinel, M., and La Vecchia, C. (2000). Selected micronutrients and oral and pharyngeal cancer. *International Journal of Cancer*, *86*(1), 122-127.

Nelson, M. A. Jr., and Chaudhry, A. P. (1966). Effects of tocopherol, Vitamin E, deficient diet on some oral, para-oral, and hematopoietic tissues of the rat. *Journal of Dental Research*, *45*(4), 1072-1077.

Neralla, M., Jayabalan, J., George, R., Rajan, J., and P. S. K. M. H. A. (2019). Role of nutrition in rehabilitation of patients following surgery for oral squamous cell carcinoma. *International Journal of Research in Pharmaceutical Sciences*, *10*(4), 3197-3203.

Newman, M. G., Takei, H. H., Klokkevold, P. R., and Carranza, F. A. (2011). Carranza's clinical periodontology (11th ed.). Elsevier Health Sciences.

Nishida, M., Grossi, S. G., Dunford, R. G., Ho, A. W., Trevisan, M., and Genco, R. J. (2000). Dietary Vitamin C and the risk for periodontal disease. *Journal of Periodontology*, *71*(8), 1215-1223.

Nompleggi, D., Bell, S. J., Blackburn, G. L., and Bistrian, B. R. (1989). Overview of gastrointestinal disorders due to diabetes mellitus: Emphasis on nutritional support. *Journal of Parenteral and Enteral Nutrition*, *13*(1), 84-91.

Ogorek, C. P., Davidson, L., Fisher, R. S., and Krevsky, B. (1991). Idiopathic gastroparesis is associated with a multiplicity of severe dietary deficiencies. *The American Journal of Gastroenterology*, *86*(4), 423.

Palmer, C. A. (2001). Important relationships between diet, nutrition, and oral health. *Nutrition in Clinical Care*, *4*(1), 4-14.

Parkman, H. P., Yates, K. P., Hasler, W. L., Nguyan, L., Pasricha, P. J., *et al.* (2011). Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology*, *141*(2), 486-498.

Parrish, C. R., and Pastors, J. G. (2007). Nutritional management of gastroparesis in people with diabetes. *Diabetes Spectrum*, *20*(4), 231.

Pathak, M. U., Shetty, V., and Kalra, D. (2016). Trace elements and oral health: A systematic review. *Journal of Advanced Oral Research*, *7*(2), 12-20.

Patini, R., Favetti Giaquinto, E., Gioco, G., Castagnola, R., Perrotti, V., Rupe, C., ... and Lajolo, C. (2024). Malnutrition as a risk factor in the development of oral cancer: A systematic literature review and meta-analyses. *Nutrients*, *16*(3), 360.

Pena, M. J., Rocha, J. C., and Borges, N. (2015). Amino acids, glucose metabolism and clinical relevance for phenylketonuria management. Annals of Nutritional Disorders & Therapy, 2(3), 1026.

Petersen, P. E., Bourgeois, D., Ogawa, H., Estupinan-Day, S., and Ndiaye, C. (2005). The global burden of oral diseases and risks to oral health. Bulletin of the World Health Organization, 83(9), 661–669. https://doi.org/10.1590/S0042-96862005000900011.

Prá, D., Rech Franke, S. I., Pegas Henriques, J. A., and Fenech, M. (2009). A possible link between iron deficiency and gastrointestinal carcinogenesis. *Nutrition and Cancer*, *61*(4), 415-426.

Prasad, M. P., Krishna, T. P., Pasricha, S., Quereshi, M. A., and Krishnaswamy, K. (1995). Diet and oral cancer: A case-control study. *Asia Pacific Journal of Clinical Nutrition*, *4*(2), 259-264.

Rushing, B. R., Tilley, S., Molina, S., Schroder, M., and Sumner, S. (2022). Commonalities in metabolic reprogramming between tobacco use and oral cancer. *International Journal of Environmental Research and Public Health*, *19*(16), 10261.

Sardaro, N., Della Vella, F., Incalza, M. A., Di Stasio, D., Lucchese, A., *et al.* (2019). Oxidative stress and oral mucosal diseases: An overview. *In vivo*, *33*(2), 289-296.

Sarode, G., Maniyar, N., Sarode, S. C., Jafer, M., Patil, S., and Awan, K. H. (2020). Epidemiologic aspects of oral cancer. *Disease-a-Month*, *66*(12), 100988.

Schantz, S. P., and Yu, G. P. (2002). Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer. *Archives of Otolaryngology-Head & Neck Surgery*, *128*(3), 268-274.

Shaik, P. S., and Pachava, S. (2017). The role of vitamins and trace elements on oral health: A systematic review. *International Journal of Medical Reviews*, *4*(1), 22-31.

Shankar, P., Boylan, M., and Sriram, K. (2010). Micronutrient deficiencies after bariatric surgery. *Nutrition*, *26*(11-12), 1031-1037.

Shetty, S. R., Babu, S., Kumari, S., Shetty, P., Hegde, S., and Karikal, A. (2013). Role of serum trace elements in oral precancer and oral cancer: A biochemical study. *Journal of Cancer Research and Therapeutics*, *1*(1), 1-3.

Singh, M., Tiwari, S., Singh, M., and Singh, M. P. (2015). Efficacy of antioxidant vitamins and trace element levels in the prognosis of oral cancer. *Journal of Oral Medicine, Oral Surgery, Oral Pathology and Oral Radiology*, *1*(4), 160-164.

Sokol, R. J. (1994). Fat-soluble vitamins and their importance in patients with cholestatic liver diseases. *Gastroenterology Clinics of North America*, *23*(4), 673-705.

Sonis, S. T. (2021). A hypothesis for the pathogenesis of radiation-induced oral mucositis: When biological challenges exceed physiologic protective mechanisms. Implications for pharmacological prevention and treatment. *Supportive Care in Cancer*, *29*(9), 4939-4947.

Spafford, M. F., Koch, W. M., Reed, A. L., Califano, J. A., Xu, L. H., *et al.* (2001). Detection of head and neck squamous cell carcinoma among exfoliated oral mucosal cells by microsatellite analysis. *Clinical Cancer Research*, *7*(3), 607-612.

Stich, H. F., Rosin, M. P., Hornby, A. P., Mathew, B., Sankaranarayanan, R., and Nair, M. K. (1988). Remission of oral leukoplakias and micronuclei in tobacco and betel quid chewers treated with beta-carotene and with beta-carotene plus Vitamin A. *International Journal of Cancer*, *42*(2), 195-199.

Suba, Z., and Ujpál, M. (2007). Disorders of glucose metabolism and risk of oral cancer. *Fogorvosi Szemle*, *100*(5), 250-257.

Tummolo, A., Carella, R., De Giovanni, D., Paterno, G., Simonetti, S., *et al.* (2023). Micronutrient deficiency in inherited metabolic disorders requiring diet regimen: A brief critical review. *International Journal of Molecular Sciences*, *24*(23), 17024.

Varma, D., Gupta, S., and Mandal, A. K. (2007). Role of p53 and bcl2 as markers of Vitamin A response in premalignant lesions of the oral cavity. *Indian Journal of Pathology and Microbiology*, *50*(1), 15-17.

Wang, Y., Zhang, X., Wang, S., Li, Z., Hu, X., *et al.* (2022). Identification of metabolism-associated biomarkers for early and precise diagnosis of oral squamous cell carcinoma. *Biomolecules*, *12*(3), 400.

Warnakulasuriya, S. (2009). Food, nutrition and oral cancer. In M. Wilson (Ed.), Food constituents and oral health: Current status and future prospects (pp. 273–295). Woodhead Publishing. https://doi.org/10.1533/9781845696290.2.273.

Williams, H. K. (2000). Molecular pathogenesis of oral squamous carcinoma. *Molecular Pathology*, *53*(4), 165.

Winn, D. M. (1995). Diet and nutrition in the etiology of oral cancer. *The American Journal of Clinical Nutrition*, *61*(2), 437S-445S.

Woolfe, S. N., Hume, W. R., and Kenney, E. B. (1980). Ascorbic acid and periodontal disease: A review of the literature. *The Journal of the Western Society of Periodontology/ Periodontal Abstracts*, *28*(2), 44-56.

Xanthakos, S. A. (2009). Nutritional deficiencies in obesity and after bariatric surgery. *Pediatric Clinics of North America*, *56*(5), 1105.

Yakin, M., Gavidi, R. O., Cox, B., and Rich, A. (2017). Oral cancer risk factors in New Zealand. *New Zealand Medical Journal*, *130*(1451), 30-38.

Yang, R., Arem, R., and Chan, L. (1984). Gastrointestinal tract complications of diabetes mellitus: Pathophysiology and management. *Archives of Internal Medicine*, *144*(6), 1251-1256.

Zhang, X., Chen, Z., Khuri, F. R., and Shin, D. M. (2007). Induction of cell cycle arrest and apoptosis by a combined treatment with 13-cis-retinoic acid, interferon-α2a, and

α-tocopherol in squamous cell carcinoma of the head and neck. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*, *29*(4), 351-361.

Zheng, W., Blot, W. J., Diamond, E. L., Norkus, E. P., Spate, V., *et al.* (1993). Serum micronutrients and the subsequent risk of oral and pharyngeal cancer. *Cancer Research*, *53*(4), 795-798.

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