Biomedicine & Pharmacotherapy 109 (2019) 391–401

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Role of vitamin D and vitamin D receptor (VDR) in oral cancer

Nazanin Fathi[a,b], Elham Ahmadian[c], Shahriar Shahi[c], Leila Roshangar[b], Haroon Khan[d], Maryam Kouhsoltani[e], Solmaz Maleki Dizaj[c,f], Simin Sharifi[c,*]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Stem Cells Research Center, Tabriz University of Medical Sciences, Iran
[c] Dental and Periodontal Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Pharmacy, Abdul Wali khan university, Mardan, 23200, Pakistan
[e] Department of Oral and Maxillofacial Pathology, School of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Keywords:
VDR
Vitamin D
Oral cancer

ABSTRACT

Oral cancer is known as one of the most common cancers, with a poor prognosis, related to delayed clinical diagnosis, either due to the lack of particular biomarkers related to the disease or costly therapeutic alternatives. Vitamin D executes its functions by interacting with the vitamin D receptor (VDR), both in healthy and diseased individuals, including oral cancer. This review discusses the role of vitamin D and VDR on tumorigenesis, emphasizing on oral cancer. Furthermore, regulation of VDR expression, mechanisms of anticancer effects of calcitriol, oral cancer chemoresistance and its relation with VDR and polymorphisms of *VDR* gene will be discussed. The manuscript is prepared mainly using the information collected from PubMed and MEDLINE.

1. Introduction

Vitamin D and its receptor (VDR) earned increasing importance during the last two decades as they play an essential role in the calcium and phosphate metabolism and also homeostasis [1]. On the other hand, the importance of attention to vitamin D as well as VDR increased whenever it was revealed to effect noteworthy clinical problems such as diabetes, cardiovascular disease, and cancers [2–4].

Recently, the role of vitamin D to various disease progressions and mortality of cancer has drawn attention in epidemiological and preclinical studies. The higher level of circulating vitamin D is strongly related to reducing the risk of progression a variety type of cancers (bladder, breast, colorectal, gastric, ovarian, kidney, hematological, lung, prostate, head and neck, pancreatic liver, and also skin cancers). It has been shown that vitamin D could inhibit the proliferation and differentiation of tumor cells. The active form of the fat-soluble metabolite, 1α,25(OH)2D3, exert its performance on various tissues with binding to the nuclear vitamin D receptor (VDR) [5]. Moreover, the presence of VDR expression in a number of malignant tumor tissues is reflective of the role of VDR in influencing cancer etiology. On the other hand, it has been illustrated that the activity of the VDR-vitamin D complex could be altered by VDR polymorphisms [6–8].

Oral cancer is a type of malignant neoplasm that involving the lip or oral cavity. Because oral squamous cell carcinoma (OSCC) consists of more than 90% of oral cancers, it is conventionally defined as OSCC [9]. The timely detection and immediate treatment is the most effective procedure to decrease morbidity and mortality in oral cancer [10]. More recently, prevention and also treatments efficacious of vitamin D has been examined in the wide range of cancers. The data obtained from preclinical studies strongly support the cancer prevention properties of vitamin D because of its pro-apoptotic, anti-proliferative and anti-angiogenic performances against the wide range of cancer cells [11].

As regards to the numerous studies have been supported on the vitamin D, and its receptor plays a vital role in cancer's etiology, nevertheless, no comprehensive review on the association between oral cancer and vitamin D/VDR system is available. In this article, we reviewed the updated evidence related to the role of this system in oral cancers. Information is collected from the National Library of Medicine's PubMed database, and we discussed the role of vitamin D and VDR in oral cancer [6].

2. Vitamin D synthesis

A group of fat-soluble secosteroids that known as vitamin D is responsible for rising absorption of phosphate, magnesium, and calcium,

* Corresponding author at: Dental and Periodontal Research Center, Tabriz University of Medical Sciences, Golgasht Street, Daneshgah Ave., Tabriz, Iran.
E-mail address: sharifis@tbzmed.ac.ir (S. Sharifi).

https://doi.org/10.1016/j.biopha.2018.10.102
Received 17 September 2018; Received in revised form 18 October 2018; Accepted 20 October 2018

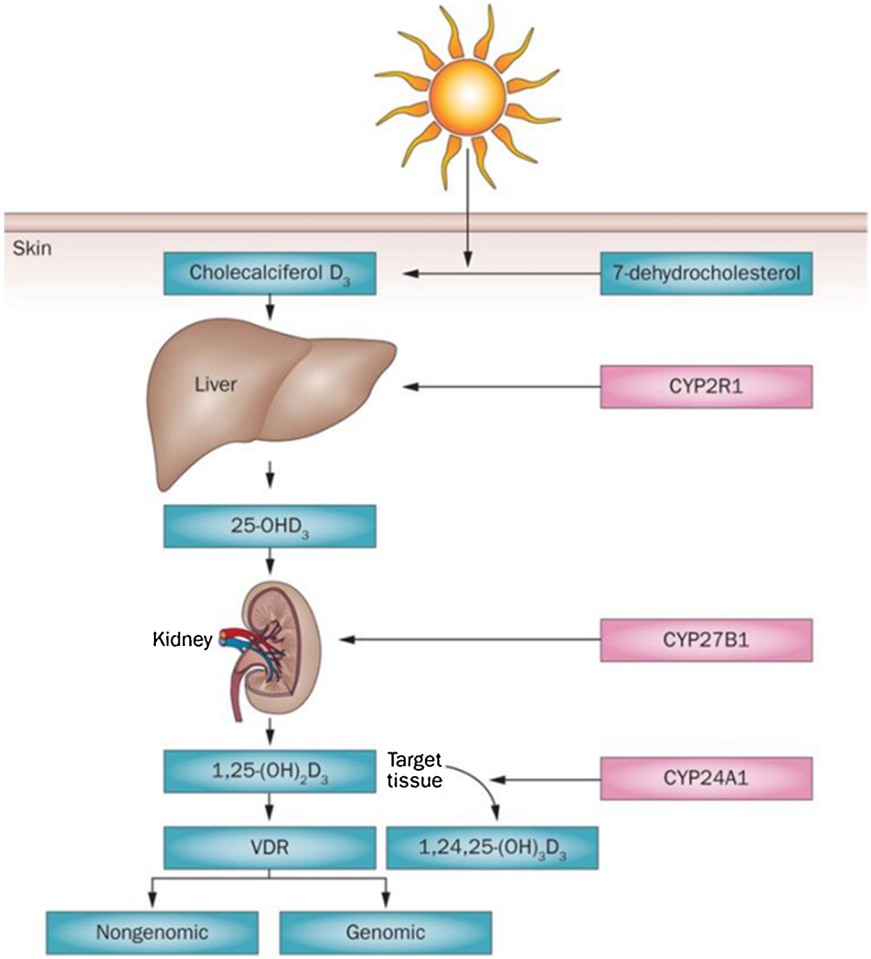

Fig. 1. Systemic vitamin D metabolism (adapted from ref. [18] with permission).Vitamin D synthesis commonly starts in the skin tissue, where 7-dehydrocholesterol converts to cholecalciferol by ultraviolet B radiation. Cholecalciferol D3 is an inactive form, and before the active 1α,25-dihydroxy vitamin D3 (calcitriol) is formed, it undergoes two hydroxylation steps. Hepatic CYP2R1 mediated 25-hydroxylation and renal CYP27B1 mediated 1α-hydroxylation. 1α,25-dihydroxyvitamin D3 that is the active form of vitamin D that couple to the vitamin D receptor (VDR) and mediates fast effects by additional ligand (nongenomic), binding pocket, or genomic effects by the genomic pocket. 24-hydroxylation inactivated all of the vitamin D circulating forms.

in the intestine [12]. In human, vitamin D_3 (known as cholecalciferol) and vitamin D_2 (known as ergocalciferol) are the most important compounds in this group [13]. There are two different ways Vitamin D is acquired: dietary source and non-dietary source from sunlight exposure [14,15]. The UVB radiation exactingly regulated the vitamin D synthesis. At first, in the epithelium of the bowel with starts oxidation the cholesterol to 7-dehydrocholesterol, create pro-vitamin D3. Followed by the pro-vitamin D3 transferred to skin and with the effect of ultraviolet radiation at wavelengths from 270 to 300 nm converted to pre-vitamin D3. Followed by pre-vitamin D3 isomerizes to vitamin D3 and cholecalciferol, in a temperature-dependent reaction. Activation of vitamin D3 happens by two hydroxylations and create 1α,25(OH)2D3 (calcitriol that is as the biological active form of vitamin D) [16]. By the microsomal and mitochondrial vitamin D 25-hydroxylases (CYP27A1), calcitriol first one takes place in the liver. The 25(OH) D (calcidiol) is ordinarily applicable in different studies to estimate the vitamin D level as it has physiological higher concentration [8]. The second hydroxylation is performed by 1-hydroxylase (CYP27B1) in the renal mitochondria (Fig. 1). Furthermore, 24-hydroxylation inactivated all the circulating forms of vitamin D [16,17]. It is noteworthy, the synthesis of calcitriol is not only done in renal cells, even can as well as be established in skin, keratinocytes, prostate and cancer cells [9,10,11,12].

2.1. VDR related genomic mechanism of calcitriol action

The biological actions of calcitriol are mostly exerted through genomic actions mediated by the VDR (Fig. 2). Initially, calcitriol joins to the VDR, so retinoid X receptor (RXR) induce its dimerization, then formed a complex to vitamin D response elements (VDREs) binds into several regulatory areas which are located in promoter sites and distal regions of target genes that enrollment as co-modulators [18–22]. The calcitriol has been shown several rapid cellular actions through non-genomic related pathways [23]. As well as, it needs the VDR and the endoplasmic reticulum stress protein57 (ERP57; also known as 1,25D3–MARRS and GRP58) [24], that involved in the protection of calcitriol *versus* DNA damage that was induced by sunlight and also skin cancer [25].

3. VDR

The vitamin D receptor is a member of the nuclear receptors' superfamily with its gene longs 75 kb that is mapped on long arm of the chromosome 12 [26]. The previous evidence demonstrated the functions of VDR are much wider than the commonly known functions of vitamin D or calcium metabolism. The importance of VDR has been shown as an inflammatory mediator; its role is also suggested in estrogen-related pathways and insulin-like growth factor signaling by *in vitro* and *in vivo* studies [27]. In addition, the existence of VDR in the numerous tumor tissues is suggestive of its role in tumorigenesis [6].

During the last decade, our understanding of 1,25(OH)2D3 metabolism, as well as biological activities, has significantly improved. In the twentieth century, it has been reported that VDR plays an important role in maintaining skeletal health and calcium homeostasis. Additionally, VDR is related to other effects: anti-inflammatory and anti-fibrosis status, diabetic nephropathy prevention, reduction of proteinuria, hypertension and atherosclerosis, alignment of proliferation and differentiation [28–37]. It seems that the identification of VDR in tissues is essential to realize the physiopathological importance of vitamin D and may have the potential for the development of innovative modalities for targeted therapy. Interestingly, since VDR was

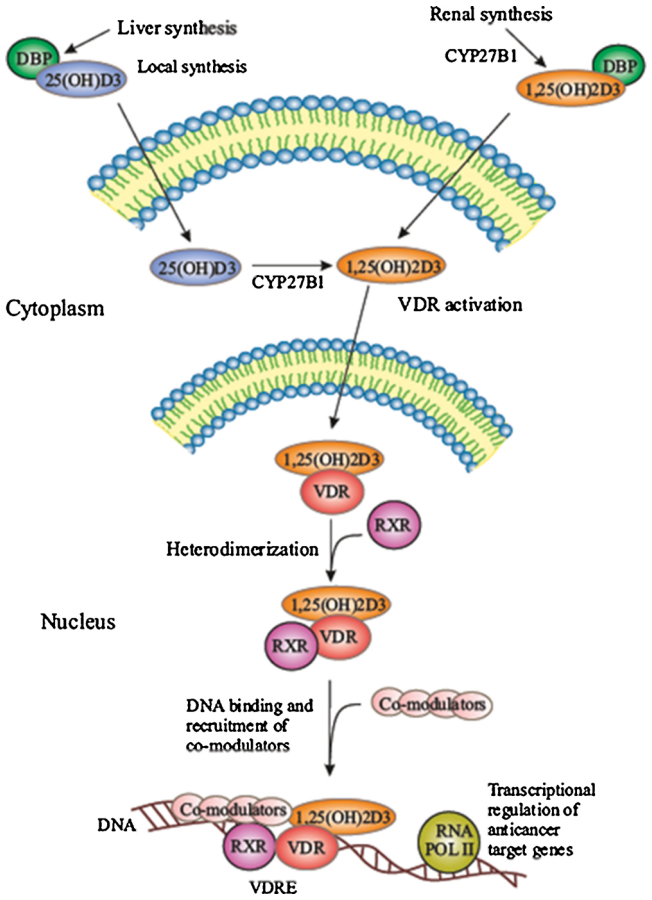

Fig. 2. VDR related genomic mechanism of calcitriol action. Both 25-(OH)D3 (calcidiol) and 1,25-(OH)2D3 (calcitriol) circulate bound to a specific carrier protein as known vitamin D binding protein (DBP). Conversion of 25(OH)D3 to 1,25-(OH)2D3 mediated with a CYP27B1 enzyme in the target cells. The 1,25-(OH)2D3 biological activities are mediated by VDR protein. Binding of 1,25-(OH)2D3 to VDR and retinoid X receptor (RXR) dimerization and its transportation to the nucleus. The complex of ligand-bound VDR–RXR couple to vitamin D response elements (VDREs) in several regulatory regions which is located in the target genes promoters, following on this causes the employment of co-activators or co-repressors, which respectively cause positive or negative regulations in transcription of target genes.

discovered three decades ago, more than fifty targets have been identified relating to vitamin D functions [38–41].

3.1. Regulation of VDR expression

The regulation of VDR expression is multifaceted; formed by environment, genetics, and epigenetics. Studying the interactions and association roles of these facets for gene regulation could be facilitated to the better understanding of the predisposition and evolution of VDR-related diseases such as cancer. Various environmental factors control the VDR, among which are age, diet, sun exposure, infection and pollution [42–46]. The *VDR* gene heterogeneity in several diseases and populations maybe owing to divergent lineages to evolutionary relationships causing in distinct clusters of diverse geography [47]. Instead, VDR DNA shows a regulation role in infections, cancer and some other diseases by several epigenetic mechanisms such as methylation [48]. It was illustrated the *VDR* gene regulated through various hormones including retinoic acid, parathyroid hormone (PTH) and glucocorticoids [49,50]. Maybe the most interesting aspect is the capability of $1,25(OH)_2D_3$ to raise the expression of the *VDR* gene. Identically, VDR levels autoregulate by $1,25(OH)_2D_3$ over both transcriptional [51–53] and posttranslational [53,54] regulations. In the other case, the ligand interactions with its receptor led to increasing the stability of the VDR protein, of which the mechanism remains to be determined although the studies suggest that several enhancers located within the gene itself directly involved in autoregulation of the *VDR* gene by $1,25-(OH)_2D_3$. These studies prepared for starting to need further investigation related to *VDR* gene regulation [55].

4. Cancer prevention and anti-cancer effects of vitamin D

Natural vitamin D or synthetic compounds of vitamin D [56,57] have been shown to induce apoptosis of cancer cells and likely to play a promising role in cancer therapy. Numerous studies have proposed a strong relationship between low serum vitamin D levels and increased risk of cancer [58,59], especially by the strongest evidence in breast and colorectal cancer. Furthermore, a higher level of vitamin D intake is related to a lower risk of breast cancer [60]. More recently evidence indicated that 10,000 IU/d of calcitriol is the safe upper intake level [61] that is significantly more potent than ergocalciferol (vitamin D2). Because of the $1,25(OH)_2D_3$ multi-involved roles in the protection and regulation of normal cellular phenotypes and functions, it has been included as an anti-cancer agent.

The vitamin D anti-cancer activities have clearly demonstrated in the *in vitro* and *in vivo* animal model. In 1981, Colstonet et al. [62] presented inhibition the growth of malignant melanoma cells by the calcitriol, and Abe et al. [63]. In additional studies, reported that calcitriol led to the differentiation of HL60 leukemia cells to the macrophages lineage. The *in vitro* and *in vivo* anti-cancer ability of calcitriol has been reported in various tumors [18,21,64–69]. Genomics and proteomics screening approaches recognized a comprehensive array of VDR target genes which it intercedes the anti-cancer effects attributed to calcitriol [70–75].

The experimental evidences suggest a relationship between serum calcidiol concentration in the optimal level of 80 nmol/L (~32 ng/ml) and prevention of cancer [61,76]. According to the vitamin D status in the populations of Central Europe (CE), determined by the levels of 25-OH vitamin D are typically below the 30 ng/mL. The 25-OH vitamin D values in the wintertime of the CE population are around 21–23 ng/mL in all studied age groups, with a considerable increase in August that reaching to 42 ng/mL for children between aged 0 and 9 years, but 21 ng/mL for the elderly aged from 80 to 89 years [77]. Specially focusing on head and neck squamous cell carcinoma (HNSCC), in a study by Arem et al. [78] investigated that there is no relation between a median serum 25-OH vitamin D level at 31 nmol/L (~12 ng/ml) and oropharynx cancer in Finnish men (including n = 131 patients with OSCC).

5. Common basic mechanisms of the anti-cancer effects of calcitriol

The potential anti-cancer mechanisms of calcitriol illustrate in Fig. 3.

5.1. Induction of apoptosis

In many but not exactly all kind of cancer cells calcitriol induce apoptosis by means of cell type-specific mechanisms, mainly through induction the intrinsic pathway of apoptosis, especially *via* suppressing the expression of anti-apoptotic genes, for example, *BCL2*, and also by the pro-apoptotic genes like *BAX* stimulation [79,80]. Evaluation of critical apoptosis-regulatory genes in total RNA derived from oral cancer cell lines has revealed the occurrence of programmed cell death after calcitriol treatment. In this context, calcitriol could induces the expression of *caspase 2, 8* and *BAX* genes in a concentration dependent manner in oral cancer *in vitro* [81]. In addition, these events mediate the activation of downstream protease pathways that lead to cell removal by apoptosis [79,82]. Calcitriol-induced apoptosis delayed

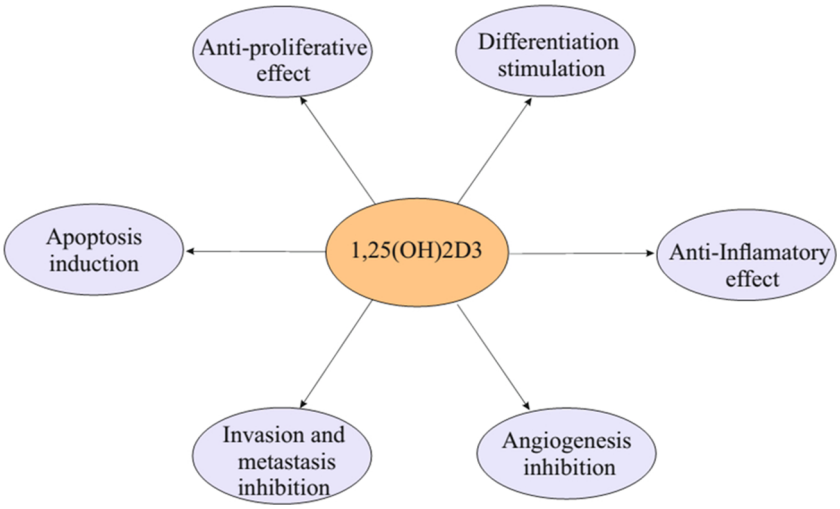

Fig. 3. Common anti-cancer mechanisms of calcitriol.

mammary gland epithelial maturation in VDR-null mice, suggest a potential role of physiological apoptosis during the development of normal mammary [83].

5.2. Anti-proliferative effects

Cyclin-dependent kinases (CDKs) play an essential role in the regulation of the cell cycle [84]. Cyclin-dependent kinase inhibitors are considered as potential anticancer agents. Calcitriol stimulates up-regulation of the cyclin-dependent kinase (CDK) inhibitors, such as p21 and p27, and reduce the activity of CDK, thus leading to the retinoblastoma protein dephosphorylation and eventual G0/G1cell cycle arrest [85–88].

Calcitriol stimulates suppression of the mitogenic signaling through some growth factors such as insulin-like growth factor1 (IGF1) through upregulation of IGF-binding protein 3 (IGFBP3) and epidermal growth factor (EGF), along with increasing the expression of growth inhibitors, for example, transforming growth factor-β (TGFβ) [89,90]. Additionally, calcitriol modulates the intracellular kinase pathways, for example, PI3K, p38 MAPK, and ERK and also suppress the proto-oncogene MYC [87,91]. Calcitriol treatment has been shown to induce the expression of cell-cycle regulatory genes such as *ornithine decarboxylase*, *c-myc* and *p53* in oral squamous cell carcinoma cell lines (SCC15,CAL27, SCC25,) [81]. The high telomerase activity may indicate high proliferation rate as seen in human cancer cells; calcitriol and analogs involved the inhibition of high telomerase activity through decreasing telomerase reverse transcriptase (TERT) mRNA expression [92]. Calcitriol also induces miR-498 that play a role in the down-regulation of TERT mRNA in some cancer cells [93].

In addition to direct anti-proliferative effects, calcitriol has been shown to mediate the chemo-preventative impact of growth inhibitors in an upward trend. Erlotinib as an epidermal growth factor receptor (EGFR) pathway inhibitor has gained importance in head and neck carcinogenesis. The latter pathway is an early event in squamous cancer initiation. Calcitriol has effectively increased the inhibitory effects of erlotinib in tumor growth of patient-derived xenograft model of HNSCC [94].

5.3. Anti-inflammatory effects

Vitamin D induces anti-inflammatory by suppression of prostaglandin action through suppression of cyclooxygenase 2 expression, stress kinases, nuclear factor KB (NF-κB) signaling, and increasing tissue inhibitor of metalloproteinases 1 and E-cadherin response. Antiproliferation by a decrease in cyclin-dependent kinases, cyclins, MYC and RB expression, and an increase in P21 and P27 expression and intracellular kinase pathway modulations such as MAPK, ERK, P38 and P13 pathways. Inflammation involved the expansion and progression of several cancers [95].

Calcitriol shows valuable anti-inflammatory activities in many cancers [69,96]. Some of important mechanisms consist of: (i) the inhibition of the prostaglandin synthesis (prostaglandins are one of the more significant contributors to the inflammatory process) by repressing the expression of cyclooxygenase 2 (COX2) and also prostaglandin signaling (through enhancing the catabolic enzyme 15-hydroxyprostaglandin dehydrogenase expression), as well as down-regulating the expression of prostaglandin receptors [97,98]; (ii) The inhibition of p38 stress kinase signaling (the p38 is one of the main MAP kinases and MAP kinase pathway, a key inflammatory signal mechanism in eukaryotic cells) through the up-regulation of MAPK phosphatase 5 and consequent down regulation the production of pro-inflammatory cytokine [99]; (iii) The suppression of NF-κB signaling [100–102].

Calcitriol supplementation in patients with HNSCC for 3 weeks between cancer diagnosis and surgical intervention has prolonged the recurrence time in a clinical study in which the anti-inflammatory property of calcitriol has been shown to have a fundamental role [103].

5.4. Stimulation of differentiation

Some cancer cells obtain a minor malignant, and more mature and normal phenotype in response to calcitriol, which indicates a pro-differentiating effect [104]. For examples, human myeloid leukemia cells inducing into macrophages and monocytes in the last stage of differentiation [88], induction of the differentiation markers for example lipid droplets, casein and some adhesion proteins in breast cancer cells [105], in prostate cancer cells increasing expression of E-cadherin, bone morphogenetic protein6 (BMP6) and prostate-specific antigen (PSA) as well as the induction the differentiation markers in colonic epithelial cell in colon cancer [104]. Other pro-differentiation effects of calcitriol are cell type-specific mechanisms consist of the regulation of JUN N-terminal kinase, β catenin, NF-κB signaling pathways and PI3K, in addition to the regulation the activity of the some transcription factors such as the CCAAT/enhancer-binding protein (C/EBP) and the activator protein 1 complex [19,104].

5.5. Inhibition of angiogenesis

Calcitriol plays a critical role in suppression of angiogenesis through inhibition of vascular endothelial growth factor (VEGF which is an essential contributor in angiogenesis) expression through repression of

interleukin-8 (IL-8) through an NF-κB-dependent manner and transcription alhypoxia-inducible factor1alpha (HIF1A) [105,106]. Additionally, calcitriol enhancing expression of pro-angiogenic factors such as VEGF, platelet-derived growth factor (PDGF), HIF1α and angiopoietin1 in tumors of VDR-null mice recommend these molecules regulate through calcitriol–VDR [107]. Other studies showed that calcitriol has a potential anti-proliferative action directly on tumor-derived endothelial cells [107]. Furthermore, it has an indirect role in decreasing COX2-generated prostaglandin E2 (PGE2) which favors angiogenesis by increasing HIF1α synthesis in cancer cells [108]. Besides, different studies have investigated the efficacy of calcitriol analogs in cancer prevention. Calcitriol has been shown to prohibit oral squamous cell carcinoma cell growth through inhibition of NF-kB and HBp17/FGFBP-1 signaling cascades which are crucial in cancer angiogenesis [109].

5.6. Inhibition of invasion and metastasis

Metastasis is the important cause of mortality in patients with cancer. In recent decades, a significant advancement in understanding the cellular and molecular basis of invasion and metastasis in cancer is achieved [110]. This section summarizes some invasion and metastasis inhibition mechanisms of calcitriol. The plasminogen activator system and matrix metalloproteinases are important promoters of cancer cell metastasis and invasion that have been illustrated the calcitriol regulate the expression of these components [111]. One of the extracellular matrix proteins is tenascin-C which it increases angiogenesis and invasion of cancer cells. Calcitriol inhibits from the expression of tenascin-C RNA in several normal or malignant epithelial cell lines [112]. Laminin receptors such as α6 and β4 integrins are related to promotion of migration and invasion of cancer cells, calcitriol decrease expression of these receptors [113]. Matrix metallopeptidase 9 (MMP9) is associated with cancer, because of its role in extracellular matrix angiogenesis and remodeling and its increase in metastatic cancer cells [114]. Calcitriol inhibits the activity of MMP9, and up-regulate tissue inhibitor of metalloproteinase1 (TIMP1) expression [115]. One of the tumor suppressor genes is *E-cadherin* which it is reversely related with metastatic potential. Calcitriol increases expression of *E-cadherin* gene, therefore inhibit invasion and metastasis of cancer cells [116].

The glutathione peroxidase-1 (*GPX1*) gene is related to the progression of tumour. Downregulating GPX1 expression inhibited salivary adenoid cystic carcinoma (SACC) cell proliferation, motility, chemoresistance, and urokinase plasminogen activator (uPA) secretion, but stimulated apoptosis *via* the NF-κB pathway. Pre-processing calcitriol suppressed the expression of NF-κB/GPX1/uPA, and subsequently inhibited cell motility in SACC cells [117].

6. Cancer and vitamin D: molecular pathological epidemiology (MPE)

An emerging field that known as MPE, provides a notable background in medical research by creating an effective link between environment or lifestyle and molecular pathologies or immunity of diseases, as well as contribute the biomarker, tailored prevention, precision medicine, and programs for treatment. In another word, the connected immunology-MPE model can provide a positive contribution to improve understanding about the interactions between environment-tumour and immune system, and also valuable immunosuppression and immunotherapy strategies in precision medicine. Proof of evidence demonstrates that adjustable agents like the levels of vitamin D influence cancer risk as well as immune system performances [118,119]. The essential role of immune system and inflammation is undeniable in etiology of cancer and also in post-transplant malignancies because of long-term immunosuppression. Additionally, dietary or intake of supplemental vitamin D and the levels of systemic vitamin D have been related to lower risks of cancer incidence and mortality [118].

In order to become clearer the roles of vitamin D in cancer prevention and immune modulation, a study with the base of immuno-MPE was focused to assess the relation between the plasma vitamin D levels and the incidence of colorectal carcinoma subtypes that classified through immune response conditions [120].

Gastrointestinal cancer due to given rich microbiota and intestinal related immune tissue and especially the carcinogenic role of inflammation in intestinal, signify exemplary diseases for the immunology-MPE model. Referring to principle studies on colorectal cancer specifies the clear insights the immunomodulating effects of vitamin D. Therefore, the capacity of vitamin D for cancer prevention is more specifically stronger for cancer that showed high-level of lymphocytic infiltrates. A likely reason for this phenomenon is that some immune cells are able to convert 25-hydroxyvitamin D [25(OH)D] to bioactive form, 1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], which can create a inhibitory effect against progression of neoplastic in patients with elicit high-level lymphocytic response to appear tumors [120,121]. On the other hand, higher 25 (OH) D levels were inversely related to the risk of colorectal cancer, irrespective the VDR expression levels in tumour cells [122]. Furthermore, there is recently epidemiologic evidence that extensive support the significance of enough vitamin D administration, including sunlight exposure, of the prevention of the various types of cancer [123].

7. Oral cancer

Oral cancer is malignant neoplasia which arises on the lip or oral cavity. Oral squamous cell carcinomas (OSCC) is important cancer which involves more than 90% of all oral cancers [124,125]. Although the mortality and incidence rates of oral cancer have reduced in industrialized countries such as the United States among recent decades, nevertheless, it has been observed increasing rate in other nations and worldwide, in general [126–128]. In developing economies due to workplace environment and social mobility have increased along with disposable revenues, the accessibility to alcohol and tobacco products has been related to increasing rates of oral cancers [129–131]. Comprehensive studies about the main risk factors related to the development of oral cancers in the United States have determined that alcohol consumption and, to a more extent, tobacco use, when combined, probably reason of 80% of oral cancer risk [128,130,132].

However, these researches have also revealed that over demographic subgroups in the population, such as stark diverse by age are varied incidence and mortality rates, but much higher rates demonstrated among minorities and sharp rises observed among females [133–137].

Oral infection related to the human papillomavirus (HPV) is another significant risk factor for pharyngeal and oral cancers (OPCs) [135]. Oral HPV infection is probably related to particular demographic subgroups, including men in addition to certain minority subgroups, that can cause some of the different geographic and geospatial OPC trends observed [136,138]. The elimination of important risk factors even after an oral cancer diagnosis can improve the prognosis, and there is evidence that such actions may decrease the risk of second tumors formation and recurrences in existing oral cancer patients [139].

8. Oral cancer, vitamin D deficiency and VDR

The OSCC development is a multi-step process that influences the important cellular pathways involved in the development of tumor and growth. It was demonstrated a variety of exogenous and endogenous incitements are leading to a multifaceted series of molecular changes contributing to cancer progression [140–142]. The anti-neoplastic activity of calcitriol was illustrated in-vitro and in-vivo studies in a wide range of cancer-related abnormalities including head and neck cancer and specifically in OSCC [143–150].

Furthermore, calcitriol has the potential to affect to cytostatic

chemotherapy and increase induction apoptosis in OSCC cells [151]. Studying the relation between the level of vitamin D in serum and its receptor (VDR) seems to be appropriate for guiding supportive treatment for individuals with precancerous lesions and OSCC patients.

Induction of apoptosis in tumors and precancerous lesions that presented VDR (VDR+) (*e.g.*, oral lichen planus or leukoplakia) through vitamin D could be beneficial for chemoprevention or may have functioned as a stimulator of apoptosis in the treatment of OSCC [57]. This hypothesis has to be assessed by clinical studies. In a Cutaneous Squamous Cell Carcinoma Murine Model, oral calcitriol supplementation caused an increasing Photodynamic therapy-induced cancer cell death [152]. Hence, application of topical and systemically vitamin D (or in combination with vitamin A derivates) probably considered as a possible novel, low side effect and adjuvant cancer treatment procedure, which can be easily presented it for VDR+ patients to the usual supplementation of clinical oral cancer treatment without any extra risk. Specifically, regard to the hypothesis of the field cancerization [153–155] it has seemed vitamin D applicated *via* systemically as the tissue of the gastrointestinal tract is very significant display toward the two major exogenous carcinogenic factors, tobacco, and alcohol. While the stimulation of carcinogenic continue may lead to second metachronous tumors in related sites [156].

Grimm et al. assessed the possibility of biologically active calcitriol or its analogs effects as a new potential target on oral tissue, so they studied to evaluate the expression of VDR in oral cancers OSCC. Their study showed evidence that reduced VDR expression in OSCC probably related to tumor reversion. Interestingly, cancer cells of a putative CD44+ cancer stem cell VDR^+ demonstrating a significant potential for the OSCC treatment. However, their outcomes could not make any conclusion on the VDR function. Application of calcitriol or its analogs as adjuvant chemoprevention can provide an effective agent for targeting adjuvant residual tumor cells and will probably help in the optimization of clinical treatment of cancer patients [157]. In another study by Sonkar et al. that examined vitamin D levels and VDR expression in the normal oral mucosa, oral cancer, and leukoplakia patients. Briefly, patients with advanced oral cancer threaten by chemoradiotherapy were assessed for the vitamin D supplementation effect on several observable quality of life (QOL) parameters, for instance, swallowing performance, oral mucositis, and overall QOL. The scores of vitamin D were considerably lower in oral cancer and leukoplakia patients as compared to healthy controls. Importantly, Vitamin D supplementation considerably decreased the toxicities correlated with therapy of advanced oral cancer, therefore improving QOL and decreasing morbidity. Sonkar study showed VDR expression increased in oral cancer, oral neoplastic lesions and premalignant lesions [158].

Deficiency and insufficiency of Vitamin D are more common in patients with oral neoplastic lesions with a priori at diagnosis. Since deficiency of vitamin D might determine increased morbidity risk of patients which is related with treatment, should be paid close attention to the repair of deficiency of vitamin D in nutrition before therapy procedures, particularly in a palliative situation. Lipworth et al. reported that dietary vitamin D intake is related to a reduced risk of squamous cell carcinoma of the esophagus (SCCE) and likely related to a decreased risk of oral and pharyngeal cancers, which were most displayed between heavy alcohol consumers and heavy smokers [159]. One of the important events happens in many cancers such as oropharyngeal cancer (OPC), applying some special effects on the metabolism of vitamin D such as changing the availability or affecting the on quality of binding to VDR. The evidence obtained from a variety of specific cancers reveal reduced VDR expression [20,160,161]. Ras activation is common in many OPC cancers, furthermore, there are some studied demonstrated that activation of Ras may weaken the activity of vitamin D-related transcription, whenever cytochrome p450 24 (CYP 24), the mitochondrial enzyme which causes decreasing of vitamin D metabolites, perhaps up-regulated and also functionally active in several cancers [162–164].

Another study confirmed that mutations of the CYP24 degraded risk of oral cancer in comparison to normal type, after adjusting for smoking status, alcohol consumption, age, and gender [165]. It seems that the rate of effect of calcitriol on gene expression be tissue-specific characteristics possibly could be explained by the varying results obtained from *in vitro* studies of gene expression in some head and neck cell lines (SC15, SCC9, SCC25 and SCC4) and squamous cell carcinoma (SCC), affected by calcitriol, which established diverse sensitivities in cell lines ranging from about 50% growth inhibition for SCC9 to the completely cell-cycle arrest at G_0/G_1 in SCC25 [166]. The more than 4500 target genes screening in SCC25 cells demonstrated 38 genes up-regulated (at least 1.5 fold), consist of protein kinases, growth factors, cell adhesion proteins, cytoskeleton proteins, some intracellular signaling molecules and also transcription factors related to regulating of cell-cycle growth and arrest [167,168].

9. Benefits of sunlight exposure on oral cancer

Indeed, the amount of vitamin D is little in majority of foods unless they are s enriched, that shows humans need to sunlight to obtain enough vitamin D stores. For example, although in the United States an eight glass of fortified milk contains 100 IU of vitamin D, enough sun exposure of the skin to cause a slight pinkness in Caucasian skin lead to synthesis the about an oral dose of 20,000 IU of vitamin D [169,170]. Regarding these findings, may explain that the epidemiologic studies with increased sun exposure among certain populations and in certain geographic areas were related to decrease risk at all tumor sites and cancer mortality. Data that obtained from more than 100 countries have revealed the strong, negative relations between solar UV-B exposure for 15 types of malignancies and noteworthy effects observed among nine other cancers, consist of the larynx and oral cavity/pharynx cancers [20,169–173].

10. Polymorphisms in *VDR* gene, cancer risk, and prognosis in oral cancer

The studies showed the variations near key genes involved in hydroxylation and transportation of vitamin D and cholesterol synthesis have related with the status of vitamin D. Evaluation of genetic variation of these loci demonstrated in high risk of vitamin D insufficiency individuals. Recently, a large number of studies paid close attention to the relevance of restriction fragment length polymorphisms in the *VDR* gene in different types of cancer. It has been considered that polymorphisms in VDR possibly influence both prognosis and risk and occurrence of cancer. Although, surveys often show inconclusive results in investigating the relations between specific VDR polymorphisms and different types of cancer [93]. It have been reported that there are significant associations in VDR polymorphisms within cancers of bladder (Fok1), colorectal (Fok1, Bsm1), ovary (Fok1, Apa1), skin (Fok1, Bsm1, A-1210), renal cell carcinoma (Taq1, Apa1), prostate (Bsm1, Fok1, Taq1, poly (A)) and breast (Taq1, Fok1, Bsm1, Apa1, poly (A)). But, contradictory results have been reported for the most of malignancies [124]. A study of genome-wide relation to recognizing genes related with deficiency of vitamin D has determined special single nucleotide polymorphisms (SNPs) in numerous genes that could foresee the levels of circulating 25-OH vitamin D [174]. SNPs in the *VDR* gene may also influence both the cancer progression and risk of cancer occurrence. Małodobra-Mazur et al. study illustrated a genetic correlation between the risk and occurrence of oral cavity carcinoma and rs2238135 in the *VDR* gene [175].

Another study by Bektaş et al. determined that in the distribution of VDR Taq I genotype was a significant difference in OSCC patients compared with healthy controls. VDR Tt genotype in OSCC patients was demonstrated to be at considerably higher risk than persons with other genotypes. Especially, female with OSCC was subjected to a higher risk for oral cancer. These findings indicate that the VDR Taq I

polymorphism might relate to susceptibility to OSCC and it probably helped as a prevention method in the future [176]. The genetic polymorphisms of VDR and genes that involved in the metabolism of vitamin D such as *CYP24B1* and *CYP27B1* might influence susceptibility to OSCC. Additionally, Zeljic et al. study indicated that polymorphism of *CYP24A1* gene might be affected on the susceptibility to oral cancer and polymorphism of *VDR FokI* gene can be an area of interest as a prognostic marker, as it has been shown that it is related to worse survival [165].

11. Oral cancer chemoresistance and its relation with VDR

Chemoresistance is a likely cause of relapse and metastasis, confronting the progress of clinical outcome in cancer patients, and remains as one of the main challengeable obstacles to cancer therapy [177–181]. The main reason for mortality and morbidity in OSCC is poor chemotherapy response and fundamental resistance to the majority of anti-cancer drugs [182,183]. It was demonstrated resistance to apoptosis is as a key factor for the tumorigenesis of OSCC, which is related to tumor recurrence and radio-, and chemotherapy resistance [184–186]. Hence overcoming the resistance to treatment of oral neoplastic lesions is a major challenge. Achievement of such therapeutic effective agents that led to more accurately identify so might help create an improved response and consequently reduce the return of oral cancer [158]. Vitamin D is one example of these agents, which has been illustrated have induced apoptosis, anti-proliferative and anti-invasive properties in some cancer cell types such as OSCC and oral pre-cancerous lesions [143,148,150,187,188]. It is also hypothesized that the combination of vitamin D with chemotherapy of oral cancer showed increasing effectiveness [151]. Studying serum vitamin D level and its corresponding VDR seems to be appropriate for guiding supportive therapy for patients with pre-cancerous lesions and OSCC. The low VDR expression is also an adverse prognostic sign for OSCC patient's survival [157]. Moreover, Grimm and coworkers measured and correlated serum vitamin D levels (calcidiol) with tissue-related VDR expression in OSCC patients. The natural or synthetic vitamin D compounds induce apoptosis in oral pre-cancerous lesions, and OSCC could be useful for chemoprevention [56]. Additionally, locally or systemically applied to these compounds probably leads to more sensitization of OSCC to apoptosis associated with radio-, and chemotherapy treatment [140].

12. Discussion

Recent studies focused on the vitamin D effects on the prevention and treatment of the wide range of cancers is reported elsewhere. Preclinical studies strongly support the importance of vitamin D in prevention of cancer by exerting a wide range of cellular functions, including pro-apoptotic, anti-angiogenic, anti-inflammatory, anti-proliferative, anti-invasion and anti-metastatic effects on cancer cells [70]. The active form of vitamin D, calcitriol, which exerts bioactivities by binding to the nuclear VDR in different tissues. Of clinical importance, a wide range of tumor tissues express the VDR, and that the receptor has the potential to influences cancer etiology [11].

Oral calcitriol supplementation able to increase the effectiveness of photodynamic therapy on tumor cell death of cutaneous squamous cell carcinoma in a murine model [152]. Hence, topical or/and systemically applicated vitamin D may offer a new nontoxic, adjuvant to the treatment of cancer, which can be easily present with classic protocols without any supplementary clinical cancer therapy risk for VDR+ patients. Calcitriol has been illustrated to increase expression of the *VDR gene* and protein in different cell types *in vitro* [189,190]. It has been proposed that calcitriol administration lead to enhance VDR expression due to an improved receptor protein lifetime and/or raise the *VDR* genes transcription [53,190]. We know the keratinocytes able to synthesize the biologically active calcitriol. However, we don´t make sure that oral precancerous or OSCCs have this ability as well. Additionally, tumor-infiltrating leucocytes and oral precancerous/tumor cells expressed inflammatory cytokines/peptides that may upregulate VDR expression in adjacent cells [191].

Study of Yuan et al. [192] strongly supports an important role for signaling of vitamin D in the pathophysiology of oral keratinocyte in-vitro and in-vivo, but a deficiency of vitamin D alone seems to be inadequate to stimulate carcinogenesis and change homeostasis of oral epithelia. Afzal et al. [193] demonstrated a low plasma level of 25-hydroxyvitamin D with increased risk of smoking-related cancer including head and neck squamous cell carcinoma (HNSCC). In this base, vitamin D may reversely alter the carcinogenicity of tobacco smoke chemical. Authors hypothesize that especially smokers may benefit from Vitamin D intake as more than 80% of OSCC are related to tobacco abuse.

As suggested for multistep carcinogenesis [142] it is indistinct based on the actual literature whether vitamin D can be standardized useful for chemoprevention in the therapy of precursor lesions or development of OSCC, but it provides a clear rationale for more researches in the OSCC carcinogenesis [140]. VDR is important in different cancer types. It is essential to note, all polymorphisms of the *VDR* gene haven't the same relation with cancer, and the importance of each polymorphism determined with the cancer site. Given these relations, it is essential to evaluate the relationship among other polymorphisms in other areas of the VDR gene and cancer. Since VDR is involved in several pathways, it is essential to assess the relations between VDR and other environmental factors, lifestyle and diet as they relate to cancer. VDR gene as a key element of further researches is acquiring a better understanding of its functionality [194].

13. Conclusion

The main purpose of this review article is to summarize the possible role of vitamin D in the development of oral cancer. Although the anticancer effects of vitamin D showed by several *in vitro* and *in vivo* studies, new evidence indicates these effects are regulated by several other factors. Further studies are required to evaluate the effects of the vitamin D system (both ligand and receptor) on the evolvement of oral cancer, and potential benefits of alleviating vitamin D deficiency on tumor growth and progression. The information provided in this article would be useful to oral epidemiologists, oral health care providers, as well as oral oncologists as they attempt to improve oral health outcomes of patients.

References

[1] M.F. Holick, T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences–, Am. J. Clin. Nutr. 87 (4) (2008) 1080S–1086S.
[2] C.F. Garland, F.C. Garland, E.D. Gorham, M. Lipkin, H. Newmark, S.B. Mohr, M.F. Holick, The role of vitamin D in cancer prevention, Am. J. Public Health 96 (2) (2006) 252–261.
[3] T.J. Wang, M.J. Pencina, S.L. Booth, P.F. Jacques, E. Ingelsson, K. Lanier, E.J. Benjamin, R.B. D'Agostino, M. Wolf, R.S. Vasan, Vitamin D deficiency and risk of cardiovascular disease, Circulation 117 (4) (2008) 503–511.
[4] A.G. Pittas, M. Chung, T. Trikalinos, J. Mitri, M. Brendel, K. Patel, A.H. Lichtenstein, J. Lau, E.M. Balk, Systematic review: vitamin D and cardiometabolic outcomes, Ann. Intern. Med. 152 (5) (2010) 307–314.
[5] S. Christakos, P. Dhawan, Y. Liu, X. Peng, A. Porta, New insights into the mechanisms of vitamin D action, J. Cell. Biochem. 88 (4) (2003) 695–705.
[6] E. Deuster, U. Jeschke, Y. Ye, S. Mahner, B. Czogalla, D. Vitamin, VDR in gynecological cancers—a systematic review, Int. J. Mol. Sci. 18 (11) (2017) 2328.
[7] A.G. Uitterlinden, Y. Fang, J.B. van Meurs, H.A. Pols, J.P. van Leeuwen, Genetics and biology of vitamin D receptor polymorphisms, Gene 338 (2) (2004) 143–156.
[8] P. Vaughan-Shaw, F. O'sullivan, S. Farrington, E. Theodoratou, H. Campbell, M. Dunlop, L. Zgaga, The impact of vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: systematic review and meta-analysis, Br. J. Cancer 116 (8) (2017) 1092.
[9] T. Sritippho, P. Chotjumlong, A. Iamaroon, Roles of human papillomaviruses and p16 in oral cancer, Asian Pac. J. Cancer Prev. 16 (15) (2015) 6193–6200.
[10] B.L. Janotha, K. Tamari, Oral squamous cell carcinoma: focusing on interprofessional collaboration, Nurse Pract. 42 (4) (2017) 26–30.
[11] R.A. Ness, D.D. Miller, L. Wei, The role of vitamin D in cancer prevention, Chin. J. Nat. Med. 13 (7) (2015) 481–497.

[12] S. Christakos, P. Dhawan, A. Porta, L.J. Mady, T. Seth, Vitamin D and intestinal calcium absorption, Mol. Cell. Endocrinol. 347 (1–2) (2011) 25–29.
[13] M.F. Holick, High prevalence of vitamin D inadequacy and implications for health, Mayo Clin. Proc. 81 (3) (2006) 353–373.
[14] B.W. Hollis, Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D, J. Nutr. 135 (2) (2005) 317–322.
[15] C. Carlberg, The physiology of vitamin D—far more than calcium and bone, Front. Physiol. 5 (2014) 335.
[16] H.F. DeLuca, History of the discovery of vitamin D and its active metabolites, Bonekey Rep. 3 (2014).
[17] P. Tuohimaa, Vitamin D, aging, and cancer, Nutr. Rev. 66 (Suppl. 2) (2008) S147–S152.
[18] R. Bouillon, G. Carmeliet, L. Verlinden, E. van Etten, A. Verstuyf, H.F. Luderer, L. Lieben, C. Mathieu, M. Demay, Vitamin D and human health: lessons from vitamin D receptor null mice, Endocr. Rev. 29 (6) (2008) 726–776.
[19] K.K. Deeb, D.L. Trump, C.S. Johnson, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, Nat. Rev. Cancer 7 (9) (2007) 684.
[20] J.C. Fleet, M. DeSmet, R. Johnson, Y. Li, Vitamin D and cancer: a review of molecular mechanisms, Biochem. J. 441 (1) (2012) 61–76.
[21] M.R. Haussler, G.K. Whitfield, I. Kaneko, C.A. Haussler, D. Hsieh, J.-C. Hsieh, P.W. Jurutka, Molecular mechanisms of vitamin D action, Calcif. Tissue Int. 92 (2) (2013) 77–98.
[22] J.W. Pike, M.B. Meyer, K.A. Bishop, Regulation of target gene expression by the vitamin D receptor-an update on mechanisms, Rev. Endocr. Metab. Disord. 13 (1) (2012) 45–55.
[23] M.R. Haussler, P.W. Jurutka, M. Mizwicki, A.W. Norman, Vitamin D receptor (VDR)-mediated actions of 1α, 25 (OH) 2vitamin D3: genomic and non-genomic mechanisms, Best Pract. Res. Clin. Endocrinol. Metab. 25 (4) (2011) 543–559.
[24] I. Nemere, N. Garbi, G. Hammerling, K.J. Hintze, Role of the 1, 25D3-MARRS receptor in the 1, 25 (OH) 2D3-stimulated uptake of calcium and phosphate in intestinal cells, Steroids 77 (10) (2012) 897–902.
[25] V.B. Sequeira, M.S. Rybchyn, W. Tongkao-on, C. Gordon-Thomson, P.J. Malloy, I. Nemere, A.W. Norman, V.E. Reeve, G.M. Halliday, D. Feldman, The role of the vitamin D receptor and ERp57 in photoprotection by 1α, 25-dihydroxyvitamin D3, Mol. Endocrinol. 26 (4) (2012) 574–582.
[26] S.Y. Yoo, P.S. Kim, H.-K. Hwang, S.-H. Lim, K.-W. Kim, S.-J. Choe, B.-M. Min, J.-K. Kook, Identification of non-mutans streptococci organisms in dental plaques recovering on mitis-salivarius bacitracin agar medium, J. Microbiol. 43 (2) (2005) 204–208.
[27] J.M. Valdivielso, E. Fernandez, Vitamin D receptor polymorphisms and diseases, Clin. Chim. Acta 371 (1–2) (2006) 1–12.
[28] L. Yang, J. Ma, X. Zhang, Y. Fan, L. Wang, Protective role of the vitamin D receptor, Cell. Immunol. 279 (2) (2012) 160–166.
[29] Z. Zhang, L. Sun, Y. Wang, G. Ning, A. Minto, J. Kong, R. Quigg, Y. Li, Renoprotective role of the vitamin D receptor in diabetic nephropathy, Kidney Int. 73 (2) (2008) 163–171.
[30] Y.C. Li, J. Kong, M. Wei, Z.-F. Chen, S.Q. Liu, L.-P. Cao, 1, 25-Dihydroxyvitamin D 3 is a negative endocrine regulator of the renin-angiotensin system, J. Clin. Invest. 110 (2) (2002) 229–238.
[31] J.R. Wu-Wong, M. Nakane, J. Ma, X. Ruan, P.E. Kroeger, Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells, Atherosclerosis 186 (1) (2006) 20–28.
[32] S.C. Manolagas, D.M. Provvedini, C.D. Tsoukas, Interactions of 1, 25-dihydroxyvitamin D3 and the immune system, Mol. Cell. Endocrinol. 43 (2–3) (1985) 113–122.
[33] H.P. Koeffler, K. Hirji, L. Itri, 1, 25-Dihydroxyvitamin D3: in vivo and in vitro effects on human preleukemic and leukemic cells, Cancer Treat. Rep. 69 (12) (1985) 1399–1407.
[34] D. Branisteanu, P. Leenaerts, B. Damme, R. Bouillon, Partial prevention of active Heymann nephritis by lα, 25 dihydroxyvitamin D3, Clin. Exp. Immunol. 94 (3) (1993) 412–417.
[35] M. Raman, A.N. Milestone, J.R. Walters, A.L. Hart, S. Ghosh, Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer, Therap. Adv. Gastroenterol. 4 (1) (2011) 49–62.
[36] K. Müller, P. Haahr, M. Diamant, K. Rieneck, A. Kharazmi, K. Bendtzen, 1, 25-Dihydroxyvitamin D3 inhibits cytokine production by human blood monocytes at the post-transcriptional level, Cytokine 4 (6) (1992) 506–512.
[37] X. Tan, Y. Li, Y. Liu, Therapeutic role and potential mechanisms of active Vitamin D in renal interstitial fibrosis, J. Steroid Biochem. Mol. Biol. 103 (3–5) (2007) 491–496.
[38] H.F. DeLuca, Overview of general physiologic features and functions of vitamin D, Am. J. Clin. Nutr. 80 (6) (2004) 1689S–1696S.
[39] W.E. Stumpf, Vitamin D sites and mechanisms of action: a histochemical perspective. Reflections on the utility of autoradiography and cytopharmacology for drug targeting, Histochem. Cell Biol. 104 (6) (1995) 417–427.
[40] W.E. Stumpf, M. Sar, F.A. Reid, Y. Tanaka, H.F. DeLuca, Target cells for 1, 25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid, Science 206 (4423) (1979) 1188–1190.
[41] Y. Wang, J. Zhu, H.F. DeLuca, Where is the vitamin D receptor? Arch. Biochem. Biophys. 523 (1) (2012) 123–133.
[42] C.J. Lamberg-Allardt, T.A. Outila, M.U. Kärkkäinen, H.J. Rita, L.M. Valsta, Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? J. Bone Miner. Res. 16 (11) (2001) 2066–2073.
[43] M.F. Holick, Vitamin d deficiency, N. Engl. J. Med. 357 (3) (2007) 266–281.
[44] A. Sachan, R. Gupta, V. Das, A. Agarwal, P.K. Awasthi, V. Bhatia, High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India, Am. J. Clin. Nutr. 81 (5) (2005) 1060–1064.
[45] P.T. Liu, S. Stenger, H. Li, L. Wenzel, B.H. Tan, S.R. Krutzik, M.T. Ochoa, J. Schauber, K. Wu, C. Meinken, Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response, Science 311 (5768) (2006) 1770–1773.
[46] T. Hagenau, R. Vest, T. Gissel, C. Poulsen, M. Erlandsen, L. Mosekilde, P. Vestergaard, Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis, Osteoporos. Int. 20 (1) (2009) 133.
[47] A. Vogel, C.P. Strassburg, M.P. Manns, Genetic association of vitamin D receptor polymorphisms with primary biliary cirrhosis and autoimmune hepatitis, Hepatology 35 (1) (2002) 126–131.
[48] S.A. Abedin, C.M. Banwell, K.W. Colston, C. Carlberg, M.J. Campbell, Epigenetic corruption of VDR signalling in malignancy, Anticancer Res. 26 (4A) (2006) 2557–2566.
[49] J.W. Pike, M.B. Meyer, The vitamin D receptor: new paradigms for the regulation of gene expression by 1, 25-dihydroxyvitamin D3, Endocrinol. Metab. Clin. North Am. 39 (2) (2010) 255–269.
[50] L.M. ESTEBAN, J.A. EISMAN, E.M. GARDINER, Vitamin D Receptor Promoter and Regulation of Receptor Expression, Vitamin D, 2nd ed., Elsevier, 2005 pp. 193–217.
[51] L.A. Zella, S. Kim, N.K. Shevde, J.W. Pike, Enhancers located within two introns of the vitamin D receptor gene mediate transcriptional autoregulation by 1, 25-dihydroxyvitamin D3, Mol. Endocrinol. 20 (6) (2006) 1231–1247.
[52] E.M. COSTA, M.A. HIRST, D. FELDMAN, Regulation of 1, 25-dihydroxyvitamin D3 receptors by vitamin D analogs in cultured mammalian cells, Endocrinology 117 (5) (1985) 2203–2210.
[53] D.J. Mangelsdorf, J.W. Pike, M.R. Haussler, Avian and mammalian receptors for 1, 25-dihydroxyvitamin D3: in vitro translation to characterize size and hormone-dependent regulation, Proc. Natl. Acad. Sci. U. S. A. 84 (2) (1987) 354–358.
[54] K.D. Healy, M.A. Frahm, H.F. DeLuca, 1, 25-Dihydroxyvitamin D3 up-regulates the renal vitamin D receptor through indirect gene activation and receptor stabilization, Arch. Biochem. Biophys. 433 (2) (2005) 466–473.
[55] L.A. Zella, M.B. Meyer, R.D. Nerenz, S.M. Lee, M.L. Martowicz, J.W. Pike, Multifunctional enhancers regulate mouse and human vitamin D receptor gene transcription, Mol. Endocrinol. 24 (1) (2010) 128–147.
[56] R. Nair, A. Maseeh, Vitamin D: the “sunshine” vitamin, J. Pharmacol. Pharmacother. 3 (2) (2012) 118.
[57] K. Sundaram, Y. Sambandam, E. Tsuruga, C.L. Wagner, S.V. Reddy, 1α, 25-dihydroxyvitamin D3 modulates CYP2R1 gene expression in human oral squamous cell carcinoma tumor cells, Horm. Cancer 5 (2) (2014) 90–97.
[58] K.Z. Guyton, T.W. Kensler, G.H. Posner, Cancer chemoprevention using natural vitamin D and synthetic analogs, Annu. Rev. Pharmacol. Toxicol. 41 (1) (2001) 421–442.
[59] S. Tretli, G.G. Schwartz, P.A. Torjesen, T.E. Robsahm, Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study, Cancer Causes Control 23 (2) (2012) 363–370.
[60] L.N. Anderson, M. Cotterchio, R. Vieth, J.A. Knight, Vitamin D and calcium intakes and breast cancer risk in pre-and postmenopausal women, Am. J. Clin. Nutr. 91 (6) (2010) 1699–1707.
[61] R.P. Heaney, Vitamin D in health and disease, Clin. J. Am. Soc. Nephrol. 3 (5) (2008) 1535–1541.
[62] K. Colston, M.J. Colston, D. Feldman, 1, 25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture, Endocrinology 108 (3) (1981) 1083–1086.
[63] E. Abe, C. Miyaura, H. Sakagami, M. Takeda, K. Konno, T. Yamazaki, S. Yoshiki, T. Suda, Differentiation of mouse myeloid leukemia cells induced by 1 alpha, 25-dihydroxyvitamin D3, Proc. Natl. Acad. Sci. U. S. A. 78 (8) (1981) 4990–4994.
[64] F.S. Cheung, F.J. Lovicu, J.K. Reichardt, Current progress in using vitamin D and its analogs for cancer prevention and treatment, Expert Rev. Anticancer Ther. 12 (6) (2012) 811–837.
[65] C. Leyssens, L. Verlinden, A. Verstuyf, Antineoplastic effects of 1, 25 (OH) 2D3 and its analogs in breast, prostate and colorectal cancer, Endocr. Relat. Cancer 20 (2) (2013) R31–R47.
[66] C.J. Rosen, J.S. Adams, D.D. Bikle, D.M. Black, M.B. Demay, J.E. Manson, M.H. Murad, C.S. Kovacs, The nonskeletal effects of vitamin D: an Endocrine Society scientific statement, Endocr. Rev. 33 (3) (2012) 456–492.
[67] J.Y. Tang, T. Fu, C. Lau, D.H. Oh, D.D. Bikle, M.M. Asgari, Vitamin D in cutaneous carcinogenesis: part I, J. Am. Acad. Dermatol. 67 (5) (2012) 803. e1–803. e12.
[68] D.L. Trump, K. Deeb, C.S. Johnson, Vitamin D: considerations in the continued development as an agent for cancer prevention and therapy, Cancer J. (Sudbury, Mass.) 16 (1) (2010) 1.
[69] A.V. Krishnan, D. Feldman, Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemoprevention and treatment, Endocr. Relat. Cancer 17 (1) (2010) R19–R38.
[70] D. Feldman, A.V. Krishnan, S. Swami, E. Giovannucci, B.J. Feldman, The role of vitamin D in reducing cancer risk and progression, Nat. Rev. Cancer 14 (5) (2014) 342.
[71] A.V. Krishnan, R. Shinghal, N. Raghavachari, J.D. Brooks, D.M. Peehl, D. Feldman, Analysis of vitamin D-regulated gene expression in LNCaP human prostate cancer cells using cDNA microarrays, Prostate 59 (3) (2004) 243–251.
[72] H.J. Lee, H. Liu, C. Goodman, Y. Ji, H. Maehr, M. Uskokovic, D. Notterman, M. Reiss, N. Suh, Gene expression profiling changes induced by a novel Gemini Vitamin D derivative during the progression of breast cancer, Biochem. Pharmacol. 72 (3) (2006) 332–343.

[73] S.L. Maund, W.W. Barclay, L.D. Hover, L.S. Axanova, G. Sui, J.D. Hipp, J.C. Fleet, A. Thorburn, S.D. Cramer, Interleukin-1α mediates the antiproliferative effects of 1, 25-dihydroxyvitamin D3 in prostate progenitor/stem cells, Cancer Res. 71 (15) (2011) 5276–5286.
[74] D.M. Peehl, R. Shinghal, L. Nonn, E. Seto, A.V. Krishnan, J.D. Brooks, D. Feldman, Molecular activity of 1, 25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray analysis, J. Steroid Biochem. Mol. Biol. 92 (3) (2004) 131–141.
[75] S. Swami, N. Raghavachari, U.R. Muller, Y.P. Bao, D. Feldman, Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray, Breast Cancer Res. Treat. 80 (1) (2003) 49–62.
[76] P. Tuohimaa, Y.-R. Lou, Optimal serum calcidiol concentration for cancer prevention, Anticancer Res. 32 (1) (2012) 373–381.
[77] P. Pludowski, W.B. Grant, H.P. Bhattoa, M. Bayer, V. Povoroznyuk, E. Rudenka, H. Ramanau, S. Varbiro, A. Rudenka, E. Karczmarewicz, Vitamin d status in central Europe, Int. J. Endocrinol. 2014 (2014).
[78] H. Arem, S. Weinstein, R. Horst, J. Virtamo, K. Yu, D. Albanes, C.C. Abnet, Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men, Cancer Epidemiol. Prev. Biomark. 20 (6) (2011) 1178–1184.
[79] S.E. Blutt, T.J. McDonnell, T.C. Polek, N.L. Weigel, Calcitriol-induced apoptosis in LNCaP cells is blocked by overexpression of Bcl-2, Endocrinology 141 (1) (2000) 10–17.
[80] N. Fathi, G. Rashdi, S. Sharifi, STAT3 and apoptosis challenges in cancer, Int. J. Biol. Macromol. 117 (1) (2018) 993–1001.
[81] K. Kingsley, M.A. Keiserman, C.J. Bergman, Interactive effects of 1, 25-dihydroxyvitamin D3 and soy protein extract (SPE) on oral cancer growth in vitro: evidence for potential functional relationships, Funct. Foods Health Dis. 3 (6) (2013) 183–202.
[82] M. Simboli-Campbell, C.J. Narvaez, K. VanWeelden, M. Tenniswood, J. Welsh, Comparative effects of 1, 25 (OH) 2 D 3 and EB1089 on cell cycle kinetics and apoptosis in MCF-7 breast cancer cells, Breast Cancer Res. Treat. 42 (1) (1997) 31–41.
[83] D. Matthews, E. LaPorta, G.M. Zinser, C.J. Narvaez, J. Welsh, Genomic vitamin D signaling in breast cancer: insights from animal models and human cells, J. Steroid Biochem. Mol. Biol. 121 (1–2) (2010) 362–367.
[84] I. Diaz-Padilla, L.L. Siu, I. Duran, Cyclin-dependent kinase inhibitors as potential targeted anticancer agents, Invest. New Drugs 27 (6) (2009) 586.
[85] S.E. Blutt, E.A. Allegretto, J.W. Pike, N.L. Weigel, 1, 25-dihydroxyvitamin D3 and 9-cis-retinoic acid act synergistically to inhibit the growth of LNCaP prostate cells and cause accumulation of cells in G1, Endocrinology 138 (4) (1997) 1491–1497.
[86] O. Flores, Z. Wang, K.E. Knudsen, K.L. Burnstein, Nuclear targeting of cyclin-dependent kinase 2 reveals essential roles of cyclin-dependent kinase 2 localization and cyclin E in vitamin D-mediated growth inhibition, Endocrinology 151 (3) (2010) 896–908.
[87] S.S. Jensen, M.W. Madsen, J. Lukas, L. Binderup, J. Bartek, Inhibitory effects of 1α, 25-dihydroxyvitamin D3 on the G1–S phase-controlling machinery, Mol. Endocrinol. 15 (8) (2001) 1370–1380.
[88] M. Liu, M.-H. Lee, M. Cohen, M. Bommakanti, L.P. Freedman, Transcriptional activation of the Cdk inhibitor p21 by vitamin D3 leads to the induced differentiation of the myelomonocytic cell line U937, Genes Dev. 10 (2) (1996) 142–153.
[89] J. Welsh, Cellular and molecular effects of vitamin D on carcinogenesis, Arch. Biochem. Biophys. 523 (1) (2012) 107–114.
[90] B.J. Boyle, X.-y. Zhao, P. Cohen, D. Feldman, Insulin-like growth factor binding protein-3 mediates 1α, 25-dihydroxyvitamin D3 growth inhibition in the LNCaP prostate cancer cell line through p21/WAF1, J. Urol. 165 (4) (2001) 1319–1324.
[91] J.N.P. Rohan, N.L. Weigel, 1α, 25-dihydroxyvitamin D3 reduces c-Myc expression, inhibiting proliferation and causing G1 accumulation in C4-2 prostate cancer cells, Endocrinology 150 (5) (2009) 2046–2054.
[92] J.-i. Hisatake, T. Kubota, Y. Hisatake, M. Uskokovic, S. Tomoyasu, H.P. Koeffler, 5, 6-trans-16-ene-vitamin D3: a new class of potent inhibitors of proliferation of prostate, breast, and myeloid leukemic cells, Cancer Res. 59 (16) (1999) 4023–4029.
[93] R. Kasiappan, Z. Shen, K. Anfernee, U. Jinwal, J. Tang, P. Lungchukiet, Y. Sun, P. Kruk, S.V. Nicosia, X. Zhang, 1, 25-Dihydroxyvitamin D3 suppresses telomerase expression and human cancer growth through microRNA-498, J. Biol. Chem. 287 (49) (2012) 41297–41309.
[94] K.D. Bothwell, T. Shaurova, M. Merzianu, A. Suresh, M.A. Kuriakose, C.S. Johnson, P.A. Hershberger, M. Seshadri, Impact of short-term 1, 25-dihydroxyvitamin D3 on the chemopreventive efficacy of erlotinib against oral cancer, Cancer Prev. Res. 8 (9) (2015) 765–776.
[95] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (7203) (2008) 436.
[96] A.V. Krishnan, D. Feldman, Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D, Annu. Rev. Pharmacol. Toxicol. 51 (2011) 311–336.
[97] A.V. Krishnan, S. Swami, L. Peng, J. Wang, J. Moreno, D. Feldman, Tissue-selective regulation of aromatase expression by calcitriol: implications for breast cancer therapy, Endocrinology 151 (1) (2010) 32–42.
[98] J. Moreno, A.V. Krishnan, S. Swami, L. Nonn, D.M. Peehl, D. Feldman, Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells, Cancer Res. 65 (17) (2005) 7917–7925.
[99] L. Nonn, L. Peng, D. Feldman, D.M. Peehl, Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D, Cancer Res. 66 (8) (2006) 4516–4524.
[100] B.-Y. Bao, J. Yao, Y.-F. Lee, 1α, 25-dihydroxyvitamin D 3 suppresses interleukin-8-mediated prostate cancer cell angiogenesis, Carcinogenesis 27 (9) (2006) 1883–1893.
[101] M. Cohen-Lahav, S. Shany, D. Tobvin, C. Chaimovitz, A. Douvdevani, Vitamin D decreases NFκB activity by increasing IκBα levels, Nephrol. Dial. Transplant. 21 (4) (2006) 889–897.
[102] X.-P. Yu, T. Bellido, S.C. Manolagas, Down-regulation of NF-kappa B protein levels in activated human lymphocytes by 1, 25-dihydroxyvitamin D3, Proc. Natl. Acad. Sci. U. S. A. 92 (24) (1995) 10990–10994.
[103] S. Hari, V. Vasudevan, S. Kasibhotla, D. Reddy, M. Venkatappa, D. Devaiah, Anti-inflammatory dietary supplements in the chemoprevention of oral cancer, Cancer Res. Front. 2 (3) (2016) 380–395.
[104] E. Gocek, G.P. Studzinski, Vitamin D and differentiation in cancer, Crit. Rev. Clin. Lab. Sci. 46 (4) (2009) 190–209.
[105] N. Pendás-Franco, J.M. González-Sancho, Y. Suárez, O. Aguilera, A. Steinmeyer, C. Gamallo, M.T. Berciano, M. Lafarga, A. Muñoz, Vitamin D regulates the phenotype of human breast cancer cells, Differentiation 75 (3) (2007) 193–207.
[106] M. Ben-Shoshan, S. Amir, D.T. Dang, L.H. Dang, Y. Weisman, N.J. Mabjeesh, 1α, 25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells, Mol. Cancer Ther. 6 (4) (2007) 1433–1439.
[107] I. Chung, G. Han, M. Seshadri, B.M. Gillard, W.-d. Yu, B.A. Foster, D.L. Trump, C.S. Johnson, Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis in vivo, Cancer Res. 69 (3) (2009) 967–975.
[108] R. Fukuda, B. Kelly, G.L. Semenza, Vascular endothelial growth factor gene expression in colon cancer cells exposed to prostaglandin E2 is mediated by hypoxia-inducible factor 1, Cancer Res. 63 (9) (2003) 2330–2334.
[109] S.N.Z. Rosli, T. Shintani, Y. Hayashido, S. Toratani, E. Usui, T. Okamoto, 1α,25(OH)2D3 down-regulates HBp17/FGFBP-1 expression via NF-κB pathway, J. Steroid Biochem. Mol. Biol. 136 (2013) 98–101.
[110] T.A. Martin, L. Ye, A.J. Sanders, J. Lane, W.G. Jiang, Cancer Invasion and Metastasis: Molecular and Cellular Perspective, (2013).
[111] K. Koli, J. Keski-Oja, 1aa, 25-Dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells, Cell Growth Diff.-Publ. Am. Assoc. Cancer Res. 11 (4) (2000) 221.
[112] J.M. González-Sancho, M. Alvarez-Dolado, A. Muñoz, 1, 25-Dihydroxyvitamin D3 inhibits tenascin-C expression in mammary epithelial cells, FEBS Lett. 426 (2) (1998) 225–228.
[113] V. Sung, D. Feldman, 1, 25-Dihydroxyvitamin D3 decreases human prostate cancer cell adhesion and migration, Mol. Cell. Endocrinol. 164 (1-2) (2000) 133–143.
[114] M. Morini, M. Mottolese, N. Ferrari, F. Ghiorzo, S. Buglioni, R. Mortarini, D.M. Noonan, P.G. Natali, A. Albini, The α3β1 integrin is associated with mammary carcinoma cell metastasis, invasion, and gelatinase B (mmp-9) activity, Int. J. Cancer 87 (3) (2000) 336–342.
[115] B.-Y. Bao, S.-D. Yeh, Y.-F. Lee, 1α, 25-dihydroxyvitamin D 3 inhibits prostate cancer cell invasion via modulation of selective proteases, Carcinogenesis 27 (1) (2005) 32–42.
[116] M. Campbell, E. Elstner, S. Holden, M. Uskokovic, H. Koeffler, Inhibition of proliferation of prostate cancer cells by a 19-nor-hexafluoride vitamin D3 analogue involves the induction of p21waf1, p27kip1 and E-cadherin, J. Mol. Endocrinol. 19 (1) (1997) 15–27.
[117] Z. Huang, Y. Liu, Z. Huang, H. Li, X. Gan, Z. Shen, 1, 25-Dihydroxyvitamin D3 alleviates salivary adenoid cystic carcinoma progression by suppressing GPX1 expression through the NF-κB pathway, Int. J. Oncol. 48 (3) (2016) 1271–1279.
[118] R. Dou, K. Ng, E.L. Giovannucci, J.E. Manson, Z.R. Qian, S. Ogino, Vitamin D and colorectal cancer: molecular, epidemiological and clinical evidence, Br. J. Nutr. 115 (9) (2016) 1643–1660.
[119] S. Ogino, J.A. Nowak, T. Hamada, D.A. Milner Jr., R. Nishihara, Insights into pathogenic interactions among environment, host, and tumor at the crossroads of molecular pathology and epidemiology, Annu. Rev. Pathol. Mech. Dis. 14 (2018) 83–103.
[120] M. Song, R. Nishihara, M. Wang, A.T. Chan, Z.R. Qian, K. Inamura, X. Zhang, K. Ng, S.A. Kim, K. Mima, Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status, Gut 65 (2) (2016) 296–304.
[121] S. Ogino, J.A. Nowak, T. Hamada, A.I. Phipps, U. Peters, D.A. Milner Jr., E.L. Giovannucci, R. Nishihara, M. Giannakis, W.S. Garrett, Integrative analysis of exogenous, endogenous, tumour and immune factors for precision medicine, Gut 67 (6) (2018) 1168–1180.
[122] S. Jung, Z.R. Qian, M. Yamauchi, K.A. Bertrand, K.C. Fitzgerald, K. Inamura, S.A. Kim, K. Mima, Y. Sukawa, X. Zhang, Predicted 25 (OH) D score and colorectal cancer risk according to vitamin D receptor expression, Cancer Epidemiol. Prev. Biomark. 23 (8) (2014) 1628–1637.
[123] I. Shui, E. Giovannucci, Vitamin D Status and Cancer Incidence and Mortality, Sunlight, Vitamin D and Skin Cancer, (2015), p. 33.
[124] S. Gandini, P. Gnagnarella, D. Serrano, E. Pasquali, S. Raimondi, Vitamin D Receptor Polymorphisms and Cancer, Sunlight, Vitamin D and Skin Cancer, Springer, 2014 pp. 69–105.
[125] Y. Chen, H. Huang, L. Lin, C. Lin, Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan, Oral Oncol. 35 (2) (1999) 173–179.
[126] K. Kingsley, C. Bergman, M. Keiserman, Oral cancer risk and vitamin D status, intake and supplementation: a review, Open Access Cancer 1 (1) (2013) 1.
[127] D.M. Saman, A review of the epidemiology of oral and pharyngeal carcinoma: update, Head Neck Oncol. 4 (1) (2012) 1.
[128] M.P. Curado, M. Hashibe, Recent changes in the epidemiology of head and neck cancer, Curr. Opin. Oncol. 21 (3) (2009) 194–200.
[129] P.E. Petersen, Oral cancer prevention and control–the approach of the World

Health Organization, Oral Oncol. 45 (4) (2009) 454–460.
[130] W.J. Blot, J.K. McLaughlin, D.M. Winn, D.F. Austin, R.S. Greenberg, S. Preston-Martin, L. Bernstein, J.B. Schoenberg, A. Stemhagen, J.F. Fraumeni, Smoking and drinking in relation to oral and pharyngeal cancer, Cancer Res. 48 (11) (1988) 3282–3287.
[131] N.C.f.H, Statistics, Health, United States, 2009: With Special Feature on Medical Technology, (2010).
[132] P.A. Swango, Cancers of the oral cavity and pharynx in the United States: an epidemiologic overview, J. Public Health Dent. 56 (6) (1996) 309–318.
[133] C.H. Shiboski, S.C. Shiboski, S. Silverman, Trends in oral cancer rates in the United States, 1973–1996, Community Dent. Oral Epidemiol. 28 (4) (2000) 249–256.
[134] S.L. Tomar, Trends and patterns of tobacco use in the United States, Am. J. Med. Sci. 326 (4) (2003) 248–254.
[135] A.K. Chaturvedi, Epidemiology and clinical aspects of HPV in head and neck cancers, Head Neck Pathol. 6 (1) (2012) 16–24.
[136] K. Kingsley, S. O'Malley, M. Ditmyer, M. Chino, Analysis of oral cancer epidemiology in the US reveals state-specific trends: implications for oral cancer prevention, BMC Public Health 8 (1) (2008) 87.
[137] L.S. Weglicki, Tobacco use assessment: what exactly is your patient using and why is it important to know? Ethn. Dis. 18 (Suppl. 3) (2008) S3-1-6.
[138] A. Bunnell, N. Pettit, N. Reddout, K. Sharma, S. O'Malley, M. Chino, K. Kingsley, Analysis of primary risk factors for oral cancer from select US states with increasing rates, Tob. Induc. Dis. 8 (1) (2010) 5.
[139] S. Warnakulasuriya, Living with oral cancer: epidemiology with particular reference to prevalence and life-style changes that influence survival, Oral Oncol. 46 (6) (2010) 407–410.
[140] M. Grimm, M. Cetindis, T. Biegner, M. Lehman, A. Munz, P. Teriete, S. Reinert, Serum vitamin D levels of patients with oral squamous cell carcinoma (OSCC) and expression of vitamin D receptor in oral precancerous lesions and OSCC, Med. Oral Patol. Oral Cir. Bucal 20 (2) (2015) e188.
[141] S.K. Choudhari, M. Chaudhary, A.R. Gadbail, A. Sharma, S. Tekade, Oxidative and antioxidative mechanisms in oral cancer and precancer: a review, Oral Oncol. 50 (1) (2014) 10–18.
[142] T. Tanaka, M. Tanaka, T. Tanaka, Oral carcinogenesis and oral cancer chemoprevention: a review, Patholog. Res. Int. 2011 (2011).
[143] J. Kornfehl, M. Formanek, A. Temmel, B. Knerer, M. Willheim, Antiproliferative effects of the biologically active metabolite of vitamin D3 (1, 25 [OH] 2 D 3) on head and neck squamous cell carcinoma cell lines, Eur. Arch. Oto-Rhino-Laryngol. 253 (6) (1996) 341–344.
[144] B.E.-D. Mostafa, H.M. Abdelmageed, M.M. El-Begermy, M.S. Taha, T.A.-E. Hamdy, A. Omran, N. Lotfy, Value of vitamin D assessment in patients with head and neck squamous cell cancer before treatment, Egypt. J. Otolaryngol. 32 (4) (2016) 279.
[145] L. Lu, J. Qiu, S. Liu, W. Luo, Vitamin D3 analogue EB1089 inhibits the proliferation of human laryngeal squamous carcinoma cells via p57, Mol. Cancer Ther. 7 (5) (2008) 1268–1274.
[146] G. Hager, J. Kornfehl, B. Knerer, G. Weigel, M. Formanek, Molecular analysis of p21 promoter activity isolated from squamous carcinoma cell lines of the head and neck under the influence of 1, 25 (OH) 2 vitamin D3 and its analogs, Acta Otolaryngol. 124 (1) (2004) 90–96.
[147] X. Zhao, D. Yu, J. Yang, K. Xue, Y. Liu, C. Jin, Knockdown of Snail inhibits epithelial–mesenchymal transition of human laryngeal squamous cell carcinoma Hep-2 cells through the vitamin D receptor signaling pathway, Biochem. Cell Biol. 95 (6) (2017) 672–678.
[148] J. Osafi, A. Hejazi, D.D. Stutz, M.A. Keiserman, C.J. Bergman, K. Kingsley, Differential effects of 1, 25-dihydroxyvitamin D3 on oral squamous cell carcinomas in vitro, J. Diet. Suppl. 11 (2) (2014) 145–154.
[149] X. Gan, B. Chen, Z. Shen, Y. Liu, H. Li, X. Xie, X. Xu, H. Li, Z. Huang, J. Chen, High GPX1 expression promotes esophageal squamous cell carcinoma invasion, migration, proliferation and cisplatin-resistance but can be reduced by vitamin D, Int. J. Clin. Exp. Med. 7 (9) (2014) 2530.
[150] J.D. Meier, D.J. Enepekides, B. Poirier, C.A. Bradley, J.S. Albala, D.G. Farwell, Treatment with 1-alpha, 25-dihydroxyvitamin D3 (vitamin D3) to inhibit carcinogenesis in the hamster buccal pouch model, Arch. Otolaryngol. Head Neck Surg. 133 (11) (2007) 1149–1152.
[151] Z. Dalirsani, S. Farajnia, Y. Javadzadeh, M. Mehdipour, S. Koozegari, The effects of 5-fluorouracil alone and in combination with 13-cis retinoic acid and vitamin D3 on human oral squamous cell carcinoma lines, J. Contemp. Dent. Pract. 13 (3) (2012) 345–350.
[152] S. Anand, K.R. Rollakanti, R.L. Horst, T. Hasan, E.V. Maytin, Combination of oral vitamin D3 with photodynamic therapy enhances tumor cell death in a murine model of cutaneous squamous cell carcinoma, Photochem. Photobiol. 90 (5) (2014) 1126–1135.
[153] D.P. Slaughter, H.W. Southwick, W. Smejkal, "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin, Cancer 6 (5) (1953) 963–968.
[154] P.V. Angadi, J. Savitha, S.S. Rao, Y. Sivaranjini, Oral field cancerization: current evidence and future perspectives, Oral Maxillofac. Surg. 16 (2) (2012) 171–180.
[155] T.Y.D. Cheng, G.E. Goodman, M.D. Thornquist, M.J. Barnett, S.A. Beresford, A.Z. LaCroix, Y. Zheng, M.L. Neuhouser, Estimated intake of vitamin D and its interaction with vitamin A on lung cancer risk among smokers, Int. J. Cancer 135 (9) (2014) 2135–2145.
[156] X. León, M. del Prado Venegas, C. Orús, M. López, J. García, M. Quer, Influence of the persistence of tobacco and alcohol use in the appearance of second neoplasm in patients with a head and neck cancer. A case–control study, Cancer Causes Control 20 (5) (2009) 645–652.
[157] M. Grimm, D. Alexander, A. Munz, J. Hoffmann, S. Reinert, Is 1, 25-dihydroxyvitamin D 3 receptor expression a potential Achilles' heel of CD44+ oral squamous cell carcinoma cells? Target. Oncol. 8 (3) (2013) 189–201.
[158] A. Anand, S. Singh, A.A. Sonkar, N. Husain, K.R. Singh, S. Singh, J.K. Kushwaha, Expression of vitamin D receptor and vitamin D status in patients with oral neoplasms and effect of vitamin D supplementation on quality of life in advanced cancer treatment, Contemp. Oncol. 21 (2) (2017) 145.
[159] L. Lipworth, M. Rossi, J. McLaughlin, E. Negri, R. Talamini, F. Levi, S. Franceschi, C. La Vecchia, Dietary vitamin D and cancers of the oral cavity and esophagus, Ann. Oncol. 20 (9) (2009) 1576–1581.
[160] P.K. Ha, S.S. Chang, C.A. Glazer, J.A. Califano, D. Sidransky, Molecular techniques and genetic alterations in head and neck cancer, Oral Oncol. 45 (4) (2009) 335–339.
[161] G. Cadoni, S. Boccia, L. Petrelli, P. Di Giannantonio, D. Arzani, A. Giorgio, E. De Feo, M. Pandolfini, P. Gallì, G. Paludetti, A review of genetic epidemiology of head and neck cancer related to polymorphisms in metabolic genes, cell cycle control and alcohol metabolism, Acta Otorhinolaryngol. Ital. 32 (1) (2012) 1.
[162] W. Luo, P.A. Hershberger, D.L. Trump, C.S. Johnson, 24-Hydroxylase in cancer: impact on vitamin D-based anticancer therapeutics, J. Steroid Biochem. Mol. Biol. 136 (2013) 252–257.
[163] G.P. Levin, C. Robinson-Cohen, I.H. De Boer, D.K. Houston, K. Lohman, Y. Liu, S.B. Kritchevsky, J.A. Cauley, T. Tanaka, L. Ferrucci, Genetic variants and associations of 25-hydroxyvitamin D concentrations with major clinical outcomes, JAMA 308 (18) (2012) 1898–1905.
[164] D. Goltzman, J. White, R. Kremer, Studies of the effects of 1, 25-dihydroxyvitamin D on skeletal and calcium homeostasis and on inhibition of tumor cell growth, J. Steroid Biochem. Mol. Biol. 76 (1-5) (2001) 43–47.
[165] K. Zeljic, G. Supic, M. Stamenkovic Radak, N. Jovic, R. Kozomara, Z. Magic, Vitamin D receptor, CYP27B1 and CYP24A1 genes polymorphisms association with oral cancer risk and survival, J. Oral Pathol. Med. 41 (10) (2012) 779–787.
[166] N. Akutsu, R. Lin, Y. Bastien, A. Bestawros, D.J. Enepekides, M.J. Black, J.H. White, Regulation of gene expression by 1α, 25-dihydroxyvitamin D3 and its analog EB1089 under growth-inhibitory conditions in squamous carcinoma cells, Mol. Endocrinol. 15 (7) (2001) 1127–1139.
[167] K. Kingsley, C. Bergman, M. Keiserman, C. Mobley, Oral cancer risk and vitamin D status, intake and supplementation, OA Cancer 1 (6) (2013).
[168] R. Lin, Y. Nagai, R. Sladek, Y. Bastien, J. Ho, K. Petrecca, G. Sotiropoulou, E.P. Diamandis, T.J. Hudson, J.H. White, Expression profiling in squamous carcinoma cells reveals pleiotropic effects of vitamin D3 analog EB1089 signaling on cell proliferation, differentiation, and immune system regulation, Mol. Endocrinol. 16 (6) (2002) 1243–1256.
[169] W.B. Grant, Ecological studies of the UVB–vitamin D–cancer hypothesis, Anticancer Res. 32 (1) (2012) 223–236.
[170] E. Giovannucci, Vitamin D Status and Cancer Incidence and Mortality, Sunlight, Vitamin D and Skin Cancer, Springer, 2008 pp. 31–42.
[171] A.V. Krishnan, D.L. Trump, C.S. Johnson, D. Feldman, The role of vitamin D in cancer prevention and treatment, Rheum. Dis. Clin. 38 (1) (2012) 161–178.
[172] L. Yin, N. Grandi, E. Raum, U. Haug, V. Arndt, H. Brenner, Meta-analysis: serum vitamin D and breast cancer risk, Eur. J. Cancer 46 (12) (2010) 2196–2205.
[173] C.D. Toner, C.D. Davis, J.A. Milner, The vitamin D and cancer conundrum: aiming at a moving target, J. Acad. Nutr. Diet. 110 (10) (2010) 1492–1500.
[174] T.J. Wang, F. Zhang, J.B. Richards, B. Kestenbaum, J.B. Van Meurs, D. Berry, D.P. Kiel, E.A. Streeten, C. Ohlsson, D.L. Koller, Common genetic determinants of vitamin D insufficiency: a genome-wide association study, Lancet 376 (9736) (2010) 180–188.
[175] M. Małodobra-Mazur, A. Paduch, A. Lebioda, M. Konopacka, J. Rogoliński, C. Szymczyk, J. Wierzgoń, A. Maciejewski, E. Chmielik, A. Jonkisz, VDR gene single nucleotide polymorphisms and their association with risk of oral cavity carcinoma, Acta Biochim. Pol. 59 (4) (2012).
[176] K. Bektaş-Kayhan, M. Ünür, I. Yaylim-Eraltan, H.A. Ergen, B. Toptaş, G. H, A. Karadeniz, T. Isbir, Association of vitamin D receptor Taq I polymorphism and susceptibility to oral squamous cell carcinoma, In Vivo 24 (5) (2010) 755–759.
[177] O. Molavi, F. Narimani, F. Asiaee, S. Sharifi, V. Tarhriz, A. Shayanfar, M. Hejazi, R. Lai, Silibinin sensitizes chemo-resistant breast cancer cells to chemotherapy, Pharm. Biol. 55 (1) (2017) 729–739.
[178] N. Samadi, P. Ghanbari, M. Mohseni, M. Tabasinezhad, S. Sharifi, H. Nazemieh, M.R. Rashidi, Combination therapy increases the efficacy of docetaxel, vinblastine and tamoxifen in cancer cells, J. Cancer Res. Ther. 10 (3) (2014) 715.
[179] M. Mohseni, N. Samadi, P. Ghanbari, B. Yousefi, M. Tabasinezhad, S. Sharifi, H. Nazemiyeh, Co-treatment by docetaxel and vinblastine breaks down P-glycoprotein mediated chemo-resistance, Iran. J. Basic Med. Sci. 19 (3) (2016) 300.
[180] T.O. Bakhshaiesh, M. Armat, D. Shanehbandi, S. Sharifi, B. Baradaran, M.S. Hejazi, N. Samadi, Arsenic trioxide promotes paclitaxel cytotoxicity in resistant breast cancer cells, Asian Pac. J. Cancer Prev. 16 (13) (2015) 5191–5197.
[181] M. Armat, T.O. Bakhshaiesh, M. Sabzichi, D. Shanehbandi, S. Sharifi, O. Molavi, J. Mohammadian, M.S. Hejazi, N. Samadi, The role of Six1 signaling in paclitaxel-dependent apoptosis in MCF-7 cell line, Bosn. J. Basic Med. Sci. 16 (1) (2016) 28.
[182] M. Grimm, Prognostic value of clinicopathological parameters and outcome in 484 patients with oral squamous cell carcinoma: microvascular invasion (V+) is an independent prognostic factor for OSCC, Clin. Transl. Oncol. 14 (11) (2012) 870–880.
[183] M. Pérez-Sayáns, J.M. Suárez-Peñaranda, G.-D. Pilar, F. Barros-Angueira, J.M. Gándara-Rey, A. García-García, Hypoxia-inducible factors in OSCC, Cancer Lett. 313 (1) (2011) 1–8.
[184] N. Sinha, S. Mukhopadhyay, D.N. Das, P.K. Panda, S.K. Bhutia, Relevance of cancer initiating/stem cells in carcinogenesis and therapy resistance in oral cancer, Oral Oncol. 49 (9) (2013) 854–862.

[185] M. Grimm, S. Schmitt, P. Teriete, T. Biegner, A. Stenzl, J. Hennenlotter, H.-J. Muhs, A. Munz, T. Nadtotschi, K. König, A biomarker based detection and characterization of carcinomas exploiting two fundamental biophysical mechanisms in mammalian cells, BMC Cancer 13 (1) (2013) 569.
[186] V. Richard, P. Sebastian, M.G. Nair, S.N. Nair, T.T. Malieckal, T.S. Kumar, M.R. Pillai, Multiple drug resistant, tumorigenic stem-like cells in oral cancer, Cancer Lett. 338 (2) (2013) 300–316.
[187] K. Satake, E. Takagi, A. Ishii, Y. Kato, Y. Imagawa, Y. Kimura, M. Tsukuda, Antitumor effect of vitamin A and D on head and neck squamous cell carcinoma, Auris Nasus Larynx 30 (4) (2003) 403–412.
[188] J. Prudencio, N. Akutsu, N. Benlimame, T. Wang, Y. Bastien, R. Lin, M.J. Black, M.A. Alaoui-Jamali, J.H. White, Action of low calcemic 1α, 25-dihydroxyvitamin D3 analogue EB1089 in head and neck squamous cell carcinoma, J. Natl. Cancer Inst. 93 (10) (2001) 745–753.
[189] E.M. Costa, D. Feldman, Measurement of 1, 25-dihydroxyvitamin D3 receptor turnover by dense amino acid labeling: changes during receptor up-regulation by vitamin D metabolites, Endocrinology 120 (3) (1987) 1173–1178.
[190] R.J. Wiese, A. Uhland-Smith, T.K. Ross, J.M. Prahl, H. DeLuca, Up-regulation of the vitamin D receptor in response to 1, 25-dihydroxyvitamin D3 results from ligand-induced stabilization, J. Biol. Chem. 267 (28) (1992) 20082–20086.
[191] J. Reichrath, L. Rafi, S.M. Müller, D. Mink, K. Reitnauer, W. Tilgen, W. Schmidt, M. Friedrich, Immunohistochemical analysis of 1, 25-dihydroxyvitamin D 3 receptor in cervical carcinoma, Histochem. J. 30 (8) (1998) 561–567.
[192] F.-N.F. Yuan, J. Valiyaparambil, M.C. Woods, H. Tran, R. Pant, J.S. Adams, S.M. Mallya, Vitamin D signaling regulates oral keratinocyte proliferation in vitro and in vivo, Int. J. Oncol. 44 (5) (2014) 1625–1633.
[193] S. Afzal, S.E. Bojesen, B.G. Nordestgaard, Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer, Clin. Chem. 59 (5) (2013) 771–780.
[194] M.L. Slattery, Vitamin D receptor gene (VDR) associations with cancer, Nutr. Rev. 65 (s2) (2007).