Role of Hormones in Oral Squamous Cell Carcinoma - An Update

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Abstract: *Background*: Hormones have been recognized as regulator of the cell growth, differentiation and maturation. It has become increasingly evident that hormone may play a crucial role in the genesis and progression of several cancers like those of breast, ovary, testis, thyroid, prostrate including oral cancer.

Aim: Present overview aims to discuss and provide data on possible role of various hormones including stress hormone, sex hormone, parathyroid and related hormone protein, melatonin and active metabolite of vitamin D3 in causation and progression of Oral squamous cell carcinoma (OSCC).

Data Acquisition: A systematic search of existing literature was carried out for the keywords like hormones and cancer, hormones and oral cancer or OSCC utilizing the Google, Google Scholar and PubMed databases for extraction, assortment and compilation of data.

Inference: In conclusion, we found that hormones are directly or indirectly involved in the pathogenesis of the OSCC and can be utilized in its management and prevention.

Keywords: Cancer, Hormones, Oral squamous cell carcinoma, Steroids.

INTRODUCTION

Cancer is a disease concerned with dynamic alterations in the genome which impel progressive transformation of normal cells into malignant phenotypes. Tumorigenesis is a multistep process and is typified by six essential hallmarks as suggested by Hanahan and Weinberg (2000). These alterations act synergistically and dictate tumor development and progression and violate anticancer defense mechanism [1]. Accumulating evidences suggest that tumor microenvironment actively collaborate with tumor cells and plays a vital role in tumor growth, progression, angiogenesis and metastasis [2, 3].

Hormones are recognized as controller of the cell growth, differentiation and maturation. They can directly or indirectly affect tumor growth and progression and have a critical role in function and metabolism as well [4]. Hormone associated cancers like those of breast, ovary, testis, thyroid, prostrate pose a quite distinctive mechanism of carcinogenesis [5]. Literature search fetched up few researches and reviews linking the role of hormones and oral cancer [6-9]. Endogenous and exogenous hormones act by exciting cell proliferation thus increasing the risk of mutations in their normal target cells as well as stimulating the growth of the mutated cells thereby providing chance for random genetic errors [5, 10].

Present overview attempts to discuss and provide data on possible role of various hormones including stress hormone, sex hormone, parathyroid and related hormone protein, melatonin and active metabolite of vitamin D3 in particular relation to Oral squamous cell carcinoma [OSCC]. A systematic search of existing literature was carried out for the keywords like hormones and cancer, hormones and oral cancer or oral squamous cell carcinoma utilizing the google and PubMed database for extraction and collection of data for the purpose of review.

STRESS HORMONE AND CANCER

It has been observed that alterations in physical health does not only depend upon biological factors but also rely on socio-behavioral factors. The influence of stress, chronic depression, social support and other psychological factors on cancer onset and progression have been studied in several clinical and epidemiological studies and such effects are potentially substantiated by cellular and molecular researches [11, 12]. These factors in turn lead to deregulation of the hypothalamic-pituitary-adrenal (HPA) axis and worsens the immune response [11, 13]. There are effective interactions between bio-behavioral factors and health

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behavioral risk factors like smoking, insomnia, alcohol abuse and obesity which further add to cancer risk [14]. Depression and cancer usually emerge concomitantly and may be associated with elevated cancer risk, cancer progression and mortality [12].

It is hypothesized that stress has a dual effect on immune function. On one hand, stress performs an immune-suppressive role in conditions like infections and cancer while it being immune-enhancing in other situations such as allergic, autoimmune and inflammatory diseases. Acute stress boosts innate and adaptive immunity whereas chronic stress deregulates immune responses [15, 16].

Stress hormones can exert direct effect on tumor cells and dysregulate the production of cytokines, chemokines and growth factors responsible for growth and progression of cancer [12, 17]. IL-6 being a versatile cytokine, have a role in angiogenesis, tumoral progression [18] bone invasion [19], recurrence, metastasis and poor prognosis [20].

Role of Stress Hormone in Oral Squamous Cell Carcinoma

It has been stated that patients suffering from head and neck cancer (HNC) have high psychological distress levels [21, 22] and is significantly correlated with advanced stage cancer [21]. Stress mediators mainly nor-epinephrine (NE) can up regulate IL-6 secretion and stimulate tumor cell proliferation [6]. Elevated catecholamine's levels were found in OSCC patients and it was closely related to clinical stage, grade [23] and progression [24] of OSCC.

MELATONIN AND CANCER

Melatonin is primarily secreted by pineal gland although it can be secreted by various extra-pineal tissues and organs like retina, ciliary body, lens, brain, thymus, airway epithelium, bone marrow, gut, ovary, testicle, placenta, lymphocytes and skin [25]. Melatonin has now been recognized as a potent antioxidant and immune-modulator [26].

Melatonin exerts oncostatic action through following mechanisms:

1. ***As an antioxidant***-Melatonin has the ability to scavenge free radical and regulates the expression of the anti-oxidative enzymes like glutathione peroxidase, superoxide dismutase and catalase [26, 27].

2. ***Cell growth inhibition/ anti-proliferative actions-*** Administration of nano-concentration of melatonin in experimental animal models and cancer cell lines has been shown to inhibit cell proliferation [28].

3. ***As an anti-apoptotic agent***-Mediated through its action on T-helper lymphocytes and its precursors [29].

4. ***As neuro-immunomodulator***- Melatonin augments the production of several cytokines and growth factors like IL-1, IL-6, IL-12 and tumor necrosis factor (TNF) and causes quantitative and functional enhancement of Natural killer cells. Melatonin regulates cell dynamics, including haemopoietic and immune cells lineages concerned with host immunity [29].

5. ***Anti-angiogenic effects***- Melatonin inhibits endothelin-converting enzyme-1, thus reduces formation of endothelin-1, which is considered as a potent stimulator of angiogenesis [30].

6. ***Therapeutic role***- Melatonin has anti-cachectic, anti-asthenic, thrombopoietic and cytostatic properties [31, 32]. It can be effectively used as an adjunct in case of untreatable cancer patients and for the prevention of chemotherapy-induced toxicity [32].

Role of Melatonin in Oral Squamous Cell Carcinoma

Melatonin is said to have a pivotal role in shielding the oral cavity due to its antioxidant, anti-carcinogenic and immunomodulatory properties [26].

Nakamura E *et al.* (2008) found that absence of MTNR1A (Melatonin receptor 1A) is significantly associated with tumor size and a shorter overall survival in OSCC patients [33]. By its action against free radicals, melatonin may protect against develop-ment of potentially malignant disorders and cancer [34].

SEX HORMONES (STEROIDS) AND CANCER

Reznikov A (2015) advocated that steroid dependent tumors share some common features like: 1) They are of epithelial origin, mostly carcinomas 2) Although, they don't have crucial role in intiatiation of tumorigenesis but disturbance in their receptors and signaling pathways does have significant input. 3) Steroids significantly influence proliferation of cancer

cells and encourage their progression. 4) Any kind of mutation in BRCA1 gene involved in androgen and estrogen receptors signaling will lead to tumorigenesis 5) Epithelial-stromal interaction do have vital role in pathogenesis of hormone-dependent cancers. 6) Hormone deprivation remedy is effectively utilized in palliative cure of prostate, mammary and endometrium cancers and their metastasis. 7) In reponse to hormone deprivation therapy, signaling rearrangements and alteration occurs inside tumor [4].

Endocrine setting is an imperative factor in case of cancers expressing sex hormone receptors such as breast, prostate, endometrial and oral cancers [35]. The complex biological effects of estrogen are mediated by estrogen receptors. Mechanisms claimed to be responsible for its tumorigenic action are: 1) stimulation of cellular proliferation through their receptor-mediated hormonal activity 2) direct genotoxic effects via cytochrome P450 (CYP)-mediated metabolic activation 3) induction of aneuploidy [36, 37].

Androgen also plays a crucial role in the normal development and differentiation of a variety of cell and tissue types by influencing the transcription and translation of various genes. Experimental analyses have shown that androgen modulate the expression of proto-oncogenes (like c-myc) and apoptotic factors (like the bcl-2 family) in lacrimal, salivary and prostatic tissues as well as in cell line models [38].

Alcohol intake is associated with increased levels of concentration of sex hormones in circulation which consecutively may increase hormone-dependent cancer risk [39].

Role of Sex Hormones in Oral Squamous Cell Carcinoma

Oral cancer is associated with high male predilection in most populations. This gender-specific risk for cancer raised two assumptions:

1) Deleterious factors affecting particularly only male patients

2) Common risk factors affecting both sexes, but females being spared due to some defense mechanisms owing to their special hormonal and metabolic features [9].

Egloff AM *et al.* (2009) found that EGFR (Epidermal growth factor receptor) and ER (Estrogen receptor) cross-talk promote tumor invasion and disease progression leading to poor prognosis [40]. Yoo YH (2001) demonstrated that estrogen metabolism in HNC patient is different and abnormal compared to healthy controls and estrogen metabolites may constitute putative biological marker for individuals at increased risk of HNC [41].

Bhatavdekar *et al.* (1994) observed higher levels of FSH, LH, prolactin, estradiol, progesterone and DHEA (dehydroepiandrosterone) with concomitant lower levels of testosterone and DHEA-S (dehydroepiandrosterone sulfate) in tongue cancer patients [42] Bauernhofer *et al.* (2011) confirmed higher levels of PRLR (Prolactin receptor) expression to be an independent prognostic factor for overall survival and disease-free survival in HNC patients [43]. Collela G *et al.* (2011) observed decreased expression of AR (Androgen Receptor) transcripts and increased expression of ER α (Estrogen Receptor alpha) transcripts in OSCC specimens [44]. Suba Z *et al.* (2007) favored the estrogen deficiency hypothesis in oral cancer etiology in postmenopausal women [9]. Lukits *et al.* (2007) found frequent expressions of ER. It was inferred that antiestrogens, ER or aromatase inhibitors may have a therapeutic role in the management of HNC [35].

PARATHYROID HORMONE-RELATED PROTEIN (PTHRP) AND CANCER

Bone invasion in cancer is chiefly mediated by osteoclasts rather than by cancer cells directly [45]. Parathyroid hormone-related protein (PTHrP) is reported to have a prime pathogenetic role in stimulating osteoclastic activity and osteolytic bone lesion in breast cancer. Also, antibodies to PTHrP may decrease the development of destructive bone lesions and invasion of tumor cells into the bone [46]. Another mechanism by which PTHrP mediate tumor invasion and metastasis is by influencing cell adhesion to the extracellular matrix via up regulation of specific integrin subunits [47]. Serum PTHrP is a useful determinant of hypercalcemia and bone metastasis in breast and lung carcinoma [48].

Role of Parathyroid Hormone-Related Protein (PTHrP) in Oral Squamous Cell Carcinoma

Advanced OSCC frequently involves bone invasion and reflects adverse prognosis [49]. Tumor-derived PTHrP play a vital role in bone invasion and bone metastasis, mediated by osteoclasts [50]. Co-expression of PTHrP and parathyroid hormone-related protein type 1 receptor (PTHR1) is considered to be a

poor predictor of patient survival. Loss of heterozygosity (LOH) and microsatellite instability (MSI) in PTHR1 may be involved in oral carcinogenesis [51].

Over expression of Parathyroid hormone like hormone (PTHLH)/PTHrP promotes the cancer cell cycle and hasten progression of OSCC. It was observed that expression of PTHrP protein gradually increases with the degree of pathological differentiation signifying poor prognosis and significantly low survival [52]. PTHrP promotes the malignancies of oral cancers cells via downstream of epidermal growth factor receptor (EGFR) signaling [53]. FP Dunne *et al.* (1995) proposed that tumor derived PTHrP is a potent biochemical marker of invasion by OSCC and affect growth and differentiation of tumor and resorption of bone [8]. Hypercalcemia is a well documented paraneoplastic syndrome associated with advanced HNSCC due to production of ectopic PTH-like substances from the tumor and appears to be a poor prognostic indicator [54].

VITAMIN D ACTIVE METABOLITE AND CANCER

Vitamin D active metabolite (1α,25(OH)2D3) via action on vitamin D receptor (VDR) mediates multiple functions including regulation of cell differentiation, proliferation and apoptosis. Calcitriol or vitamin D analogues have anti-proliferative, pro-apoptotic and anti-angiogenic effects and can be administered as preventative and therapeutic anticancer agents [55].

Several epidemiological analyses have revealed an association between low serum 25(OH) D3 levels and increased risk for breast, colorectal and prostate cancers [56-58].

Role of Vitamin D Metabolites in Oral Squamous Cell Carcinoma

VDR gene polymorphism, haplotypes and polymorphism of genes involved in vitamin D metabolism pathway may predict oral cancer risk and survival. It is observed that CYP24A1 gene polymorphism might influence susceptibility to OSCC while VDR FokI polymorphism could be considered as an independent poor prognostic marker [59].

Vitamin D3 reduces tumor growth and assist in activation of apoptosis of genetically damaged cells and restricting damaged cells growth and multiplification [60]. Significantly raised expression of VDR was found in precancerous lesions and OSCC. Thus, vitamin D compounds overcome apoptosis resistance of VDR+ oral precancerous and malignant cells and therefore could be utilized in chemoprevention [61].

INFERENCE

In view of the significant contribution of hormones in cancer, we have reviewed the available literature relating hormones and OSCC and believe that hormones do play an elementary role in carcinogenesis and may influence growth and differentiation of tumor. Moreover, they can be utilized in management and prevention of oral cancer.

CONFLICT OF INTEREST

The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

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REFERENCES

[1] Hanahan D and Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57-70. https://doi.org/10.1016/S0092-8674(00)81683-9

[2] Chery A. Whipple. Tumor talk: understanding the conversation between the tumor and its microenvironment. Can Cell Microenviron 2015; 2.

[3] Mueller MM, Fusenig NE. Friends or foes-bipolar effects of the tumor stroma in cancer. Nat Rev Cancer 2004; 4:839-49. https://doi.org/10.1038/nrc1477

[4] Reznikov A. Hormonal impact on tumor growth and progression. Experimental Oncology 2015; 37: 162-172.

[5] Henderson BE and Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000; 21(3): 427-433. https://doi.org/10.1093/carcin/21.3.427

[6] Bernabe DG, Tamae AC, Biasoli ER *et al*. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain, Behavior, and Immunity 2011; 25: 574-583. https://doi.org/10.1016/j.bbi.2010.12.012

[7] Nath A, Anand V and Anshu AK *et al*. Significantly high levels of estrogen and MDA together induce tumor progression in Oral squamous cell carcinoma 2014; 8: 18-25.

[8] Dunne FP, Bowden SJ, Brown JS, *et al*. Parathyroid hormone related protein in oral squamous cell carcinomas invading the mandible. Clin Pathol 1995; 48: 300-303. https://doi.org/10.1136/jcp.48.4.300

[9] Suba Z. Gender-related hormonal risk factors for oral cancer. Pathology oncology research 2007; 13(3). https://doi.org/10.1007/BF02893499

[10] Waldum HL, Brenna E, Sandvik AK, *et al*. Hormones and carcinogenesis. Endocrine-Related Cancer.1998; 5: 45-48. https://doi.org/10.1677/erc.0.0050045

[11] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol 2004; 5: 617-625. https://doi.org/10.1016/S1470-2045(04)01597-9

[12] Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry 2003; 54: 269-282. https://doi.org/10.1016/S0006-3223(03)00566-3

[13] Glaser R, MacCallum RC, Laskowski BF *et al*. Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. J Gerontol A Biol Sci Med Sci 2001; 56: 477-82. https://doi.org/10.1093/gerona/56.8.M477

[14] Gotay CC. Behavior and cancer prevention. J Clin Oncol 2005; 23: 301-310. https://doi.org/10.1200/JCO.2005.06.069

[15] Dhabhar FS. Enhancing versus Suppressive Effects of Stress on Immune Function: Implications for Immunoprotection versus Immunopathology. Allergy, Asthma, and Clinical Immunology 2008; 4: 2-11. https://doi.org/10.1186/1710-1492-4-1-2

[16] Dhabhar FS and McEwen BS. Acute stress enhances while chronic stress suppresses cell-mediated immunity *in vivo*: a potential role for leukocyte trafficking. Brain Behav Immun. 1997; 11: 286-306. https://doi.org/10.1006/brbi.1997.0508

[17] Ardestani SK, Inserra P and Solkoff D *et al*.The role of cytokines and chemokines on tumor progression: a review. Cancer Detect 1999; 23: 215-225. https://doi.org/10.1046/j.1525-1500.1999.99021.x

[18] Heikkila K, Ebrahim S and Lawlor DA. Systematic review of the association between circulating interleukin-6 (IL-6) and cancer. Eur. J. Cancer 2008; 44: 937-945. https://doi.org/10.1016/j.ejca.2008.02.047

[19] Okamoto M, Hiura K, Ohe G *et al*. Mechanism for bone invasion of oral cancer cells mediated by interleukin-6 *in vitro* and *in vivo*. Cancer 2000; 89: 1966-1975. https://doi.org/10.1002/1097-0142(20001101)89:9<1966::AID-CNCR13>3.0.CO;2-R

[20] Duffy SA, Taylor JM, Terrell JE *et al*. Interleukin-6 predicts recurrence and survival among head and neck cancer patients. Cancer 2008; 113: 750-757. https://doi.org/10.1002/cncr.23615

[21] Kugaya A, Akechi T, Okuyama T *et al*. Prevalence, predictive factors, and screening for psychologic distress in patients with newly diagnosed head and neck cancer. Cancer 2000; 88: 2817-2823. https://doi.org/10.1002/1097-0142(20000615)88:12<2817::AID-CNCR22>3.0.CO;2-N

[22] Chen SC, Liao CT, Lin CC *et al*. Distress and care needs in newly diagnosed oral cavity cancer patients receiving surgery. Oral Oncol 2009; 45: 815-820. https://doi.org/10.1016/j.oraloncology.2009.01.001

[23] Li Bo, Li Li, Guo Daimo *et al*. Assessment of mental health status in oral squamous cell carcinoma patients and its correlation with catecholamines level. Shanghai Journal of Stomatology 2013; 22: 671-675.

[24] Shang ZJ, Liu K, Liang DF. Expression of beta (2)-adrenergic receptor in oral squamous cell carcinoma. J. Oral Pathol. Med 2009; 38: 371-376. https://doi.org/10.1111/j.1600-0714.2008.00691.x

[25] Cengiz S and Wang HL. Melatonin and Oral Cavity International Journal of Dentistry 2012; 2012.

[26] Cutando A, Moreno GG, Arana C *et al*. Melatonin: potential functions in the oral cavity. Journal of Periodontology 2007; 78: 1094-1102. https://doi.org/10.1902/jop.2007.060396

[27] Srinivasan V, Spence DW, Pandi-Perumal SR *et al*. Therapeutic Actions of Melatonin in Cancer: Possible Mechanisms. Integr Cancer Ther 2008; 7: 189-203. https://doi.org/10.1177/1534735408322846

[28] Santos GG, Antolin I, Herrera F *et al*. Melatonin induces apoptosis in human neuroblastoma cancer cells. Journal of Pineal Research 2006; 41: 130-135. https://doi.org/10.1111/j.1600-079X.2006.00342.x

[29] Miller SC, Pandi PSR, Esquifino AI *et al*. The role of melatonin in immunoenhancement: potential application in cancer. International Journal of Experimental Pathology 2006; 87: 81-87. https://doi.org/10.1111/j.0959-9673.2006.00474.x

[30] Mehta A and Kaur G. Potential role of melatonin in prevention and treatment of oral carcinoma. Indian Journal of Dentistry.2014; 5(2). https://doi.org/10.4103/0975-962X.135269

[31] Lissoni P. Is there a role for melatonin in supportive care? Supportive Care in Cancer 2002; 10: 110-116. https://doi.org/10.1007/s005200100281

[32] Mirick DK and Davis S. Melatonin as a biomarker of circadian dysregulation. Cancer Epidemiology Biomarkers and Prevention 2008; 17: 3306-3313. https://doi.org/10.1158/1055-9965.EPI-08-0605

[33] Nakamura E, Kozaki KI, Tsuda H *et al*. Frequent silencing of a putative tumor suppressor gene melatonin receptor 1 A (MTNR1A) in oral squamous-cell carcinoma. Cancer Science 2008; 99: 1390-1400. https://doi.org/10.1111/j.1349-7006.2008.00838.x

[34] Chaiyarit P, Ma N, Hiraku Y *et al*. Nitrative and oxidative DNA damage in oral lichen planus in relation to human oral carcinogenesis. Cancer Science 2005; 96: 553-559. https://doi.org/10.1111/j.1349-7006.2005.00096.x

[35] Lukits RE, Raso E, Ladanyi A *et al*. Molecular identification, expression and prognostic role of estrogen- and progesterone receptors in head and neck cancer. Int J Oncol 2007; 30: 155-60. https://doi.org/10.3892/ijo.30.1.155

[36] Russo J and Russo IH. The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol 2006; 102: 89-96. https://doi.org/10.1016/j.jsbmb.2006.09.004

[37] Russo J, Hasan Lareef M, Balogh G *et al*. Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells. J Steroid Biochem Mol Biol 2003; 87: 1-25. https://doi.org/10.1016/S0960-0760(03)00390-X

[38] McEwan IJ. Molecular mechanisms of androgen receptor-mediated gene regulation: structure-function analysis of the AF-1 domain. Endocrine- Related Cancer 2004; 11: 281-293. https://doi.org/10.1677/erc.0.0110281

[39] Chhim AS, Fassier P, Martel PL *et al*. Prospective association between alcohol intake and hormone dependent cancer risk: modulation by dietary fiber intake. Am J Clin Nutr 2015; 102: 182-189. https://doi.org/10.3945/ajcn.114.098418

[40] Egloff AM. Cross-Talk between Estrogen Receptor and Epidermal Growth Factor Receptor in Head and Neck Squamous Cell Carcinoma. Clin Cancer Res 2009; 15: 6529-40. https://doi.org/10.1158/1078-0432.CCR-09-0862

[41] Yoo HJ, Sepkovic DW, Bradlow HL *et al*. Estrogen metabolism as a risk factor for head and neck cancer. Otolaryngol Head Neck Surg 2001; 124: 241-7. https://doi.org/10.1067/mhn.2001.113507

[42] Bhatavdekar J, Patel D, Vora H *et al*. Circulating hormones in patients with tongue cancer. Oncol Rep 1994; 1: 463-4. https://doi.org/10.3892/or.1.2.461

[43] Bauernhofer T, Pichler M, Wieckowski E *et al*. Prolactin receptor is a negative prognostic factor in patients with squamous cell carcinoma of the head and neck. Br J Cancer 2011; 104: 1641-8. https://doi.org/10.1038/bjc.2011.131

[44] Colella G, Izzo G, Carinci F *et al*. Expression of sexual hormones receptors in oral squamous cell carcinoma. Int J Immunopathol Pharmacol 2011; 24: 129-132. https://doi.org/10.1177/03946320110240S222

[45] Semba I, Matsuuchi H and Miura Y. Histomorphometric analysis of osteoclastic resorption in bone directly invaded by gingival squamous cell carcinoma. J Oral Pathol Med 1996; 25: 429-435. https://doi.org/10.1111/j.1600-0714.1996.tb00292.x

[46] Guise TA, Yin JJ, Taylor SD *et al*. Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis. J Clin Invest 1996; 98: 1544-1549. https://doi.org/10.1172/JCI118947

[47] Shen X and Falzon M. PTH-related protein modulates PC-3 prostate cancer cell adhesion and integrin subunit profile. Mol Cell Endocrinol 2003; 199: 165-177. https://doi.org/10.1016/S0303-7207(02)00287-3

[48] Hiraki A, Ueoka H, Bessho A *et al*. Parathyroid hormone-related protein measured at the time of first visit is an indicator of bone metastases and survival in lung carcinoma patients with hypercalcemia. Cancer 2002; 95: 1706-1713. https://doi.org/10.1002/cncr.10828

[49] Ebrahimi A, Murali R, Gao K *et al*. The prognostic and staging implications of bone invasion in oral squamous cell carcinoma. Cancer 2011; 117: 4460-7. https://doi.org/10.1002/cncr.26032

[50] Takayama Y, Mori T, Nomura T *et al*. Parathyroid-related protein plays a critical role in bone invasion by oral squamous cell carcinoma. International Journal of Oncology 2010; 36: 1387-1394.

[51] Miyashita H, Mori S, Fukumoto Y *et al*. Loss of heterozygosity of the PTH/PTHRP type 1 receptor in oral squamous cell carcinoma. Molecular medicine reports 2008; 1: 821-825. https://doi.org/10.3892/mmr_00000034

[52] Lv Z, Wu X, Cao W *et al*. Parathyroid hormone-related protein serves as a prognostic indicator in oral squamous cell carcinoma. Journal of Experimental & Clinical Cancer Research 2014; 33:100. https://doi.org/10.1186/s13046-014-0100-y

[53] Yamada T, Tsuda M, Ohba Y *et al*. PTHrP promotes malignancy of human oral cancer cell downstream of the EGFR signaling. Biochem. Biophys. Res. Commun 2008; 368: 575-581. https://doi.org/10.1016/j.bbrc.2008.01.121

[54] Dorman EB, Yang H, Vaughan CW *et al*. The incidence of hyeprcalcemia in squamous cell carcinoma of the head and neck. Head Neck Surg 1984; 7: 95-98. https://doi.org/10.1002/hed.2890070202

[55] Deeb KK, Trump DL and Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer Therapeutics. Nature Reviews 2007; 7: 684-700. https://doi.org/10.1038/nrc2196

[56] Li H, Stampfer MJ, Hollis JB *et al*. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Med 2007; 4(3): e103. https://doi.org/10.1371/journal.pmed.0040103

[57] Bertone-Johnson ER, Chen WY, Holick MF *et al*. Plasma 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol. Biomarkers Prev 2005; 14: 1991-1997. https://doi.org/10.1158/1055-9965.EPI-04-0722

[58] Garland CF, Comstock GW, Garland FC *et al*. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet 1989; 2: 1176-1178. https://doi.org/10.1016/S0140-6736(89)91789-3

[59] Zeljic K, Supic G, Stamenkovic Radak M *et al*. Vitamin D receptor, CYP27B1 and CYP24A1 genes polymorphisms association with oral cancer risk and survival. J Oral Pathol Med 2012; 41: 779-87. https://doi.org/10.1111/j.1600-0714.2012.01164.x

[60] Rabata A. Antitumor Effects of Vitamin D3 (1α, 25(OH) 2D3) on Oral Squamous Cell Carcinoma in Hamsters. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2015; 14: 106-112.

[61] Grimm M, Cetindis M, Biegner T *et al*. 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 2015; 20: e188-95. https://doi.org/10.4317/medoral.20368

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