




The Relationship Between Vitamin D Deficiency and Laryngeal Cancer: A Case-control Study in Mashhad, Iran

Ehsan Khadivi ¹, Negar Moghaddas^{2, *}, Hamidreza Rasti Boroujeni³, Bashir Rasoulian¹, Mohammadreza Afzalzadeh¹, Maryam Emadzadeh⁴ and Fatemeh Forouzanfar⁵

¹Sinus and Surgical Endoscopic Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

²ENT Specialist, Head and Neck Surgeon, Mashhad, Iran

³Aja University of Medical Sciences, Tehran, Iran

⁴Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Neuroscience Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

*Corresponding author: ENT Specialist, Head and Neck Surgeon, Mashhad, Iran. Email: msn7189@gmail.com

Received 2023 March 06; Revised 2023 May 06; Accepted 2023 May 15.

Abstract

Background: Despite the high prevalence of head and neck cancers in Iran, no studies have been conducted to investigate the relationship between vitamin D levels and these cancers. Many Iranians suffer from vitamin D deficiency, which underscores the importance of conducting these studies in Iran.

Objectives: This study aims at investigating the relationship between vitamin D levels and laryngeal cancer.

Methods: This 1:1 matched case-control study included 216 patients in Mashhad, Iran, who had not consumed vitamin D supplements for 3-months before study onset. Participants were grouped in 2 categories; the case group, which consisted of patients with laryngeal cancer whose squamous cell carcinoma was confirmed pathologically for the first time (new cases), and the control group, which consisted of individuals who did not have any cancer at the time of the study, confirmed by indirect laryngoscopy, and were identical to the patient group in terms of other risk factors for laryngeal cancer (smoking and alcohol abuse). First, the relevant checklist (including age, occupation, consumption of tobacco, alcohol use, etc., history of contact with mustard gas, wood, stone, metal, and cement industry, as well as history of reflux in the individual and cancer in relatives) was completed for all case and control group members. After taking blood samples, they were evaluated for serum levels of vitamin D3. Data were analyzed using chi-square, Mann-Whitney U or independent sample *t*-tests. Logistic regression was also used to determine the relation between vitamin D level and laryngeal cancer.

Results: Mean age, sex and risk factors of laryngeal cancer were not significantly different between the two groups. Vitamin D level was significantly lower in patients with laryngeal cancer compared to control group (16.02 ± 3.62 ng/mL vs 25.19 ± 3.40 ($P < 0.001$)). Logistic regression analysis showed that vitamin D level is independently related to laryngeal cancer and has a protective effect on this neoplasm (OR = 0.54, 95%CI: 0.46 - 0.63, $P < 0.001$).

Conclusions: A lower vitamin D level may be related to laryngeal cancer. However, the role of vitamin D deficiency as a risk factor for head and neck cancers and whether the treatment of this condition could prevent the incidence of such cancers is a matter of future investigations.

Keywords: Vitamin D, Laryngeal Cancer, Squamous Cell Carcinoma

1. Background

Head and neck cancers represent the sixth most common cancer globally and is responsible for more than 5% of human malignancies. Head and neck cancer is a general term for epithelial malignancies of the nasal cavity, paranasal sinuses, oral cavity, larynx, and pharynx (1, 2). Several risk factors including tobacco consumption, alcohol use, and human papillomavirus infection have been recognized for head and neck cancers (3, 4). It has been

demonstrated that the rate of some cancers is lower in regions with more exposure to UV light. This is believed to be due to increased production of vitamin D in these populations (5, 6). The importance of attention to vitamin D increases when it is known to affect significant medical problems such as cancers, cardiovascular diseases, and diabetes (7). The importance of attention to vitamin D increases whenever it is known to affect significant medical problems such as cancers, cardiovascular diseases, and diabetes (8-10). Vitamin D has been linked to cancer devel-

opment. The antitumor properties of vitamin D were first proposed by Peller and Stephenson (11) and Apperly (12) in the 1940s when they reported a lower incidence of all other malignancies except skin cancers. This hypothesis was supported by further investigations that showed an increased prevalence of colorectal, prostate, and breast cancer among individuals with vitamin D deficiency (8, 13, 14). The majority of patients with head and neck cancer have a higher incidence of vitamin D deficiency compared to age- and sex-matched healthy controls (15). An association between low serum levels of vitamin D and a higher tumor incidence has been reported (16, 17). Additionally, the anti-tumor function of the immune system also appears to depend on an adequate supply of vitamin D (18, 19). The role of vitamin D deficiency in head and neck cancers, especially laryngeal cancer, is controversial, and few studies have investigated the association between them. It was shown that vitamin D deficiency is an independent predictor of head and neck squamous cell carcinoma mortality (20). However, another observational study found no association between head and neck cancer outcome and vitamin D level (21). Vitamin D deficiency was also not found to be a risk factor for laryngeal cancer according to a retrospective study by Arem et al. (22). Conversely, a large high-quality study revealed that a higher circulating vitamin D level associates with lower incident of larynx and hypopharynx cancer combined (23). Few studies have addressed the association between larynx malignancies and vitamin D levels in Iran. Regarding the high prevalence of vitamin D deficiency in Iran (over half of the population) (24), determining the relationship between vitamin D levels and laryngeal cancer is important since it could be a preventable risk factor for this cancer.

2. Objectives

This study aimed at evaluating the association between larynx malignancies and vitamin D levels.

3. Methods

This 1: 1 matched case-control study was performed from January 2021 to March 2022 in Ghaem and Imam Reza hospitals, Mashhad, Iran. All the participants consented to enter the study. The study protocol was approved by the Mashhad University of Medical Sciences (MUMS) ethical committee (ethical code: [IR.MUMS.MEDICAL.REC.1401.186](#)).

3.1. Participants

Participants between the ages of 35 to 85 who consented to participate in the study were included. The case

group consisted of patients who had histologically confirmed laryngeal cancer. By convenience sampling, data of relevant patients who referred to the mentioned hospitals between 2021 and 2022 was gathered. The control group were selected from healthy individuals and were matched by the case group in terms of sex, age, and alcohol and cigarette consumption. Patients with immunodeficiency conditions that affect the serum vitamin D levels and those who consumed vitamin D supplements 3 months before study onset were excluded. The relevant checklist (including age, occupation, consumption of tobacco, alcohol use, etc.; history of contact with mustard gas, wood, stone, metal, and cement industry; as well as history of reflux in the individual and cancer in relatives) was completed for all case and control group members. Ten milliliters of peripheral blood were collected from each participant (centrifuged at 3000 rpm at 4°C for 10 min). All samples were stored at -80°C before measurements of circulating 25OHD concentration.

3.2. Sample Size and Statistical Analysis

Sample size was estimated based on the data reported serum level of vitamin D as 32 ± 2.7 in healthy population and 31 ± 2.5 in those with head and neck malignancies (22). Considering $\alpha = 0.05$ and $\beta = 0.2$ the minimum sample size was calculated as 108 individuals in each group. Categorical and continuous variables were presented as frequency (%) and mean \pm standard deviation, respectively. Chi-square test was used to compare the categorical variables between study groups. To compare the continuous measures between the two groups, independent samples T-test or Mann-Whitney test were used. Logistic regression analysis was used to determine the predictive factors of laryngeal cancer. P-values below 0.05 was considered statistically significant.

4. Results

A total of 216 participants were enrolled, of which 108 had laryngeal cancer, and 108 were healthy controls. The mean age of patients with laryngeal cancer was 58.87 ± 10.77 years and 58.75 ± 10.89 for the control group ($P = 0.93$). The gender distribution, social and family history were not significantly different between the study groups. None of the participants had a history of Mustard gas exposure. Occupational exposure was significantly more frequent in patients with laryngeal cancer compared to healthy controls (Table 1).

The vitamin D level was 16.0 ± 3.6 ng/mL in the laryngeal cancer group and 25.19 ± 3.40 ng/mL in the control group ($P < 0.001$). Table 2 indicates the frequency of vitamin D deficiency in each study group.

Table 1. Baseline Characteristics of Study Participants^a

Variable	Study Groups		P Value ^b
	Laryngeal Cancer Group (n = 108)	Control Group (n = 108)	
Age (y)	58.87 ± 10.77	58.75 ± 10.89	0.93 ^c
Gender (female)	32 (29.6)	36 (33.3)	0.56
Mustard gas inhalation	0	0	> 0.99
Social and family history			
Hookah	69 (63.9)	67 (62.0)	0.78
Opium	41 (38.0)	34 (31.5)	0.32
Naswar	8 (7.4)	4 (3.7)	0.23
Alcohol	22 (20.4)	20 (18.5)	0.73
Smoking pack/year	13.25 ± 5.36	13.08 ± 5.43	0.81
Family history of cancer	21 (19.4)	12 (11.1)	0.09
Underlying diseases			
GERD	68 (63.0)	54 (50.0)	0.06
Occupation			
			0.05
Self-employee	30 (27.8)	42 (23.1)	
Unemployed	31 (28.7)	40 (38.9)	
Housekeeper	11 (10.2)	13 (12.0)	
Farmer	20 (18.5)	6 (5.6)	
Worker	8 (7.4)	13 (12.0)	
Government employee	9 (8.3)	8 (7.4)	
Occupational exposure			
			< 0.001
Wood	17 (15.7)	4 (3.7)	
Stone	2 (1.9)	1 (0.9)	
Metal	3 (2.8)	2 (2.8)	
Cement	16 (14.8)	7 (6.5)	
Total	38 (35.2)	14 (13.0)	

^a Data are presented as mean ± standard deviation (SD) or frequency (%).^b Chi-square the was used unless otherwise stated.^c Independent sample *t*-test**Table 2.** Mean Vitamin D Level and Frequency of Vitamin D Deficiency in Study Groups^a

Variable	Study Groups		P Value
	Laryngeal Cancer Group (n = 108)	Control Group (n = 108)	
Vitamin D (ng/mL)	16.0 ± 3.6	25.19 ± 3.40	< 0.001 ^b
Vitamin D deviancy			
			< 0.001 ^c
Deficiency	101 (93.5%)	6 (5.6%)	
Insufficient or normal	7 (6.5%)	102 (94.4%)	

^a Data are presented as mean ± SD or frequency (%).^b Independent sample *t*-test^c Chi-square test

Significant variable in univariate analysis were entered to the logistic regression model to find out their role in laryngeal cancer. The logistic regression analysis showed that the vitamin D level has a protective effect against laryngeal cancer (OR = 0.54, 95%CI = 0.46 to 0.63, P < 0.001) (Table 3).

Table 3. Predictors of Laryngeal Cancer Using Logistic Regression (Enter Method)

Variables	Odds Ratio	95% CI	P-Value
Serum level of vitamin D	0.54	0.46 - 0.63	< 0.001
Wood	1.61	0.33 - 7.81	0.55
Sement	0.40	0.05 - 2.93	0.36
Reflux	1.84	0.66 - 5.11	0.24
Family history of cancer	2.37	0.65 - 8.65	0.19
Naswar	4.32	0.61 - 30.59	0.14

5. Discussion

According to evidence, vitamin D is an essential regulator of calcium and bone homeostasis. Studies have shown a potential role for vitamin D in head and neck cancer. Vitamin D, as a prohormone, undergoes two-step metabolism, resulting in the production of biologically active metabolite.

During exposure to sunlight, dehydrocholesterol in the skin absorbs UV radiation and is converted to previtamin D₃. The liver converts vitamin D to 25-hydroxyvitamin D (25(OH)D), or calcifediol.

Another hydroxylation step of active vitamin D formation takes place in the kidney, to become the active form of vitamin D, 1 α -25-dihydroxyvitamin D (1,25(OH)₂D), or calcitriol. The dominant function of vitamin D in its hormonal form calcitriol and functions systemically via the vitamin D receptor, which is present in several tissues and cells. Our study showed that the vitamin D level is lower in laryngeal cancer group. The relation between head and neck cancers and vitamin D levels has been rarely studied, and the results are highly controversial. In 2021, two research groups systematically reviewed the literature on the relation between vitamin D levels and head and neck cancers. Makitie et al. (25) reviewed 13 articles. In their research and found that despite the higher prevalence of vitamin D deficiency among patients with head and neck cancer compared to the normal population, there is no evidence for a causal relationship. On the other hand, Pu et al. (26) reviewed 16 studies with a total of 81908 cases. Their meta-analysis showed that higher circulating vitamin D levels have a protective effect against head and neck cancers (OR (95% CI): 0.68 (0.59 to 0.78)). In a study by

Anand et al. (27), vitamin D scores were significantly lower in patients with oral neoplasms compared to healthy controls. Besides, vitamin D supplementation markedly decreased the therapy-related toxicities, therefore decreasing morbidity and improving quality of life in patients with oral neoplasms. One study showed that 25(OH)D supplements improved the immune function of patients with head and neck cancer by temporarily decreasing the number of CD34-positive cells and enhancing the number of IL-12 and IFN- γ -neurotransmitters (28). In one study, giving 1,25(OH)₂D treatment before surgery in head and neck squamous cell carcinoma patients rises the plasma levels of both type 1 and type 2 T helper cell system mediators. 1,25(OH)₂D also enhanced the levels of the tumorigenic and angiogenic mediators IL-8 and VEGF in plasma, but not in cancerous tissue (18). Several factors may explain the discrepancy in the literature. Firstly, not all the populations have similar baseline vitamin D level. Vitamin D is higher in most developed countries compared to developing countries, which highlights the importance of conducting multicenter studies. Secondly, while some studies have included a mixture of smokers and non-smokers in the final analysis (14), most studies, including our investigation, solely evaluated the smoking subjects (14). This study had some limitations; changes in diet and exposure to sunlight during the study were not investigated. Also, the participant's history of alcohol consumption and smoking, as well as exposure to carcinogenic substances were not assessed. Moreover, a larger sample size would have been preferable.

5.1. Conclusions

A lower vitamin D level may be associated with laryngeal cancer. However, the potential role of vitamin D deficiency as a risk factor for head and neck cancers and whether addressing this deficiency could prevent the incidence of such cancers requires further investigation in the future.

Acknowledgments

This article is resulted from a thesis (991948; IR.MUMS.MEDICAL.REC.1401.186) performed at Mashhad University of Medical sciences. The authors would like to thank Clinical Research Development Unit of Ghaem Hospital for participation in data analysis.

Footnotes

Authors' Contribution: Ehsan Khadivi and Negar Moghaddas conceived and designed the evaluation and

drafted the manuscript. Maryam Emadzadeh and Fate-meh Forouzanfar participated in designing the evaluation, performed parts of the statistical analysis and helped to draft the manuscript. Hamidreza Rasti Boroujeni and Bashir Rasoulian re-evaluated the clinical data, revised the manuscript and performed the statistical analysis and revised the manuscript. Negar Moghaddas collected the clinical data, interpreted them and revised the manuscript. Mohammadreza Afzalzadeh, and Ehsan Khadivi re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests: The authors declare no potential conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The study protocol was approved by the Mashhad University of Medical Sciences (MUMS) ethical committee (ethical code: [IR.MUMS.MEDICAL.REC.1401.186](https://doi.org/10.1016/j.oraloncology.2015.03.015)).

Funding/Support: This research was supported by a grant (991948) from the Vice-Chancellor for Research and Technology, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. (Dr. Ehsan Khadivi).

Informed Consent: Informed consent was obtained from the participants.

References

- Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. 2008;**371**(9625):1695-709. [PubMed ID: [18486742](https://pubmed.ncbi.nlm.nih.gov/18486742/)]. [PubMed Central ID: [PMC7720415](https://pubmed.ncbi.nlm.nih.gov/PMC7720415/)]. [https://doi.org/10.1016/S0140-6736\(08\)60728-X](https://doi.org/10.1016/S0140-6736(08)60728-X).
- Gazdzicka J, Golabek K, Strzelczyk JK, Ostrowska Z. Epigenetic Modifications in Head and Neck Cancer. *Biochem Genet*. 2020;**58**(2):213-44. [PubMed ID: [31712935](https://pubmed.ncbi.nlm.nih.gov/31712935/)]. [PubMed Central ID: [PMC7113219](https://pubmed.ncbi.nlm.nih.gov/PMC7113219/)]. <https://doi.org/10.1007/s10528-019-09941-1>.
- Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). *Oral Oncol*. 2015;**51**(8):727-30. [PubMed ID: [26066977](https://pubmed.ncbi.nlm.nih.gov/26066977/)]. <https://doi.org/10.1016/j.oraloncology.2015.03.015>.
- Dhull AK, Atri R, Dhankhar R, Chauhan AK, Kaushal V. Major Risk Factors in Head and Neck Cancer: A Retrospective Analysis of 12-Year Experiences. *World J Oncol*. 2018;**9**(3):80-4. [PubMed ID: [29988794](https://pubmed.ncbi.nlm.nih.gov/29988794/)]. [PubMed Central ID: [PMC6031231](https://pubmed.ncbi.nlm.nih.gov/PMC6031231/)]. <https://doi.org/10.14740/wjon1104w>.
- International Agency for Research on Cancer. *Vitamin D and Cancer, IARC Working Group Report Volume 5*. Lyon, France: International Agency for Research on Cancer; 2008.
- Abraham J, Dowling K, Florentine S. Can Optimum Solar Radiation Exposure or Supplemented Vitamin D Intake Reduce the Severity of COVID-19 Symptoms? *Int J Environ Res Public Health*. 2021;**18**(2). [PubMed ID: [33467131](https://pubmed.ncbi.nlm.nih.gov/33467131/)]. [PubMed Central ID: [PMC7829816](https://pubmed.ncbi.nlm.nih.gov/PMC7829816/)]. <https://doi.org/10.3390/ijerph18020740>.
- Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev*. 2013;**12**(10):976-89. [PubMed ID: [23542507](https://pubmed.ncbi.nlm.nih.gov/23542507/)]. <https://doi.org/10.1016/j.autrev.2013.02.004>.
- Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, et al. The role of vitamin D in cancer prevention. *Am J Public Health*. 2006;**96**(2):252-61. [PubMed ID: [16380576](https://pubmed.ncbi.nlm.nih.gov/16380576/)]. [PubMed Central ID: [PMC1470481](https://pubmed.ncbi.nlm.nih.gov/PMC1470481/)]. <https://doi.org/10.2105/AJPH.2004.045260>.
- Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;**117**(4):503-11. [PubMed ID: [18180395](https://pubmed.ncbi.nlm.nih.gov/18180395/)]. [PubMed Central ID: [PMC2726624](https://pubmed.ncbi.nlm.nih.gov/PMC2726624/)]. <https://doi.org/10.1161/CIRCULATIONAHA.107.706127>.
- Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J*. 2017;**474**(8):1321-32. [PubMed ID: [28341729](https://pubmed.ncbi.nlm.nih.gov/28341729/)]. <https://doi.org/10.1042/BCJ20170042>.
- Peller S, Stephenson C. Skin Irritation and Cancer in the U. S. Navy. *Am J Med Sci*. 1937;**194**(3):326-33. <https://doi.org/10.1097/00000441-193709000-00004>.
- Apperly FL. The relation of solar radiation to cancer mortality in North America. *Cancer Res*. 1941;**1**(3):191-5.
- Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2004;**13**(9):1502-8. [PubMed ID: [15342452](https://pubmed.ncbi.nlm.nih.gov/15342452/)].
- Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*. 2006;**98**(7):451-9. [PubMed ID: [16595781](https://pubmed.ncbi.nlm.nih.gov/16595781/)]. <https://doi.org/10.1093/jnci/djj101>.
- Orell-Kotikangas H, Schwab U, Osterlund P, Saari-Lahti K, Makitie O, Makitie AA. High prevalence of vitamin D insufficiency in patients with head and neck cancer at diagnosis. *Head Neck*. 2012;**34**(10):1450-5. [PubMed ID: [22287291](https://pubmed.ncbi.nlm.nih.gov/22287291/)]. <https://doi.org/10.1002/hed.21954>.
- Afzal S, Bojesen SE, Nordestgaard BG. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. *Clin Chem*. 2013;**59**(5):771-80. [PubMed ID: [23503722](https://pubmed.ncbi.nlm.nih.gov/23503722/)]. <https://doi.org/10.1373/clinchem.2012.201939>.
- Reijnen PLM, Soeters PB. Vitamin D: A magic bullet or a myth? *Clin Nutr*. 2020;**39**(9):2663-74. [PubMed ID: [31959477](https://pubmed.ncbi.nlm.nih.gov/31959477/)]. <https://doi.org/10.1016/j.clnu.2019.12.028>.
- Walker DD, Reeves TD, de Costa AM, Schuyler C, Young MR. Immunological modulation by 1alpha,25-dihydroxyvitamin D3 in patients with squamous cell carcinoma of the head and neck. *Cytokine*. 2012;**58**(3):448-54. [PubMed ID: [22450225](https://pubmed.ncbi.nlm.nih.gov/22450225/)]. [PubMed Central ID: [PMC3340440](https://pubmed.ncbi.nlm.nih.gov/PMC3340440/)]. <https://doi.org/10.1016/j.cyto.2012.03.002>.
- Young MR, Day TA. Immune regulatory activity of vitamin d3 in head and neck cancer. *Cancers (Basel)*. 2013;**5**(3):1072-85. [PubMed ID: [24202334](https://pubmed.ncbi.nlm.nih.gov/24202334/)]. [PubMed Central ID: [PMC3795379](https://pubmed.ncbi.nlm.nih.gov/PMC3795379/)]. <https://doi.org/10.3390/cancers5031072>.
- Bochen F, Balensiefer B, Korner S, Bittenbring JT, Neumann F, Koch A, et al. Vitamin D deficiency in head and neck cancer patients - prevalence, prognostic value and impact on immune function. *Oncoimmunology*. 2018;**7**(9). e1476817. [PubMed ID: [30228945](https://pubmed.ncbi.nlm.nih.gov/30228945/)]. [PubMed Central ID: [PMC6140588](https://pubmed.ncbi.nlm.nih.gov/PMC6140588/)]. <https://doi.org/10.1080/2162402X.2018.1476817>.
- Meyer F, Liu G, Douville P, Samson E, Xu W, Adjei A, et al. Dietary vitamin D intake and serum 25-hydroxyvitamin D level in relation to disease outcomes in head and neck cancer patients. *Int J Cancer*. 2011;**128**(7):1741-6. [PubMed ID: [20533282](https://pubmed.ncbi.nlm.nih.gov/20533282/)]. [PubMed Central ID: [PMC2990799](https://pubmed.ncbi.nlm.nih.gov/PMC2990799/)]. <https://doi.org/10.1002/ijc.25496>.
- Arem H, Weinstein SJ, Horst RL, Virtamo J, Yu K, Albanes D, et al. Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men. *Cancer Epidemiol Biomarkers Prev*. 2011;**20**(6):1178-84. [PubMed ID: [21527582](https://pubmed.ncbi.nlm.nih.gov/21527582/)]. [PubMed Central ID: [PMC311816](https://pubmed.ncbi.nlm.nih.gov/PMC311816/)]. <https://doi.org/10.1158/1055-9965.EPI-11-0153>.
- Fanidi A, Muller DC, Middttun O, Ueland PM, Vollset SE, Relton C, et al. Circulating vitamin D in relation to cancer incidence and survival of the head and neck and oesophagus in the EPIC cohort.

- Sci Rep.* 2016;**6**:36017. [PubMed ID: 27812016]. [PubMed Central ID: PMC5095706]. <https://doi.org/10.1038/srep36017>.
24. Vatandost S, Jahani M, Afshari A, Amiri MR, Heidarimoghadam R, Mohammadi Y. Prevalence of vitamin D deficiency in Iran: A systematic review and meta-analysis. *Nutr Health.* 2018;**24**(4):269–78. [PubMed ID: 30296903]. <https://doi.org/10.1177/0260106018802968>.
 25. Makitie A, Tuokkola I, Laurell G, Makitie O, Olsen K, Takes RP, et al. Vitamin D in Head and Neck Cancer: a Systematic Review. *Curr Oncol Rep.* 2020;**23**(1):5. [PubMed ID: 33216252]. [PubMed Central ID: PMC7679336]. <https://doi.org/10.1007/s11912-020-00996-7>.
 26. Pu Y, Zhu G, Xu Y, Zheng S, Tang B, Huang H, et al. Association Between Vitamin D Exposure and Head and Neck Cancer: A Systematic Review With Meta-Analysis. *Front Immunol.* 2021;**12**:627226. [PubMed ID: 33732250]. [PubMed Central ID: PMC7959800]. <https://doi.org/10.3389/fimmu.2021.627226>.
 27. Anand A, Singh S, Sonkar AA, Husain N, Singh KR, Singh S, et al. 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 (Pozn).* 2017;**21**(2):145–51. [PubMed ID: 28947884]. [PubMed Central ID: PMC5611504]. <https://doi.org/10.5114/wo.2017.68623>.
 28. Lathers DM, Clark JI, Achille NJ, Young MR. Phase 1B study to improve immune responses in head and neck cancer patients using escalating doses of 25-hydroxyvitamin D3. *Cancer Immunol Immunother.* 2004;**53**(5):422–30. [PubMed ID: 14648070]. <https://doi.org/10.1007/s00262-003-0459-7>.