

# Vitamin D and Non-Melanoma Skin Cancer

Subjects: Dermatology

Contributor: Saverio Caini

Non-melanoma skin cancers (NMSC) are the most common type of skin malignancies among humans (particularly fair-skinned populations of European descent) and its incidence rates have been on the rise globally for decades [1]. The best defined role of vitamin D in humans is in supporting the normal development and maintenance of bone tissues and in regulating calcium metabolism [7,8]. Furthermore, there is growing evidence that vitamin D plays a role in many fundamental biological processes (e.g., cell proliferation, angiogenesis, and modulation of the immune system) [9] implicated in carcinogenesis.

Keywords: vitamin D ; dietary intake ; blood concentration ; gene polymorphism ; vitamin D receptor ; vitamin D binding protein ; non-melanoma skin cancer ; basal cell cancer ; squamous cell cancer ; risk

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## 1. Introduction

Non-melanoma skin cancers (NMSC) are the most common type of skin malignancies among humans (particularly fair-skinned populations of European descent) and its incidence rates have been on the rise globally for decades [1]. The near totality of NMSC is represented by keratinocyte skin cancers (KSC), e.g., basal cell cancer (BCC) and squamous cell cancer (SCC), while other non-melanoma skin cancer types not originating from keratinocytes (e.g., Merkel cell carcinoma) are rare. The economic costs required by the management of NMSC patients are substantial because of very high NMSC incidence rates [2]. The most important environmental risk factor for NMSC is exposure of the skin to ultraviolet radiation (UV) [3]. Other established and suspected risk factors include older age, male sex, light-coloured skin, eyes and hair, use of photosensitizing medications, and having had a previous NMSC diagnosis [4][5]. Given the high NMSC disease burden, research has largely focused on identifying other preventable risk factors, and several publications have examined the role of vitamin D in the aetiology of NMSC.

Vitamin D is produced in human skin and is also found naturally in some foods [6]. In addition, vitamin D-fortified foods are available on the market, and vitamin D can be obtained by taking supplements. In the body, vitamin D is hydroxylated first in the liver to form 25-hydroxyvitamin D [25(OH)D], which is the major circulating form of vitamin D, and then in the kidney to form the physiologically active 1,25-dihydroxyvitamin D. Most vitamin D in the blood is bound to the vitamin D binding protein (VDBP). To exert its action, calcitriol binds to the vitamin D receptor (VDR): several polymorphisms of the VDR gene lead to an altered functionality of the VDR protein, and have been investigated in association with the occurrence of several diseases.

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## 2. Vitamin D and Non-Melanoma Skin Cancer

### 2.1. Vitamin D Blood Concentration and NMSC Risk

Ten studies reported a RR estimate comparing NMSC risk among those in the highest vs. lowest category of serum/plasma 25(OH)D concentration (**Table 1**) [10][11][12][13][14][15][16][17][18][19]. Of these, five were conducted in the USA, two in Denmark, and one each in Australia, Brazil, and Poland. In terms of study design, three were case-control studies [13][17][19], two were nested case-control studies [10][11], and five were cohort studies [12][14][15][16][18]. The ten studies encompassed a total of 3899 NMSC cases, of which 1569 (40.2%) were contributed by Winsløw et al. [18]. Vitamin D concentration was measured in serum in all studies except in Liang et al. [14]. The studies differed greatly both in the

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References were used to calculate the RR for the highest vs. lowest vitamin D concentration comparison, and in the degree of statistical adjustment. In particular, for three studies an unadjusted OR was calculated using data provided in the paper (33, 37, 42).

**Table 1.** Main characteristics of the studies reporting on the association between serum/plasma concentration of 25(OH)D (comparison: highest vs. lowest category) and the risk of non-melanoma skin cancer. A review. *J. Natl. Comp. Cancer Netw.* 2010, 8, 888–890.

Year	Author	Country	Study Design	Skin Cancer Type	N Cases	N Controls	Sex	Age (yrs)	Diagnosis	Exposure	Comparison	RR	95% CI	Adjusting Variables
2018	Savoye, I.; Olsen, C.M.; Whiteman, D.C.; Bijon, A.; Wald, L.; Dartois, L.; Clavel-Chapelon, F.; Boutron-Ruault, M.C.; Kuvshinov, M.	France	Case-control	NMSC	11,111	11,111	50.0%	50-75	self-reported	>29.8 vs. <16 ng/mL	2.09	0.95-4.58	age, sex, season of sampling, phenotype, UV exposure, other	
2010	Belbasis, L.; Stefanaki, I.; Stratigos, A.J.; Evangelou, E.	USA	NCC	BCC	220	220	51.8%	50-75	serum	>29.8 vs. <16 ng/mL	2.09	0.95-4.58	age, sex, season of sampling, phenotype, UV exposure, other	
2010	Gandini, S.; Palli, D.; Spadola, G.; Bendinelli, B.; Coccorocchi, G.; Stanganelli, I.; Miligi, L.; Masala, G.; Caini, S.	Italy	CC	KSC	50	14	ns	18-65	serum	≥30 vs. <30 ng/mL	0.16	0.004-1.30	none (c)	
2021	Dominguez, L.J.; Farruggia, M.; Veronese, N.; Barbagallo, M.	USA	NCC	NMSC	178	930	100.0%	2000-2017	serum	≥29.9 vs. <16 ng/mL	0.54	0.31-0.96	age, season of sampling, other	
2018	Khammissa, R.A.G.; Fourie, J.; Motswaledi, M.H.; Ballyram, R.; Lemmer, J.; Feller, L.	USA	CC	BCC	142	142	50.0%	2007-2008	serum	>30 vs. <20 ng/mL	0.18	0.08-0.37	none (c)	
2010	Asgari, M.M.; Tang, J.; Warton, M.E.; Chren, M.M.; Quesenberry, C.P., Jr.; Bikle, D.; Horst, R.L.; Orentreich, N.; Vogelman, J.H.; Friedman, G.D.	USA	cohort	BCC	416	4641	0.0%	1976-2008	plasma	4th vs. 1st quartile	2.09	1.52-2.80	age, season of sampling, UV exposure, other	
2010	Tang, J.Y.; Parimi, N.; Wu, A.; Boscardin, W.J.; Shikany, J.M.; Chren, M.M.; Cummings, S.R.; Epstein, E.H., Jr.	USA	cohort	SCC	75	75	50.0%	1976-2008	serum	≥75 vs. <75 nmol/L	1.51	1.10-2.07	age, sex, UV exposure, phenotype, other	
2007	van der Pols, J.C.; Johnson, D.A.; Jacobsen, G.R.; Kraienta, R.J.; Rao, D.S.; Kim, H.W.; Johnson, C.C.	Australia	cohort	BCC	300	1191	58.0%	1966-2007	serum	≥75 vs. <75 nmol/L	0.57	0.44-0.74	age, sex, UV exposure, phenotype, other	
2011	Lesiak, A.; Norval, M.; Wodz-Naskiewicz, K.; Pawliczak, R.; Rogowski-Tylman, M.; Sysa-Jedrzejowska, A.; Sobjanek, M.; Wlodarkiewicz, A.; Narbutt, J.	Denmark	cohort	NMSC	12,204	12,204	48.1%	1999-2011	serum	4th vs. 1st quartile	1.43	1.05-1.93	age, sex, season of sampling, other	
2012	Liang, G.; Nan, H.; Qureshi, A.A.; Han, J.	USA	CC	BCC	67	67	56.1%	2016-2017	serum	≥30 vs. <20 ng/mL	50.00	11.11-100.0	none (c)	
2013	van der Pols, J.C.; Russell, A.; Bauer, U.; Neale, R.E.; Kimlin, M.G.; Green, A.C.	Denmark	cohort	NMSC	1569	35,298	43.0%	1981-2012	plasma	≥50 vs. <25 nmol/L	3.76	2.58-5.48	age, sex, season of sampling, other	
2014	Skaaby, T.; Husemoen, L.L.; Thuesen, B.H.; Pisinger, C.; Jørgensen, T.; Roswall, N.; Larsen, S.C.; Linneberg, A.	Denmark	cohort	NMSC	398	12,204	48.1%	1999-2011	serum	4th vs. 1st quartile	1.43	1.05-1.93	age, sex, season of sampling, other	
2018	Soares, A.M.; Szejnfeld, V.L.; Enokihara, M.Y.; Michalany, N.; Castro, C.H.	USA	Case-control	NMSC	111	111	56.1%	2016-2017	serum	≥30 vs. <20 ng/mL	50.00	11.11-100.0	none (c)	
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**2.2. Vitamin D, Dietary Intake and Supplements Use and NMSC Risk** M.Z.; Zeitouni, N.C.; Larson, J.; Stefanick,

M.L. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: Post hoc analyses of the women's health initiative randomized controlled trial. *J. Clin. Oncol.* 2011, 29, 3079–3084. Five studies reported on the association between vitamin D intake (from diet, from a supplement, or both) and NMSC risk [20][21][22][23][24] (Table 2). Davies et al. reported a case-control study of 109 BCC cases and 247 controls nested in a population-based UK cohort and found no significant association between vitamin D intake from food and BCC risk [20]. Likewise, no significant association emerged in the population-based case-control study by Asgari et al., which included 415 SCC and an equal number of controls in the USA [21]. Park et al. analyzed data from the Nurses' Health and Health Professionals Follow-up prospective studies and reported an increased risk of BCC (but not SCC) among those in the highest quintile of total vitamin D intake (food + supplements) [22]. Finally, in two RCT, both conducted in the USA, NMSC was compared in a study participants in the Nurses' Health and Health Professionals Follow-up studies. Both studies reported no significant association between vitamin D intake and NMSC risk [23][24].

**Table 2.** Main characteristics of the studies reporting on the association between vitamin D intake (from foods, supplements, or both) and the risk of non-melanoma skin cancer.

Author, Year	Country	Study Design	Skin Cancer Type	N Cases	N Controls	% at Risk	Age (yrs)	Years of Exposure	Exposure	Comparison	RR	95% CI	Adjusting
28. Morgado-Agudila, P.; Rey-Sanchez, P.; Gil-Fernandez, M.C.; Rodriguez-Velasco, F.J. Vitamin D Receptor Polymorphisms and Non-Melanoma Skin Cancer Risk: A Case-Control Study. <i>J. Clin. Med.</i> 2020, 9, 3819.	Spain	Case-control	BCC	109	247	52.3%	mean 72.5, range 43–85	1998–2010	food	by 2.08 microg/d	1.07	1.35–1.32	age, sex, phenotype, other
29. Filshil, S.C.; de Vries, E.; van Meurs, J.B.; Fang, Y.; Stricker, B.H.; Witteler, A.C.; Nijsten, F. Vitamin D Binding Protein Polymorphisms are not associated with development of (multiple) basal cell carcinomas. <i>Exp. Dermatol.</i> 2010, 19, 1103–1105.	UK	NCC	BCC	109	247	52.3%	mean 72.5, range 43–85	1998–2010	food	by 2.08 microg/d	1.07	1.35–1.32	age, sex, phenotype, other
30. Han, J.; Colditz, G.A.; Hunter, D.J. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. <i>Carcinogenesis</i> 2007, 28, 390–397.	USA	Case-control	BCC	109	247	52.3%	mean 72.5, range 43–85	1998–2010	supplement use ≥3 times in the past 10 years	vs. no supplement	0.46	0.95–1.32	age, sex, phenotype, other
31. Raughanem, H.; Canudas, S.; Hernandez-Alonso, P.; Becerra-Tomás, N.; Salas-Salvadó, J.; Macias-Gonzalez, M. Vitamin D Intake and the Risk of Colorectal Cancer: An Updated Meta-Analysis and Systematic Review of Case-Control and Prospective Cohort Studies. <i>Cancers</i> 2021, 13, 2814.	USA	RCT	NMSC	3338	3628	0.0%	1985–2019	1985–2019	daily supplementation	vs. placebo	1.02	0.95–1.09	age, sex, phenotype, other
32. Sun, K.; Zuo, M.; Zhang, C.; Wang, K.; Huang, D.; Zhang, H. Anti-Tumor Effect of Vitamin D Combined with Calcium on Lung Cancer: A Systematic Review and Meta-Analysis. <i>Nutr. Cancer</i> 2020, 1–10.	USA	cohort	BCC	20840	199290	38.0%	1984–2010	1984–2010	intake from food + supplements	5th vs. 1st quintile	1.10	1.05–1.17	age, sex, phenotype, UV exposure, other
33. Gagnarella, P.; Raimondi, S.; Aristarco, V.; Johansson, H.; Bellerba, F.; Corso, F.; De Angelis, S.P.; Belloni, P.; Caffi, S.; Gandini, S. Ethnicity as modifier of risk for Vitamin D receptors polymorphisms: Comprehensive meta-analysis of all cancer sites. <i>Crit. Rev. Oncol. Hematol.</i> 2021, 158, 103202.	USA	Case-control	BCC	206	206	0.0%	2004–2016	2004–2016	1000 IU/day supplementation vs. placebo (intervention arm)	vs. placebo	0.79	0.49–1.27	age, sex, UV exposure, other

**2.3. VDR and VDBP Genes Polymorphisms and NMSC Risk**

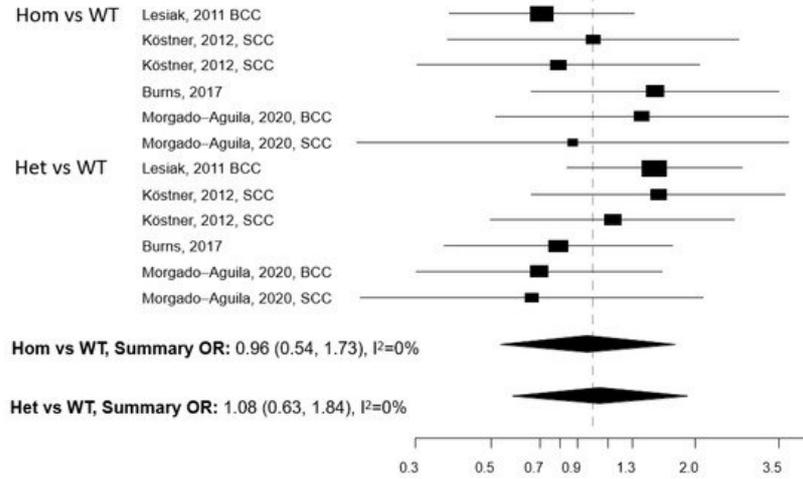
Retrieved from <https://encyclopedia.pub/entry/history/show/36435>  
 Five papers reported on the association between any of five polymorphisms of the VDR gene (Apa1, Bsm1, Cdx2, Fok1, and Taq1) and NMSC risk [13][25][26][27][28]. The studies were conducted in the USA (n = 2) and Europe (n = 3) (Table 3). Meta-analysis was conducted for three polymorphisms: Apa1, Bsm1, and Taq1: no association with NMSC risk emerged for any of these three polymorphisms, either in the Hom vs. WT or in the Het vs. WT models (Figure 1, Figure 2 and Figure 3). The heterogeneity was below 50% for all models. The relationship between Cdx2 and Fok1 polymorphism and NMSC risk was examined in the paper by Han et al. [26]: no significant association emerged in any of the models that were fitted. Instead, the Fok1 TT (Hom) genotype was reported to significantly increase BCC risk (OR = 10.14, p-value < 0.001) were also available for vitamin D from foods only, and stratified for the two sub-cohorts (Nurses' Health Study and Health Professionals Follow-up Study).

**Table 4.** Main characteristics of the studies reporting on the association between polymorphisms of the vitamin D receptor (VDR) gene and the risk of non-melanoma skin cancer.

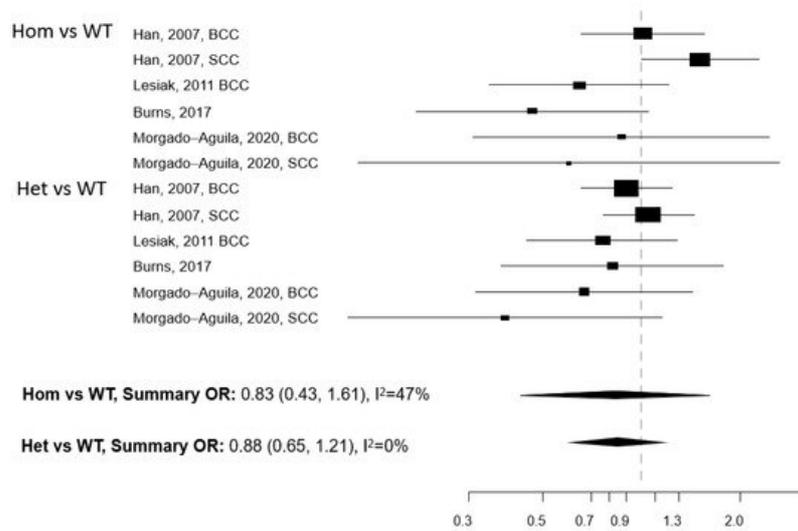
Author, Year	Country	Study Design	Skin Cancer Type	N Cases	N Controls	VDR Polymorphisms				
						Apa1	Fok1	Bsm1	Cdx2	Taq1
Han, 2007 [30]	USA	NCC	BCC	295	853		x	x	x	
			SCC	281			x	x	x	
Lesiak, 2011 [13]	Poland	hCC	BCC	142	142	x	x	x		x
Köstner, 2012 [31]	Germany	hCC	BCC	87	50	x				x
			SCC	100		x				x

Author, Year	Country	Study Design	Skin Cancer Type	N Cases	N Controls	VDR Polymorphisms				
						<i>Apa1</i>	<i>Fok1</i>	<i>Bsm1</i>	<i>Cdx2</i>	<i>Taq1</i>
Burns, 2017 [29]	USA	hCC	KSC	97	100	x		x		x
Morgado-Águila, 2020 [32]	Spain	hCC	BCC	61	73	x		x		
			SCC	20		x		x		

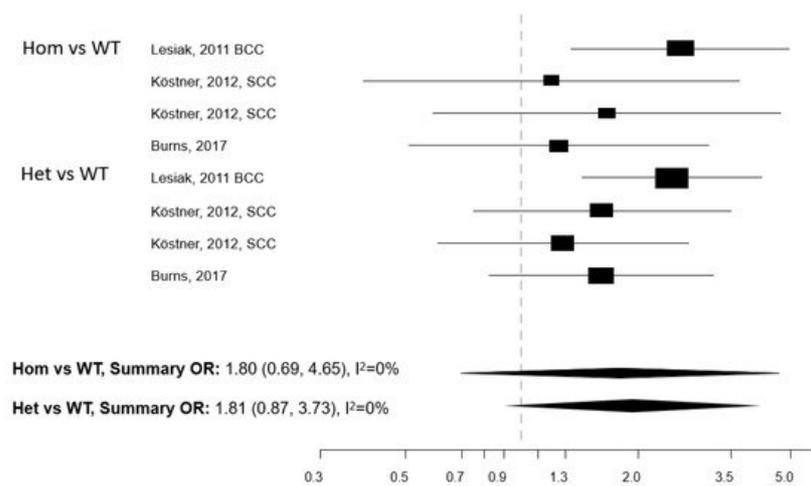
BCC: basal cell cancer. SCC: squamous cell cancer. KSC: keratinocyte skin cancer. NMSC: non-melanoma skin cancer. NCC: nested case-control study. hCC: hospital-based case-control study.



**Figure 1.** Forest plot for the association between the Apa1 polymorphism of the vitamin D receptor (VDR) gene and the risk of non-melanoma skin cancer. BCC: basal cell cancer. SCC: squamous cell cancer. RR: relative risk. Hom: homozygous. Het: heterozygous. WT: wild-type.



**Figure 2.** Forest plot for the association between the Bsm1 polymorphism of the vitamin D receptor (VDR) gene and the risk of non-melanoma skin cancer. BCC: basal cell cancer. SCC: squamous cell cancer. RR: relative risk. Hom: homozygous. Het: heterozygous. WT: wild-type.



**Figure 3.** Forest plot for the association between the Taq1 polymorphism of the vitamin D receptor (VDR) gene and the risk of non-melanoma skin cancer. BCC: basal cell cancer. SCC: squamous cell cancer. RR: relative risk. Hom: homozygous. Het: heterozygous. WT: wild-type.

A single study that considered polymorphisms in the VDBP gene and NMSC risk [29]. The study relied on 7983 participants, of which 235 developed BCC during follow-up. BCC was not associated with the two polymorphisms of the VDBP gene (rs7041 and rs4588) that were investigated, despite some limited evidence of an age-specific effect.

There was some evidence that individuals with higher measured plasma or serum 25(OH)D concentration were at increased NMSC risk. However, studies were greatly heterogeneous, which suggests caution in drawing conclusions, particularly regarding the magnitude of the possible association. Vitamin D intake was associated with a mild increase in BCC risk in the large observational study by Park et al.; however, this finding was not confirmed in another four studies, two of which had a RCT design. Finally, NMSC risk was not associated with any single polymorphism of the VDR or VDBP genes.

The association between serum/plasma 25(OH)D concentration and NMSC risk is most likely due to UV radiation exposure being causally linked to both vitamin D concentration in the blood and NMSC risk. The mild, yet significantly increased BCC risk observed among individuals with higher vitamin D intake in the large study by Park et al. is difficult to explain, particularly in light of the growing evidence in favour of a protective effect played by vitamin D supplementation against cancer at several body sites [30][31][32]. However, the finding by Park et al. was mild, limited to BCC, and not confirmed in any other study, including two vitamin D supplementation RCTs which, because of their experimental design, are expected to be less susceptible to biases (e.g., confounding and misclassification) affecting observational studies. By and large, a strong association between vitamin D intake or supplementation and NMSC risk seems unlikely, and vitamin D supplementation should continue to be considered as an effective and reasonably safe method of achieving the recommended amount of vitamin D.

Individuals carrying polymorphisms at the VDR or VDBP genes do not seem to suffer from an increased NMSC risk, with the possible exception of the VDR TaqI gene polymorphism. However, the number of studies eligible for inclusion in each gene polymorphism-specific meta-analysis model was limited, which prevents drawing firm conclusions. The studied polymorphisms of the VDR gene are known to impair the functionality of the receptor and eventually disrupt several vitamin D-linked biological pathways [8]. Considering that VDR polymorphisms may affect the risk of cancer at multiple body sites [33] and that an effect on NMSC risk cannot be ruled out a priori, we recommend that more studies are conducted in this research area.

### 3. Conclusions

The link between vitamin D metabolism per se and NMSC risk is unlikely to exist, although some findings (in particular, the positive association between vitamin D intake from diet and supplements and BCC risk reported in a large observational study) are worthy of further investigation, for instance within existing large-scale RCTs including vitamin D supplementation as an experimental arm. The cornerstone of NMSC prevention must remain limiting exposure of the skin to UV light, and vitamin D supplementation may be recommended as the preferred method to secure the multiple health benefits of adequate vitamin D concentration (which extends far beyond the possible effects on the skin) while avoiding the health risks associated with an excessive exposure of the skin to the UV radiation.