Vitamin D receptor polymorphisms and melanoma (Review)

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Abstract. Melanoma represents the most aggressive skin cancer, with an unpredictable and often treatment resistant behavior. The etiology of melanoma is multifactorial and includes both environmental and genetic factors. Recent evidence indicates that vitamin D has a role in the development and progression of melanoma. The biologically active form of vitamin D/1,25-dihydroxyvitamin D_3 acts by binding to a intranuclear receptor; vitamin D receptor (VDR). Single nucleotide polymorphisms (SNPs) in the vitamin D receptor gene may alter the expression or the function of the VDR protein leading to various diseases, including melanoma. More than 600 SNPs have been identified in the VDR gene, but only a few have been analyzed in relation to melanoma risk: FokI, TaqI, BsmI, ApaI, Cdx2, EcoRV, and BglI. Individual studies carried on small cohorts of patients reported controversial results. In an attempt to clarify the available data in the literature on this subject, we elaborated a systematic review in which we analyzed the relationship between VDR gene polymorphisms and melanoma risk and progression. We concluded that vitamin D pathway is important for the pathogenesis and the progression of cutaneous melanoma, illustrating the gene-environment interactions, but well-designed prospective studies that include data on both genotypes and phenotypes of vitamin D metabolism are essential in order to understand the mechanisms underlying the association between vitamin D and melanoma.

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1. Introduction

Melanoma represents the most aggressive skin cancer, with an unpredictable and often treatment resistant behavior. The estimated number of newly diagnosed cases of melanoma for 2018 in the United States is increasing compared to previous years (most of the cases being melanoma *in situ*), while the estimated number of disease-related deaths is decreasing (1). This trend for melanoma related deaths is present also in Europe (2), but there are important variations for different countries, the highest mortality rate being reported in the Northern part of Europe and the lowest in the Eastern part (3). The lower mortality rate reported in Eastern Europe might be underestimated due to the fact that in some countries there are no skin cancer registries, or the cutaneous melanoma is registered under different diagnosis. Skin carcinogenesis is influenced by many factors: Chemicals (4), neuroendocrine factors (5,6), and metalloproteinases (7).

Cutaneous melanoma develops from the melanocytes within the epidermis. These cells are involved in the production of melanin as a response to ultraviolet (UV) radiation. The UV exposure has controversial roles for the health of individuals. It is the main factor which influences the production of vitamin D in humans, a vitamin with multiple functions in the organism, but, at the same time, the intermittent and uncontrolled sun exposure is one of the most important risk factors for the development of melanoma. The etiology of

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melanoma is multifactorial and includes both environmental and genetic factors. Recent evidence indicates that vitamin D has a role in the development and progression of melanoma (8). The biologically active form of vitamin D/1,25-dihydroxyvitamin D_3 acts by binding to an intranuclear receptor vitamin D receptor (VDR), which is a nuclear steroid hormone receptor found in the skin and other organs (9). This receptor is encoded by the vitamin D receptor gene. Epigenetic modifications in this gene, like single nucleotide polymorphisms (SNPs) may alter the expression or the function of the VDR protein leading to various diseases, including malignancies (10).

The aim of this review was to analyze the relationship between VDR gene polymorphisms and melanoma risk and progression and to suggest new studies in order to clarify the mechanisms underlying this complex association.

2. Vitamin D synthesis and biological activity

Vitamin D can be found in the body from two sources: i) endogenous, synthesized in the skin under the action of ultraviolet radiation; and ii) exogenous, absorbed from food or supplements, but in a smaller amount. The exogenous variant can be plant-derived (ergocalciferol or vitamin D_2) or animal-derived (cholecalciferol or vitamin D_3) (11). Vitamin D_3 can be produced in the skin through a process of photolysis from 7-dehydrocholesterol, which is the penultimate compound in the synthesis of cholesterol and is concentrated in the epidermis. Following UVB radiation (290-320 nm), 7-dehydrocholesterol (pre-vitamin D_3) is converted to vitamin D_3 in the skin. Vitamin D_3 enters the blood stream and binds to an α-globulin with high affinity for vitamin D (vitamin D-binding protein). In order to be biological active, vitamin D_3 is hydroxylated in the liver by a hydroxylase (CYP2R1 or CYP27A1) into 25-hydroxyvitamin D_3 and after that in the kidney by CYP27B1 into 1,25-dihydroxyvitamin D_3 or calcitriol (the active form of vitamin D). These hydroxylases are also present in the epidermis and the keratinocytes are able to produce the active form of vitamin D_3 in 16 h, skipping the passage through the liver and the kidneys. The keratinocytes are the only cells in the organism that contain the entire pathway (12). An alternative pathway for vitamin D activation was discovered. It involves the activity of CYP11A1, an enzyme present in the human keratinocytes. CYP11A1 can hydroxylate vitamin D_3 at C17, C20, C22 and C23, resulting in multiple metabolites. CYP11A1 does not hydroxylate $25(OH)D_3$; it can hydroxylate $1(OH)D_3$ to the active product $1,20(OH)_2D_3$ (13). 1,25-dihydroxyvitamin D_3 is inactivated in the kidney, by the action of another hydroxylase (CYP24A1), and further oxidized to the excretory product - calcitroic acid. The inactivation process can start also in the skin, CYP24A1 being expressed in the keratinocytes (14).

Vitamin D exerts two types of biological activities: nongenomic and genomic. The nongenomic activity refers to the primary role of vitamin D in the regulation of calcium homeostasis and bone metabolism (11). The genomic actions are mediated through binding to the VDR. VDR has been identified in many cells in the organism: In parathyroid gland cells, pituitary gland cells, promyelocytes, lymphocytes, keratinocytes, colon cells and ovarian cells (15). It explains the other biological activities of vitamin D: Differentiation of promyelocytes to monocytes; suppression of the prepreparathyroid gene, thus preventing the proliferation of parathyroid gland cells; implication in immunomodulation (11). Vitamin D interacts with lymphocytes T helper 1 (Th1) and suppresses the inflammatory response. Deficiency of vitamin D influences the onset of different autoimmune diseases: Multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis, as well as infections, cardiovascular diseases and cancer (16).

In relation to cutaneous immunity, the effects of vitamin D are controversial. Some studies demonstrated that vitamin D can be protective against UVB-induced DNA damage. Bikle *et al* showed that the DNA damage repair was affected in VDR null mice after UVB exposure and that vitamin D accelerates DNA damage repair (17). Another study evaluated the immunological activities of vitamin D and the authors observed that vitamin D can induce immunosuppression by promoting the development of T regulatory cells (Tregs), similar to UVB radiation. In the study, the immune suppression induced by UVB was present even in VDR-deficient mice, suggesting that the mechanism for immunosuppression is different for UVB and vitamin D. The development of Tregs necessitates the presence of VDR. There are VDR polymorphisms that may influence the biological activities of vitamin D and explain, at least partially, the susceptibility to different diseases, including melanoma (18).

3. Vitamin D receptor polymorphisms and the risk of melanoma

The VDR is a member of the nuclear hormone receptor superfamily and a transcription factor. It mediates the genomic biological activities of vitamin D, including different signaling pathways with role in cell cycle progression, differentiation and apoptosis - processes that are involved in the development and progression of various cancers (19).

The VDR gene is one of the most studied genes related to vitamin D and is located on chromosome 12q13.11 (20). The gene comprises 11 exons and more than 600 SNPs have been identified within the coding region. Despite this large number, only a few polymorphisms, which are considered functional, have been analyzed in relation to melanoma risk (21-24), the most studied VDR polymorphism being: FokI, TaqI, BsmI and ApaI.

The FokI polymorphism (C/T-rs2228570, previously named rs10735810) is located on exon 2 of the coding region of the VDR gene. It alters an ACG codon located 10 base pairs upstream from the translation start codon leading to the creation of a new start codon. When the translation starts from this site, the resulting VDR protein will be longer; 427 amino acids instead of 424 amino acids (25). The shorter protein variant (corresponding to C nucleotide allele or F allele) seems to be 1.7-fold more active than the longer 427 amino acids variant (the F allele) (26). The relation between the presence of this polymorphism and the risk of melanoma seems to be controversial. The presence of the minor allele (F allele) was linked to an increased risk for melanoma in multiple studies (22,27,28), but was reported to have no effect in others (23,29,30). An interesting study was conducted by Randerson-Moor *et al* in two UK case-control data sets. In the first case-control cohort, that included 1,043 melanoma

patients and 408 controls, they found no significant difference in genotype distribution between cases and controls, while in the second cohort (299 cases and 560 controls) the T allele of the FokI polymorphism was associated with an increased risk of melanoma. The authors also performed a meta-analysis that showed the T allele of the Fok1 polymorphism was significantly associated with melanoma (28). Li *et al* showed that FokI polymorphism was not an independent factor for melanoma risk, but it interacted with other known risk factors (skin colour, the presence of nevi and family history of cancer) and modulated the melanoma risk associated with these factors. They also combined the genotypes for 3 polymorphisms (FokI, TaqI and BsmI) and showed that the combined genotype TT/Bb+BB/Ff+ff was associated with increased risk when compared to TT/bb/Ff+ff (27). The functional significance of FokI polymorphism was demonstrated in an *in vitro* study. Van Etten *et al* showed that FokI polymorphism affects immune cell behaviour, with a more active immune system for the F allele (31).

The TaqI polymorphism (rs731236) is a restriction fragment length polymorphism located in exon 9, at codon 352 of the VDR gene. It generates a silent codon change: The ATT to ATC results in an isoleucine at codon 352 (32). The linkage disequilibrium studies showed that TaqI polymorphism together with BsmI and ApaI were in strong linkage disequilibrium, while FokI polymorphism appeared to have very weak or no linkage to any of the other VDR polymorphism (33). One study reported a decreased melanoma risk by 30% for Tt and tt genotypes, compared to the TT genotype and the authors did not find any interaction between TaqI genotypes and the known melanoma risk factors (22). The same group of authors conducted another study on a larger group of patients and the T allele was significantly less frequent among melanoma cases than among controls, suggesting that T allele might protect carriers against melanoma (27). Hutchinson *et al* showed that the TaqI polymorphism was not associated with the risk for melanoma (34). Another study was also unable to find any statistical association between TaqI polymorphism and any clinical characteristic of melanoma patients (age of onset, primary tumour localization, tumour type, Breslow index) (23). The functional significance of TaqI polymorphism is not well understood. TaqI polymorphism is located near to the 3rd end of gene and is thought to affect VDR gene transcription regulation and mRNA stability (26).

The BsmI polymorphism (rs1544410) is a restriction fragment length polymorphism located in intron 8 at the 3rd end of the VDR gene. It is a silent polymorphism, it does not change the amino acid sequence of the protein (32). Due to its location, BsmI polymorphism may affect VDR gene expression and mRNA stability (26). Han et al examined the association between BsmI polymorphism and melanoma risk in 219 melanoma cases and 873 controls and found no significant association (35). One study analyzed the relationship between sun exposure, VDR FokI and BsmI polymorphisms and the risk of developing multiple primary melanoma and showed that the highest risk was found in patients with the most intense sun exposure and BB genotype. There was no association between FokI polymorphism and multiple primary melanoma (36). Li et al reported a reduced frequency of the B allele among melanoma cases than among controls,

suggesting that B allele might be protective against melanoma. The authors found a reduced risk of melanoma just for women with Bb+BB genotypes, who carried the FF genotype of FokI polymorphism (27). These studies demonstrate that the results analyzing the relationship between BsmI polymorphism and melanoma risk are controversial. One meta-analysis assessed the associations between VDR gene polymorphisms (ApaI, BsmI, Cdx2, EcoRV, FokI and TaqI) and melanoma risk and showed that the only polymorphisms that may influence the susceptibility to developing melanoma were BsmI and FokI. The B allele carriers for the BsmI polymorphism had a 15% decreased risk of melanoma compared to bb homozygote carriers. The FokI polymorphism was one of the most studied polymorphisms of the VDR gene; Hou et al analyzed 4,189 melanoma cases and 4,084 controls from 8 eligible studies and reported an 18% increased risk of melanoma for the F allele of FokI polymorphism, when compared to FF carriers (37).

The ApaI polymorphism (rs7975232) is located near the BsmI polymorphism, in intron 8 at the 3rd end of the VDR gene (32). The ApaI polymorphism was not associated with melanoma risk, neither when the haplotypes including the 3 polymorphisms in linkage disequilibrium (BsmI, ApaI, TaqI) were studied (28). The relationship between ApaI polymorphism and melanoma risk was studied by Hou *et al* and they did not find any association (37).

The Cdx2 polymorphism (rs11568820) is a guanine to adenine sequence, located in the promoter area of the VDR gene (32). The studies indicated no association between this polymorphism and melanoma risk (28,35,37).

The EcoRV polymorphism (A-1012G, rs4516035) is located in the promoter region of the VDR gene and is believed to have a role in the anticancer immune response (21). The majority of the studies reported no association between EcoRV polymorphism and melanoma risk (23,28,30,38). In one study, the A-1012G polymorphism was strongly associated with the risk of melanoma. The G allele was considered the reference and the homozygosity for the variant allele (AA genotype) increased the risk of melanoma more than 3-fold (21).

The BglI polymorphism (rs739837) is located near the stop codon in exon 9. It was reported in one study that showed no association between this polymorphism and melanoma risk (30).

In one large international, population-based case-control study of melanoma, the authors analyzed 38 VDR gene SNPs with known or suspected impact on VDR activity, in 1,207 patients with multiple primary melanoma and 2,469 with single melanoma. They found that 6 polymorphisms in the promoter, coding and 3 gene regions were significantly associated with the risk of developing multiple primary melanoma (BsmI, rs10875712, rs4760674, rs7139166, EcoRV, rs11168287) and 2 polymorphisms presented a decreased risk for multiple primary melanoma development (rs7305032, rs7965281) (10).

4. VDR polymorphisms and the prognosis of melanoma patients

There are well documented factors known to affect melanoma progression and survival. These include clinical characteristics

Table I. Characteristics of studies included in the review.

Author, year (ref.)	Country	All subjects		Studied SNP	Association with CM risk	Association with other clinicopathological factors or disease progression
		Cases	Controls			
Hutchinson, 2000 (34)	UK	316	108	FokI	FF genotype - reduced CM risk	ttff genotype - thicker Breslow
				TaqI	NA	
Halsall, 2004 (21)	UK	174	80	EcoRV	AA genotype - increased CM risk	AA genotype - thicker Breslow, metastasis development
Han, 2007 (35)	USA	219	873	FokI BsmI Cdx2	NA	-
Santonocito, 2007 (29)	Italy	112	101	BsmI	bb genotype - increased CM risk	bb genotype - thicker Breslow
				FokI EcoRV	NA	NA
Barroso, 2008 (30)	Spain	283	245	EcoRV FokI TaqI BglI	NA	-
Li, 2008 (27)	USA	805	841	TaqI	t allele - reduced CM risk	-
				BsmI	B allele - reduced CM risk	-
				FokI	f allele - increased CM risk	-
Randerson-Moor, 2009 (28)	UK	1028	402	FokI TaqI BsmI ApaI EcoRV Cdx2	NA	-
Randerson-Moor, 2009 (28)	UK	299	560	FokI	F allele - increased CM risk	-
				TaqI BsmI ApaI EcoRV Cdx2	NA	-
Gapska, 2009 (23)	Poland	763	763	FokI TaqI BsmI EcoRV	NA	NA with Breslow
Halsall, 2009 (41)	USA	176	80	EcoRV	A allele - increased MM risk	A allele - thicker Breslow, metastasis development

Table I. Continued.

Author, year (ref.)	Country	All subjects		Studied SNP	Association with CM risk	Association with other clinicopathological factors or disease progression
		Cases	Controls			
Schäfer, 2012 (42)	Germany	305	370	TaqI ApaI rs757343 rs2107301	NA	NA with Breslow
Zeljic, 2014 (38)	Serbia	117	122	FokI	F allele - increased risk	NA with clinico-pathological characteristics
				TaqI	t allele - increased risk	
				ApaI EcoRV	NA	
Mandelcorn-Monson, 2011 (36)	International	1,138 multiple CM 2,151 single CM	-	FokI	NA	-
				BsmI	BB genotype (+ highest UV exposure) - multiple CM	
Orlow, 2012 (10)	International	1,207 multiple CM 2,469 single CM	-	BsmI EcoRV rs10875712 rs4760674, rs7139166 rs11168287	Increased multiple CM risk	-
				rs7305032 rs7965281	decreased multiple CM risk	
Orlow, 2016 (43)	International	1,205 multiple CM 2,361 single CM	-	BsmI	-	B allele - protective for CM survival
				TaqI	-	t allele - protective for CM survival
Morgese, 2017 (45)	Italy	88	-	FokI	-	ff genotype - progression-free survival, histological regression, BRAF[+]
				TaqI BsmI	-	-
Orlow, 2018 (44)	International	1,206 multiple CM 2,372 single CM	-	BsmI	-	B allele - decreased risk for CM death (if high UVB exposure)
				TaqI	-	t allele - decreased risk for CM death (if high UVB exposure)

NA, not associated, '-', not studied; CM, cutaneous melanoma.

(age at diagnosis, sex, anatomic site of the tumor) and primary tumor characteristics (tumor thickness, presence of ulceration, presence of mitosis, histological regression, and presence or absence of the lymph nodes or distant metastases) (39,40). In addition, genetic factors also influence the outcome of patients with melanoma, the VDR gene polymorphisms being some of the most studied (21,34).

One study reported an association between TaqI T allele and FokI F allele and Breslow thickness. Patients with this genotype presented a Breslow index thicker than 1.5 mm (30). Another significant correlation was found between BsmI bb genotype and tumor thickness. This correlation with the tumor thickness could not be observed for FokI and A-1012G polymorphisms (29). In another study, the A allele of the A-1012G polymorphism was correlated with a thicker Breslow index and the development of metastasis (41). Schäfer *et al* analysed vitamin D metabolism-related polymorphisms for the risk and prognosis of melanoma patients and observed that none of the VDR gene tested polymorphisms (TaqI, ApaI, rs757343, rs2107301) was associated with melanoma risk as well as prognosis (42). Orlow *et al* conducted a study on 3,566 single and multiple primary melanoma cases and investigated whether VDR gene polymorphisms influence survival of patients with melanoma. The authors included 38 polymorphisms and calculated melanoma-specific survival according to each polymorphism. They observed that BsmI B allele and TaqI T allele were protective with regard to melanoma death. Other polymorphisms associated significantly with melanoma specific survival were: rs7299460, rs3782905, rs2239182, rs12370156, rs2238140 and rs7305032. None of these polymorphisms were significantly correlated with Breslow thickness, ulceration or mitosis, suggesting that VDR gene polymorphisms may influence survival in melanoma patients, but the mechanism does not imply tumour aggressiveness (43). The same group of authors published a recent study on interactions between VDR gene polymorphisms and sun exposure and their effects on survival in patients with melanoma. Six polymorphisms (BsmI, TaqI, rs1989969, rs12370156, rs2238140, rs7305032) were significantly associated with survival among patients exposed to high UVB around diagnosis. BsmI and TaqI polymorphisms remained significant after adjustment for multiple testing. For the minor alleles of BsmI and TaqI polymorphisms and the major alleles for rs1989969, rs12370156, rs2238140, rs7305032 the risk of melanoma specific death was significantly reduced for the patients with high UVB exposure in the decade of diagnosis (44).

Morgese *et al* conducted a study on the impact of VDR gene polymorphisms on the outcome of melanoma patients treated with targeted therapy. The authors observed a high rate of histological regression and BRAF positive mutation in melanoma patients with FokI polymorphism with ff genotype (homozygous recessive). This group of patients showed a significant difference in progression-free survival (21.2 months for the ff genotype vs. 3.3 months for FF+Ff genotype), after BRAF+/-MEK inhibitor therapies (45).

5. Conclusion

Data presented in this review (summarized in Table I) show that the vitamin D and the epigenetic alterations in the vitamin D receptor gene may be important for the development, progression as well as therapy response in patients with melanoma. Even though individual studies carried on small cohorts of patients reported controversial results, it seems that VDR gene polymorphisms influence the risk of melanoma. FokI F allele is associated with an increased risk of melanoma, while BsmI B allele with a decreased risk. The relation between VDR gene polymorphisms and melanoma outcome is a relatively new subject in the literature and more studies are needed to clarify the present results. The vitamin D pathway illustrates the gene-environment interactions. Thus, large, well-designed prospective studies that include data on both genotypes (vitamin D receptor gene polymorphisms and mutations in other vitamin D related genes) and phenotypes (vitamin D serum concentration) of vitamin D metabolism are essential in order to understand the mechanisms underlying the association between vitamin D and melanoma.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AFV, LEG, SS and RC contributed to the design of work. AFV, LEG, SS, RC, EC and OF were responsible for literature search and manuscript preparation. LU, APT and SV contributed to design of study, data collection, literature search, manuscript preparation, and critical revision of manuscript for important intellectual content. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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