IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 5 Ser. 4 (May. 2026), PP 80-85
www.iosrjournals.org

The Role of Vitamin D and the Vitamin D Receptor in Oral Cancer: A Narrative Review

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Abstract
Background: *Oral cancer remains a major global public health concern, with oral squamous cell carcinoma (OSCC) accounting for more than 90% of all oral malignancies. Despite advances in therapy, prognosis remains poor due to delayed diagnosis and the limited availability of disease-specific biomarkers. Vitamin D and its nuclear receptor (VDR) have attracted considerable attention over the past two decades for their pleiotropic roles extending beyond calcium and phosphate homeostasis.*
Objective: *This narrative review summarises current evidence on the role of vitamin D and VDR in tumorigenesis, with particular emphasis on oral cancer, and examines the mechanisms underlying the anticancer effects of calcitriol, the regulation of VDR expression, the contribution of VDR gene polymorphisms, and the relationship between vitamin D status and chemoresistance.*
Methods: *Peer-reviewed literature published in English was identified through PubMed, Scopus, and Web of Science using combinations of the terms "vitamin D", "vitamin D receptor", "oral cancer", "oral squamous cell carcinoma", "calcitriol", and "chemoprevention". Relevant in vitro, in vivo, and clinical studies were reviewed.*
Results: *Vitamin D, predominantly in its active form 1α,25(OH)$_2$D$_3$ (calcitriol), exerts pro-apoptotic, anti-proliferative, anti-angiogenic and anti-inflammatory effects on a wide range of cancer cells, including OSCC. VDR is expressed in many malignant tissues, and its expression has been correlated with tumour behaviour and treatment response. Epidemiological data suggest that low circulating 25-hydroxyvitamin D levels are associated with increased risk and mortality of several cancers, including head and neck squamous cell carcinoma. Calcitriol supplementation has been shown to enhance the efficacy of photodynamic therapy in preclinical models of squamous cell carcinoma.*
Conclusion: *Vitamin D and VDR represent promising targets for chemoprevention and adjuvant therapy in oral cancer. However, additional well-designed clinical trials are required to establish the therapeutic utility of vitamin D supplementation and to clarify the influence of VDR polymorphisms on individual susceptibility and treatment response.*
Keywords: *Vitamin D; Vitamin D receptor (VDR); Oral squamous cell carcinoma; Calcitriol; Chemoprevention; Tumorigenesis*

I. Introduction

Vitamin D and its receptor (VDR) have gained increasing scientific attention over the past two decades owing to their essential roles in calcium and phosphate metabolism and overall mineral homeostasis [1]. The importance of vitamin D and VDR has been further reinforced by mounting evidence implicating them in the pathogenesis of several non-skeletal disorders, including diabetes mellitus, cardiovascular disease, and a variety of malignancies [2–4].

Recently, the relationship between vitamin D status and cancer progression and mortality has been a focus of both epidemiological and preclinical investigation. Higher circulating concentrations of 25-hydroxyvitamin D have been associated with a reduced risk of several malignancies, including cancers of the bladder, breast, colon and rectum, stomach, ovary, kidney, lung, prostate, pancreas, liver, head and neck, and skin, as well as haematological malignancies [5]. The biologically active metabolite, 1α,25-dihydroxyvitamin D$_3$ [1α,25(OH)$_2$D$_3$, calcitriol], exerts its effects in target tissues primarily by binding to the nuclear VDR [5]. The presence of VDR expression in numerous malignant tumours further supports its role in cancer aetiology and progression.

Oral cancer is a malignant neoplasm arising from the lip or oral cavity. Early detection and prompt treatment remain the most effective strategies for reducing morbidity and mortality [10]. Increasing evidence supports the cancer-preventive properties of vitamin D, attributable to its pro-apoptotic, anti-proliferative, anti-inflammatory and anti-angiogenic actions on a broad spectrum of malignant cells. The present review summarises

the current understanding of vitamin D biology, the mechanisms by which vitamin D and VDR contribute to oral tumorigenesis, and the potential of vitamin D as a chemopreventive and adjuvant therapeutic agent in oral cancer.

II. Biosynthesis and Metabolism of Vitamin D

In humans, vitamin D exists in two principal forms: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) [13]. Vitamin D can be obtained from two main sources: dietary intake and endogenous cutaneous synthesis following exposure to ultraviolet B (UVB) radiation [14, 15].

Cutaneous synthesis is tightly regulated by UVB exposure. Cholesterol within keratinocytes is first oxidised to 7-dehydrocholesterol, the immediate precursor of pro-vitamin D_3. Under UVB irradiation at wavelengths between 270 and 300 nm, 7-dehydrocholesterol is photochemically converted into pre-vitamin D_3, which subsequently undergoes a temperature-dependent isomerisation to vitamin D_3 (cholecalciferol).

Cholecalciferol is biologically inert and requires two successive hydroxylation steps for activation. The first hydroxylation occurs in the liver, where vitamin D_3 is converted to 25-hydroxyvitamin D_3 [25(OH)D_3] by the enzyme CYP2R1. The second hydroxylation takes place principally in the proximal tubules of the kidney through the action of CYP27B1, generating the biologically active hormone 1α,25$(OH)_2D_3$ (calcitriol). Calcitriol acts on the intestine, kidney and bone to enhance the absorption of calcium and phosphorus, promote renal calcium reabsorption and regulate bone remodelling, thereby maintaining serum calcium and phosphate within physiological ranges and supporting skeletal mineralisation.

III. The Vitamin D Receptor (VDR)

The vitamin D receptor is a ligand-activated transcription factor belonging to the nuclear receptor superfamily [26]. Accumulating evidence indicates that the biological functions of VDR extend well beyond the regulation of vitamin D and calcium metabolism. VDR has been implicated in inflammatory signalling, oestrogen-related pathways and insulin-like growth factor signalling, as demonstrated by both in vitro and in vivo studies [27]. The expression of VDR in numerous tumour tissues further suggests a role in tumorigenesis [6].

Over the past decade, our understanding of the biological activities of calcitriol has expanded considerably. In addition to its established role in skeletal health and calcium homeostasis, VDR signalling has been associated with anti-inflammatory and antifibrotic effects, prevention of diabetic nephropathy, reduction of proteinuria, attenuation of hypertension and atherosclerosis, and regulation of cellular proliferation and differentiation [28–37]. Identification of VDR expression in specific tissues is therefore important for elucidating the physiopathological roles of vitamin D and for developing innovative, targeted therapeutic strategies.

IV. Cancer Prevention and Anticancer Effects of Vitamin D

Both naturally occurring vitamin D and synthetic analogues have been shown to induce apoptosis in cancer cells, supporting their potential utility as therapeutic agents [56, 57]. Numerous epidemiological studies have demonstrated a robust inverse relationship between serum vitamin D concentrations and cancer risk, with the strongest evidence reported for breast and colorectal carcinoma [58, 59]. Higher dietary vitamin D intake has likewise been associated with a reduced risk of breast cancer [60].

Because calcitriol exerts multifaceted effects on the maintenance of normal cellular phenotype and function, it has been considered a candidate anticancer agent. The anticancer properties of vitamin D have been clearly demonstrated in numerous in vitro and animal studies. In 1981, Colston et al. [62] reported that calcitriol inhibited the growth of malignant melanoma cells, and Abe et al. [63] subsequently demonstrated similar effects in myeloid leukaemia cells, establishing the foundation for subsequent research on the antineoplastic actions of vitamin D.

V. Molecular Pathological Epidemiology of Vitamin D in Cancer

Molecular pathological epidemiology (MPE) provides a valuable framework in modern medical research by integrating environmental and lifestyle exposures with molecular pathology and immune phenotype. This integrative approach contributes to biomarker discovery, tailored prevention, precision medicine and the design of effective treatment strategies. MPE has been particularly informative in elucidating the interactions among tumour biology, the immune microenvironment and host immunosurveillance, and is therefore relevant to the development of immunotherapy and immunomodulation strategies in oncology.

The contribution of the immune system and chronic inflammation to carcinogenesis is well established, including in post-transplant malignancies, where prolonged immunosuppression markedly increases cancer risk. Dietary and supplemental vitamin D intake, as well as circulating 25-hydroxyvitamin D concentrations, have been associated with reduced incidence and mortality from several cancers.

Oral squamous cell carcinomas (OSCCs) account for more than 90% of all oral malignancies [124, 125]. Although the incidence and mortality of oral cancer have declined in many industrialised countries, including the United States, over recent decades, the global burden continues to rise [126–128]. In low- and middle-income

countries, rising disposable incomes and increasing accessibility to tobacco and alcohol products have contributed to the upward trend in oral cancer incidence [129–131].

Tobacco use and alcohol consumption, particularly when combined, are estimated to account for approximately 80% of oral cancer risk in the United States [128, 130, 132]. Substantial disparities in incidence and mortality have been documented across demographic subgroups, with notably higher rates among certain minority populations and increasing rates among women [133–137]. Oral human papillomavirus (HPV) infection, particularly with high-risk genotypes, has emerged as an important risk factor for oropharyngeal and oral cancers (OPCs) [135]. Oral HPV infection is more prevalent in specific demographic subgroups, including men and certain minority populations, contributing to the geographic and demographic heterogeneity of OPC incidence [136, 138]. Importantly, cessation of established risk factors after diagnosis can improve prognosis and may reduce the risk of recurrent or second primary tumours.

VI. The Role of Vitamin D in Oral Cancer Chemoprevention

The chemopreventive activity of vitamin D in the oral cavity may be summarised as follows:

1. Inhibition of oral cavity carcinogenesis.
2. Reduction in the risk of developing oral cancer.
3. Reversal of premalignant lesions such as oral leukoplakia.

Oxidative damage is increasingly recognised as a contributor to the pathogenesis of cancer and may arise from poor nutritional habits and adverse lifestyle practices. Such damage can induce DNA injury, a fundamental mechanism in carcinogenesis [5]. An adequate antioxidant defence system is therefore critical in mitigating oxidative stress, and is particularly relevant to the prevention of oral and pharyngeal cancer, especially OSCC.

Although the present review focuses primarily on vitamin D, it is worth noting that other fat-soluble vitamins, particularly α-tocopherol (the most abundant and biologically active form of vitamin E), also possess relevant antioxidant and anticancer properties. α-Tocopherol is found in plant oils, margarine and green leafy vegetables, and functions as an effective antioxidant at high oxygen tensions, protecting cellular membranes from lipid peroxidation. Its principal biological actions include:

- Free radical scavenging.
- Maintenance of membrane integrity.
- Modulation of immune function.
- Inhibition of cancer cell growth and induction of differentiation.
- Cytotoxic activity against transformed cells.
- Inhibition of mutagenicity and endogenous nitrosamine formation.
- Inhibition of DNA, RNA and protein synthesis in cancer cells.

VII. Oral Cancer, Vitamin D Deficiency and VDR

The development of OSCC is a multi-step process involving alterations in several key cellular pathways governing tumour initiation, promotion and progression. A wide range of exogenous and endogenous stimuli have been shown to drive the molecular changes that culminate in oral carcinogenesis [140–142]. Calcitriol exerts antineoplastic activity in a variety of head and neck malignancies, with particular relevance to OSCC.

Induction of apoptosis in tumours and precancerous lesions that express VDR — such as oral lichen planus and leukoplakia — represents a plausible mechanism by which vitamin D may contribute to chemoprevention or augment the therapeutic response in OSCC [57]. This hypothesis warrants validation in well-designed clinical studies. In a murine model of cutaneous squamous cell carcinoma, oral calcitriol supplementation enhanced cancer cell death induced by photodynamic therapy [152]. These observations suggest that topical or systemic administration of vitamin D (alone or in combination with vitamin A derivatives) may serve as a low-toxicity adjuvant to standard oral cancer therapy in VDR-expressing patients, with minimal additional clinical risk.

Within the framework of field cancerisation [153–155], systemic vitamin D administration appears particularly relevant, given the broad exposure of the upper gastrointestinal tract to major carcinogenic factors, notably tobacco and alcohol. Persistent carcinogenic stimulation in this anatomical region predisposes patients to metachronous secondary tumours.

Vitamin D deficiency and insufficiency are frequently observed at diagnosis in patients with oral neoplastic lesions. Because hypovitaminosis D may exacerbate treatment-related morbidity, repletion of vitamin D status prior to initiating definitive therapy — particularly in the palliative setting — should be considered an integral component of supportive care.

Polymorphisms of the CYP24A1 gene have been reported to modulate oral cancer risk after adjustment for smoking status, alcohol consumption, age and sex [165]. The transcriptional effects of calcitriol appear to be tissue-specific, which may account for the variable sensitivities observed in head and neck squamous cell carcinoma cell lines (SCC4, SCC9, SCC15 and SCC25); calcitriol-induced growth inhibition ranges from

approximately 50% in SCC9 cells to complete G0/G1 cell-cycle arrest in SCC25 cells [166]. Gene expression profiling of more than 4 500 target genes in SCC25 cells identified at least 38 genes that were up-regulated by a factor of ≥1.5, including protein kinases, growth factors, cell adhesion molecules, cytoskeletal proteins, intracellular signalling components and transcription factors involved in cell-cycle regulation.

VIII. Sunlight Exposure and Oral Cancer Risk

The vitamin D content of most unfortified foods is relatively low; consequently, adequate cutaneous synthesis driven by solar UVB exposure remains the principal source of vitamin D in most populations. For comparison, in the United States an eight-ounce serving of fortified milk provides approximately 100 IU of vitamin D, whereas brief sunlight exposure sufficient to produce a slight pinkness of Caucasian skin can result in the cutaneous synthesis of vitamin D equivalent to an oral dose of approximately 20 000 IU. Such observations may help explain epidemiological findings linking increased sun exposure in particular populations and geographic regions with reduced cancer incidence and mortality at multiple sites. Ecological analyses across more than 100 countries have revealed strong inverse associations between solar UVB exposure and the incidence of at least 15 malignancies, with significant effects observed for cancers of the larynx and oral cavity, among others.

IX. Discussion

Recent investigations have explored the role of vitamin D in the prevention and treatment of a wide spectrum of malignancies. Preclinical evidence strongly supports a chemopreventive role for vitamin D through diverse cellular mechanisms, including pro-apoptotic, anti-angiogenic, anti-inflammatory, anti-proliferative, anti-invasive and anti-metastatic actions [70]. The active hormonal form of vitamin D, calcitriol, mediates these bioactivities primarily by binding to the nuclear VDR in target tissues. Clinically, a wide range of tumour tissues express VDR, providing a mechanistic basis for the influence of this receptor on cancer aetiology [11].

Oral calcitriol supplementation has been shown to potentiate photodynamic therapy-induced cell death in murine models of squamous cell carcinoma [152]. Accordingly, topical or systemic administration of vitamin D may represent a promising, low-toxicity adjuvant strategy that can be integrated with conventional cancer therapy without significantly increasing the risk profile in VDR-expressing patients. Calcitriol has additionally been shown to up-regulate VDR gene expression and protein levels in several cell types in vitro [189, 190]. Mechanistically, calcitriol-induced VDR up-regulation appears to result from both enhanced VDR mRNA transcription and increased protein stability [53, 190]. Notably, keratinocytes themselves possess the enzymatic machinery to synthesise biologically active calcitriol locally.

Yuan et al. [192] provided strong evidence supporting a role for vitamin D signalling in the pathophysiology of oral keratinocytes both in vitro and in vivo, although vitamin D deficiency alone appears insufficient to initiate carcinogenesis or disrupt oral epithelial homeostasis. Afzal et al. [193] demonstrated an association between low plasma 25-hydroxyvitamin D concentrations and increased risk of smoking-related malignancies, including head and neck squamous cell carcinoma (HNSCC). On this basis, vitamin D may attenuate the carcinogenic effects of tobacco smoke constituents. Smokers may therefore derive particular benefit from vitamin D supplementation, given that more than 80% of OSCC cases are attributable to tobacco use.

Within the framework of multi-step carcinogenesis [142], the current literature does not yet permit firm conclusions on whether standardised vitamin D supplementation can be recommended for the chemoprevention of OSCC precursor lesions or to delay disease progression; however, the existing data provide a clear rationale for further mechanistic and clinical investigation [140]. VDR is implicated in multiple cancer types, although not all VDR gene polymorphisms exhibit the same association with disease risk, and the relevance of individual polymorphisms appears to be tumour-site specific. Future research should therefore evaluate the interaction between VDR gene variants, environmental and lifestyle factors, and dietary patterns in relation to cancer risk. A deeper understanding of VDR biology will be essential for the development of personalised preventive and therapeutic strategies.

X. Conclusion

The objective of this review was to summarise current evidence regarding the role of vitamin D in the development and management of oral cancer. Although the anticancer effects of vitamin D have been demonstrated in numerous in vitro and in vivo studies, emerging evidence indicates that these effects are modulated by a complex array of cellular, genetic and environmental factors. Further investigations are required to clarify the influence of the vitamin D system — encompassing both ligand and receptor — on the development and progression of oral cancer, and to evaluate the therapeutic potential of correcting vitamin D deficiency in patients with established disease. The information summarised herein is intended to inform oral epidemiologists, oral healthcare providers and oral oncologists in their efforts to improve clinical outcomes for patients with, or at risk of, oral cancer.

Declarations
Funding: The author(s) received no specific funding for this work.
Conflicts of interest / Competing interests: The author(s) declare that they have no conflicts of interest relevant to the content of this article.
Ethics approval: Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.
Consent to participate: Not applicable.
Consent for publication: Not applicable.
Availability of data and material: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
Code availability: Not applicable.
Authors' contributions: All authors contributed to the conception, literature review, drafting and critical revision of the manuscript, and approved the final version for submission.
Acknowledgements: The authors thank colleagues at the Department for helpful discussions during the preparation of this review.

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