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Role of Food Supplements in Premalignant Lesions: A Literature Review

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Abstract

Premalignant lesions of the oral cavity are histopathological alterations in the oral epithelium linked to a higher likelihood of malignant transformation. These lesions frequently present as leukoplakia (white patches), erythroplakia (red patches), oral lichen planus, and oral submucous fibrosis. Oral cancer, categorized among head and neck malignancies, is considered the sixth most common cancer globally. While tobacco and alcohol consumption remain the primary etiological factors, increasing evidence underscores the significant role of dietary patterns in modulating cancer risk. Various dietary constituents exhibit distinct biological activities that may either mitigate or potentiate the risk of carcinogenesis. Diets rich in fruits, vegetables, curcumin, and green tea have demonstrated protective effects, primarily due to their antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative properties. In contrast, consumption of pro-inflammatory foods – particularly those high in red meat and fried products – has been associated with an increased risk of oral cancer. While certain studies suggest that some dietary supplements may offer supportive benefits in cancer prevention and management, there is no definitive scientific consensus confirming their ability to cure, prevent, or halt the progression of cancer. It is essential for individuals, particularly those undergoing cancer treatment, to consult healthcare providers before using supplements, as these products can interact with medications and potentially cause adverse effects. Numerous epidemiological investigations have found that diets abundant in antioxidants and essential nutrients are associated with a reduced risk of developing several types of cancer, including oral, lung, cervical, and gastrointestinal malignancies. Comparative studies focusing on premalignant oral lesions have examined the chemopreventive potential of various bioactive food compounds. Micronutrients are fundamental to maintaining overall and oral health, and growing evidence supports their role in cancer prevention. This discussion evaluates the therapeutic relevance of specific vitamin supplementation in managing oral potentially malignant disorders (OPMDs) and oral cancer (OC), with attention to their possible anti-cancer effects. A critical limitation in in-vivo studies lie in the complexity of isolating the specific effects of individual nutrients, given the interplay of multiple etiological variables. However, in vitro studies offer a more controlled environment, enabling a clearer understanding of the mechanisms through which certain dietary compounds exert their influence on cellular processes. In conclusion, despite inherent methodological challenges, current evidence supports the protective role of a nutrient-dense diet – particularly one abundant in fruits, vegetables, and select animal-derived products – in the prevention of oral and other malignancies. This protective effect is attributed to the synergistic action of bioactive micronutrients that modulate key pathways involved in carcinogenesis.

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INTRODUCTION

Micronutrients, such as vitamins, trace elements, and cofactors, play a crucial role in maintaining cellular and tissue balance and are essential components of human nutrition. Both deficiencies and excesses of these nutrients can contribute to diseases affecting the oral mucosa and dental hard tissues [1–3]. These complex components are essential for enzymatic processes, cellular metabolism, and the mechanisms involved in oxidative defense [3, 4]. However, an imbalance in trace elements can lead to toxicity, underscoring the need for maintaining accurate levels within the body. Understanding their various roles is crucial in preventing diseases caused by either deficiencies or excessive consumption, stressing the importance of a balanced diet [3]. Various studies suggest that certain dietary components may influence or affect cancerous cell development. As a result, specific foods might play a role in preventing and managing some types of premalignant lesions in the oral cavity. These foods could exert their effects by inducing epigenetic changes within cells, thereby altering gene expression without modifying the underlying DNA sequence. "Epigenetics" refers to such modifications in gene activity and chromatin structure that occur independently of the DNA code [4]. In 1997, the World Cancer Research Fund International and the American Institute for Cancer Research released a report presenting scientific evidence that a diet rich in fruits and vegetables is linked to a reduced risk of developing cancers of the oral cavity, pharynx, esophagus, lungs, colon, and rectum [5]. Several mechanisms have been proposed to explain the potential protective role of various dietary supplements. Antioxidants, for instance, help reduce levels of reactive oxygen species. Certain compounds present in fruits and vegetables – such as glycates and indole-3-carbinol – are believed to possess anti-cancer properties by stimulating phase II detoxifying enzymes, which aid in the removal of reactive oxygen species and support DNA repair processes [6]. Vitamins present in many dietary sources exhibit antioxidant and anti-proliferative effects on malignant cells. They also contribute to strengthening the immune system, supporting DNA synthesis, and influencing DNA methylation processes [7]. Likewise, Vitamin C, commonly found in citrus fruits, like oranges, lemons, limes, and pomelos, appears to lower the risk of developing premalignant lesions and primary cancers. While there is no established recommended dosage and limited evidence regarding its effect on cancer recurrence, the association with risk reduction remains evident [8]. Vitamin C acts as a cellular antioxidant, helping to neutralize oxidative molecules. It appears to work synergistically with vitamin E, enhancing the body's overall antioxidant defense. Additionally, vitamin C inhibits the formation of nitrosamines and prevents certain carcinogens from binding to DNA, which can otherwise cause chromosomal damage. Through these distinct mechanisms, it contributes to a reduced risk of cancer development [9–11]. On other hand, a study conducted in Brazil found that eating bananas was linked to a 77% decrease in the likelihood of being diagnosed with head and neck cancer. Bananas are rich in antioxidants such as vitamins, phenolic acids, carotenoids, and biogenic amines [12]. Fruits, like blackberries, red berries, and grapes, are rich sources of polyphenols, including resveratrol [13]. Resveratrol exhibits anti-inflammatory, antioxidant, and anti-cancer properties. It plays a role in regulating various cellular processes, including growth, division, migration, adhesion, invasion, programmed cell death (apoptosis), and the formation of new blood vessels (angiogenesis) [14]. Vegetables are rich in micronutrients, such as beta-carotene, alpha-carotene, lycopene, and vitamins A, C, and E, many of which have cancer-preventive properties. In some cases, the synergistic effect of these compounds further enhances their ability to prevent cancer development from premalignant lesions. Beta-carotene, acting as an antioxidant, helps guard against DNA damage. When converted into retinol, it contributes to essential cellular functions including adhesion, differentiation, and membrane permeability, playing a protective role particularly against oral premalignant lesions [15]. Lycopene is a naturally occurring pigment produced by plants and some microorganisms [16]. While lycopene is present in fruits, like watermelon, grapefruit, and ripe tomatoes, are considered their primary dietary source. Known for its strong antioxidant activity, lycopene has been widely researched for its potential role in preventing and managing chronic conditions, including degenerative diseases, bone disorders, and cardiovascular issues [17]. Therefore, lycopene may offer therapeutic benefits in managing potentially malignant disorders of the oral cavity [18–21]. It may also act as a protective agent against oral cancer by influencing lipid peroxidation and enhancing levels of reduced glutathione [22].

Other vegetables, like garlic, which belong to the Liliaceae family, are widely recognized for their therapeutic effects, including antioxidants, anti-cancer, anti-inflammatory, and antimicrobial activities [23]. Garlic is rich in organosulfur and flavonoid compounds, which contribute to its distinctive flavor. Additionally, it contains non-sulfur compounds that work together with these components to enhance its health-promoting effects [24]. Research exploring garlic's anti-cancer potential suggests that specific phytochemicals may enhance the activity of enzyme systems involved in detoxifying carcinogens [25].

As noted earlier, a diet rich in both fruits and vegetables is associated with a lower risk of developing premalignant lesions and various forms of cancer. While the recommended minimum intake is around 550–600 grams per day, this amount can vary depending on the types of foods consumed, the use of dietary supplements, and differences across published studies [26]. Some other researchers suggest that a cancer-preventive diet should consist of consuming up to 10 servings of vegetables daily, preferably in various forms – especially raw or incorporated into juices [27].

MOLECULAR MECHANISMS OF VARIOUS CHEMOPREVENTIVE AGENTS

Cancer stem cells contribute to tumor development by continuously multiplying and differentiating into the tumor mass. Gaining insight into the mechanisms that regulate their self-renewal is crucial for the development of anticancer therapies specifically targeting these cells. Plant-based foods often contain various minor dietary compounds that are not classified as nutrients. These non-nutrient substances can inhibit carcinogenesis through multiple mechanisms. Some act as blocking agents by preventing carcinogens from interacting with key cellular targets, while others function as suppressing agents, halting the progression of precancerous cells into malignant tumors. In some cases, a single compound may exhibit both blocking and suppressing effects, highlighting its potential role in reducing cancer risk [26]. Dietary compounds, such as curcumin, sulforaphane, soy isoflavones, epigallocatechin-3-gallate (EGCG), resveratrol, lycopene, pipeline, and vitamin D3, along with food supplements containing folate, selenium, zinc, and copper, have been recognized for their potential chemo preventive properties [27, 28]. Food supplements are recommended for their potential direct or indirect effects on the self-renewal pathways of cancer stem cells. Studies have shown that curcumin and piperine can target breast cancer stem cells, while sulforaphane has been found to inhibit pancreatic tumor-initiating cells as well as breast cancer stem cells. These findings lay the foundation for further preclinical and clinical research on dietary compounds for chemoprevention of cancer stem cells. Such approaches could lead to the development of more effective cancer prevention strategies, potentially reducing cancer resistance and recurrence, and enhancing patient survival [27].

Several known agents with potential chemopreventive properties include black raspberries, tretinoin "biofilm," vitamins A, E, and C, genistein, Spirulina extract, protocatechuic acid, costunolide, black tea polyphenols, curcumin, folic acid, selenium, zinc, copper, starch, turmeric, green tea, and the Mediterranean diet.

BLACK RASPBERRIES

Studies have shown that lyophilized black raspberries, when included in the diet, can inhibit esophageal and colon cancer. Casto et al. (2002) investigated the components of lyophilized black raspberries – such as ellagic acid, ferulic acid, and β-sitosterol – and their effects on cultured human tumor cells and cell cycle progression. The berry extract, along with ferulic acid and β-sitosterol, was found to inhibit the growth of premalignant lesions and malignant cells but had no impact on normal oral cells. On the other hand, ellagic acid inhibited both malignant and normal oral cells. Ferulic acid and β-sitosterol halted cell cycle progression at the M/G1 interface, while the berry extract did not show a specific effect on any stage of the cell cycle [29]. The authors suggested that clinical trials be conducted in human oral cancer, including a pre-surgical model to study gene expression in oral tumors and a post-surgical model to prevent recurrence and modulate the progression of premalignant lesions in the oral cavity [29].

TRETINOIN BIOFILM

Wang et al. were the first to investigate the use of mucosal adhesive film (MAF) combined with tretinoin in a biofilm form. Their study was based on the hypothesis that applying MAF topically to

deliver tretinoin could be both effective and safe for preventing oral cancer, as demonstrated in a hamster model [30].

GREEN TEA

Green tea, made from the young leaves and buds of the Camellia sinensis plant, is the second most popular beverage globally. Approximately one hour after consuming green tea, high levels of catechins and flavonoids can be found in saliva, which gradually release these compounds in the mouth. This process can contribute to preventing tooth decay and gum disease [31, 32]. Studies have suggested that the consumption of tea, especially green tea, may be inversely related to the risk of oral cancer. Several mechanisms have been proposed to explain this association. Green tea has been shown to trigger apoptosis in tumor cells in oral carcinoma, and its active compound, epigallocatechin-3-gallate (EGCG), has been found to inhibit the growth and spread of these cancer cells [31]. Epigallocatechin-3-gallate (EGCG), a compound formed by the esterification of epigallocatechin and gallic acid, is known to possess a range of beneficial properties, including antioxidant, anti-inflammatory, antiangiogenic, antiproliferative, pro-apoptotic, and anti-metastatic activities. These characteristics may contribute to its effects on the development, promotion, and progression of various types of tumors [32]. Teas, such as black (fermented), green (unfermented), and oolong (semi-fermented), are derived from the same tea plant but differ in their brewing and processing methods. Studies have shown that green and black tea preparations can inhibit tumorigenesis in various animal models, affecting different organs. However, despite these findings and numerous epidemiological studies, clear conclusions regarding the protective effects of tea consumption against cancer development in humans have yet to be established [33]. In vitro studies have indicated that green tea acts as a natural inhibitor of DNMT (DNA methyltransferase), preventing DNA hypermethylation. One key component, epigallocatechin-3-gallate (EGCG), has been shown to reverse the hypermethylation of RECK (reversion-inducing cysteine-rich protein with Kazal motifs), a well-known tumor suppressor gene. Additionally, EGCG down-regulates MMP-2 and MMP-9, which are involved in tumor progression [35]. The varying responses to green tea and its components between normal and cancerous cells have been linked to the induction of p57, a key cell cycle regulator. These findings suggest that the chemo preventive effects of green tea polyphenols may involve a p57-mediated survival pathway in normal epithelial cells, while promoting an apoptotic pathway in oral carcinoma cells [36].

CURCUMIN

Curcumin, the primary curcuminoid found in turmeric – a spice derived from a plant in the ginger family (Zingiberaceae) – is accompanied by two other curcuminoids: desmethoxycurcumin and bis-desmethoxycurcumin. These curcuminoids are natural phenolic compounds that give turmeric its characteristic yellow color. Research indicates that curcumin holds promise as a key agent in inhibiting cancer cell proliferation and invasion, particularly in oral cancer therapy. Additionally, molecules, such as CDC27, EGFR substrate 15, PPAR-alpha, and H2A histone, may contribute significantly to curcumin's anticancer effects [37, 38]. Sharma et al. (2006) were the first to show that curcumin can suppress the activation of Nuclear Factor-Kappa B (NF-κB) and cyclooxygenase-2 (COX-2) triggered by smokeless tobacco extract or nicotine-derived nitrosamine ketone (NNK) in oral premalignant and cancer cells in vitro [39]. Curcumin has been shown to influence enzyme activity in specific organs, particularly by reducing levels of matrix metalloproteinases, such as MMP-2 and MMP-9, which helps limit cancer cell invasion. It also affects epithelial-mesenchymal transition (EMT) by regulating related markers and increasing the expression of the tumor suppressor protein p53. Several studies have found that administering curcumin at a dose of 100 mg/kg for three months led to a decrease in carcinogenic effects induced by 4-nitroquinoline 1-oxide (4NQO), a compound used to generate tumors in experimental models. Additionally, curcumin reduced cellular abnormalities, modulated EMT-related gene expression, and showed protective effects against HPV-16-related changes, squamous cell carcinoma, and precancerous lesions [40].

SUPPLEMENTAL AND DIETARY VITAMIN E, VITAMIN C AND B-CAROTENE

Chandra Mouli P.E. and colleagues recommended Vitamin E for its antioxidant properties in managing oral lesions. Vitamin E may help block the activation of tobacco-specific nitrosamines, which

are known carcinogens that require metabolic activation and detoxification. Other antioxidants, including β-carotene, provitamin A, vitamin C, zinc, selenium, and spirulina, are also considered to play a protective role in the prevention of oral cancer [41]. T.N. Uma Maheswari [42] emphasized the therapeutic potential of Vitamin E in managing leukoplakia. Studies have shown that a combination of antioxidants – specifically vitamins A, E, and C – has been particularly effective, with clinical resolution observed in up to 90% [43] of cases and dysplasia regression reported in 97.5% of patients [44]. Rai Balwant, in his study, discussed the role of Vitamin E in oral cancer. He observed that patients with oral cancer often show reduced antioxidant defenses, particularly vitamins E and C, along with heightened oxidative stress. This weakened defense mechanism makes mucosal cells more susceptible to damage caused by reactive oxygen species, creating an internal environment conducive to DNA damage and disease progression. Therefore, supplementation with antioxidants, like vitamins C and E, may be beneficial for individuals with oral cancer [45]. Bhateja S. emphasized the importance of antioxidants in the management of oral mucosal lesions. Research supports the potential chemopreventive effects of antioxidant nutrients, such as beta-carotene and vitamin E, in reducing the risk of oral cavity cancer [46]. Maher et al. investigated the effectiveness of a combination of micronutrients – including retinol, vitamin E, vitamin D, B-complex vitamins, and various minerals – in the treatment of oral submucous fibrosis (OSMF) and observed notable clinical improvement [47].

PROTOCATECHUIC ACID AND COSTUNOLID

Protocatechuic acid (3,4-dihydroxybenzoic acid) is a naturally occurring simple phenolic compound commonly found across a wide range of plant species. It is present in many foods that are part of the human diet, including brown rice bran, whole grains, and onions (*Allium cepa* L.), particularly concentrated in the outer scales [48]. The preventive action of protocatechuic acid is primarily attributed to its antioxidant properties. This includes its ability to inhibit free radical formation, scavenge existing free radicals, and enhance the activity of endogenous enzymes that neutralize these radicals. Additionally, protocatechuic acid may influence enzymes involved in Phase I and II carcinogen biotransformation and could potentially block specific carcinogen binding sites on DNA molecules [49]. Suzuki et al. (2003) proposed that dietary protocatechuic acid may inhibit the progression of oral carcinogenesis induced by 4-nitroquinoline 1-oxide, with this inhibitory effect potentially linked to the suppression of cell proliferation by protocatechuic acid [50].

SELENIUM

Selenium is an essential mineral present in foods like walnuts, chicken, beef, and game meat. It possesses antioxidant properties, supports DNA repair, and exhibits pro-apoptotic effects by influencing the methylation of DNMT and histone deacetylase (HDAC) [51]. While some research has indicated a negative correlation between selenium consumption and cancer risk, recent randomized clinical trials have found that supplementing this mineral may raise the risk [52]. In the context of oral cancer, elevated serum selenium levels can serve as a protective factor when paired with a diet rich in fruits and fish, alongside a decrease in tobacco and alcohol use [53].

Zinc and Copper

Zinc is primarily present in animal-derived proteins (such as beef, pork, and lamb) and is also found in foods like nuts, cereals, legumes, and yeast. Both elevated and reduced serum levels of copper and zinc may be linked to an increased risk of oral cancer, making it important to regulate these levels through diet [54]. Zinc, together with copper, plays a crucial role in various biological processes, including the removal of free radicals via the enzymatic system. Additionally, zinc is vital for immune function, DNA synthesis, and gene transcription regulation; as a result, any changes in zinc levels can impact overall health [54, 55].

FOLIC ACID

Folic acid, also referred to as folate or vitamin B9, is present in foods such as vegetables, beans, cereals, and pasta. It occurs naturally in both plant- and animal-based foods (as folate) and is also available in supplement form as folic acid [56–58]. Folate plays a critical role in DNA methylation and

has been associated with various types of cancer, including breast, ovarian, cervical, lung, and colorectal cancers. Its levels are known to decrease with the consumption of alcohol and tobacco [59, 60]. Dietary folate contains polyglutamate side chains that undergo oxidation and hydrolysis before being absorbed. To improve its bioavailability, folate is also available in the oxidized form known as pteroylglutamic acid [61]. Folate is crucial for DNA synthesis, methylation, and cell cycle repair, all of which help regulate the risk of oral cancer due to the constant proliferation and regeneration of the oral epithelium [62]. Folate's role in DNA repair implies that a deficiency may contribute to the development of certain cancers, though the relationship is not yet fully understood. Research has shown an inverse correlation between elevated folate levels and the incidence of oropharyngeal cancer – regardless of the source or form of intake – with this protective association appearing even stronger in cases of oral cancer [63, 64]. This increased risk is particularly evident among heavy alcohol consumers who have low folate levels [58]. Likewise, alcohol disrupts folate transport and metabolism, heightening cancer risk by impairing DNA synthesis, repair, and methylation in oral epithelial squamous cells. Additionally, the conversion of ethanol to acetaldehyde in the oral cavity may further hinder folate's protective effects [65].

GENISTEIN

Genistein, a type of isoflavone found abundantly in soy, is recognized for its potential in both cancer prevention and therapy. It exhibits a wide range of biological activities, including inhibition of cell growth, promotion of tumor cell differentiation, suppression of angiogenesis, regulation of the cell cycle, and antioxidant properties. Additionally, genistein may have immunosuppressive effects. Beyond its role in oncology, it is also utilized in managing conditions such as osteoporosis, cardiovascular diseases, and symptoms associated with menopause. These health benefits can be achieved through dietary intake or supplementation of genistein at various concentrations [66, 67].

LYCOPENE

Lycopene, named after the tomato species Lycopersicum, is a vivid red pigment classified as both a carotene and a carotenoid. This phytochemical is primarily found in tomatoes but also occurs in other red-hued fruits and vegetables, like red carrots, red bell peppers, watermelons, and papayas – though it is not present in strawberries or cherries. Despite being a carotene, lycopene does not contribute to vitamin A activity. Research by Orly Livny and colleagues demonstrated that lycopene significantly inhibited the growth of KB-1 human oral cancer cells in a dose-dependent manner, whereas β-carotene was found to be considerably less effective in limiting cell proliferation [68]. The findings from their study reinforced the idea that carotenoids, particularly lycopene, could be potent anticancer agents in the development of oral cancers. In a review by Edward Giovannucci and colleagues (1999), the strongest evidence for the beneficial effects of carotenoids was noted for cancers of the prostate, lung, and stomach. The data also suggested potential benefits for cancers of the pancreas, colon, rectum, esophagus, oral cavity, breast, and cervix. However, since the data primarily come from observational studies, a definitive cause-and-effect relationship cannot be established. Additionally, tomatoes contain numerous other compounds that might interact in complex ways, possibly contributing to their anticancer effects [69, 70]. Tsao and colleagues (2004) outlined that patients with premalignant changes in the head and neck represent a diverse group and should be treated according to their molecular genotype. Those with minimal genetic alterations may respond to single-agent treatments like retinoids or other therapies. In contrast, individuals with more extensive genetic changes will require combination chemopreventive therapies. Lesions with significant genetic alterations, such as mutant p53, may benefit from targeted p53 treatments, while those expressing EGFR and COX-2 might need inhibitors targeting these pathways. Other approaches include the use of the oncolytic adenovirus dl1520 (ONYX-015), which specifically targets p53-deficient cells. Ongoing and future research includes exploring EGFR inhibitors, VEGF receptor (VEGF-R) inhibitors, demethylating agents, farnesyltransferase inhibitors, celecoxib, vitamin E, and Bowman-Birk inhibitors [71].

CONCLUSIONS

A variety of epidemiological studies suggest that diet plays a significant role in preventing different types of cancer. The effects of various foods on the body's cells are primarily mediated through

epigenetic mechanisms, which can alter genetic material. These mechanisms can also impact cancer cells, potentially altering or modifying them, thus contributing to both cancer prevention and treatment.

The positive effects of a diet rich in vegetables and fruits are attributed to numerous micronutrients, including polyphenols, lycopene, catechins, flavonoids, curcuminoids, slow-digesting starches, and minerals like selenium, zinc, and copper, along with carotenes, vitamins A, B, C, and E, folate, and omega-3 fatty acids. Some of these compounds are also present in fish and animal products. These nutrients act through various mechanisms, and when combined, they may provide synergistic effects with antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative properties. There are many chemopreventive agents in our everyday diet that exert antimutagenic effects against commonly encountered mutagens. However, in individuals with premalignant lesions or existing cancer, these agents may have limited effectiveness. In certain concentrations, these agents could potentially reverse premalignancy and offer a cure for malignancy. Future controlled clinical trials in animals and humans are essential to investigate the specific actions of these chemopreventive agents.

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