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ORIGINAL ARTICLE

Vitamin D receptor FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma: a meta-analysis

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Summary

Purpose: *The purpose of this study was to examine whether vitamin D receptor (VDR) polymorphisms are associated with susceptibility to melanoma.*

Methods: *A meta-analysis was carried out to investigate the association between the VDR FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma.*

Results: *A total of 11 studies were evaluated, which included 4,413 patients and 4,072 controls (all European). The meta-analysis revealed no association between melanoma and the BsmI B allele (odds ratio/OR=0.901, 95% confidence interval/CI=0.783–1.036, p=0.144). However, an association was shown between melanoma and the Bb+bb genotype (OR=0.868, 95% CI=0.767–0.982, p=0.025). No association was noticed between melanoma and FokI polymorphism (OR for the F allele=1.016, 95% CI=0.869–1.189, p=0.839). Moreover, melanoma risk was not associated with the TaqI, ApaI, and EcoRV polymorphisms (OR for the T allele=0.986, 95% CI=0.842–1.156, p=0.864; OR for the A allele=0.949, 95% CI=0.842–1.069, p=0.388; OR for the E allele=0.993, 95% CI=0.875–1.126, p=0.911, respectively).*

Conclusions: *This meta-analysis demonstrated that the VDR BsmI polymorphism is associated with susceptibility to melanoma in Europeans, suggesting that carrying the VDR BsmI B allele may be a protective factor against melanoma development.*

Key words: *melanoma, polymorphism, susceptibility, vitamin D receptor*

Introduction

Melanoma is a malignant tumor derived from melanocytes, which are pigment producing cells that produce melanin in response to ultraviolet (UV) light exposure. Although the etiology of melanoma is unclear, exposure to sunlight plays a role in the development of melanoma, and genetic factors are considered to contribute to its development [1].

Although the primary function of vitamin D involves the maintenance of bone mineral homeostasis, it is also involved in interleukin (IL)-2 inhibition, antibody production, and lymphocyte proliferation [2]. It has been reported that 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2 D_3$) inhibits interferon secretion and negatively regulates IL-12 production by downregulating nuclear factor-kappaB [3]. Moreover, vitamin D plays a critical regulatory role in the differentiation and proliferation of cancer cells by influencing cell cycle regulation [4]. Studies suggest that exposure to sunlight may reduce the risk of melanoma in addition to increasing the production of vitamin D in the skin [5,6], because vitamin D inhibits growth and induces apoptosis in cancer cells [7]. Thus, vitamin D may play a pivotal role in the development of melanoma.

The activity of vitamin D is dependent on the VDR, a member of the nuclear hormone receptor superfamily. The VDR gene is located on chromosome 12q13.11 [8], and 3 polymorphisms, BsmI (rs1544410), ApaI (rs7975232) (both in intron 8), and TaqI (rs731236) (in exon 9), have been iden-

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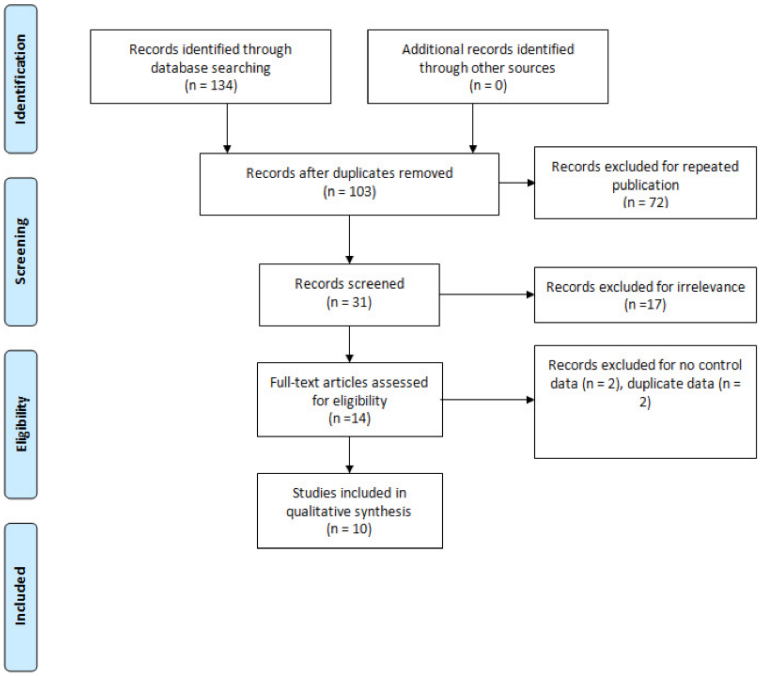


Figure 1. Flow chart illustrating the study design.

tified at the 3'-end of the gene and shown to be in strong linkage disequilibrium (LD) [9]. The other polymorphic region, FokI (rs2228570), is located in the start codon [8], and the EcoRV (rs4516035) polymorphism is located in the promoter region.

Although these VDR polymorphisms have been linked to melanoma development in several reports, some studies failed to find an association [10-19]. This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity in these studies. In order to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood of random errors that are responsible for false-positive or -negative associations [20-22], we employed a meta-analysis to determine whether the VDR FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms are associated with susceptibility to melanoma.

Methods

Identification of eligible studies and data extraction

A literary search using the MEDLINE and EMBASE citation databases was used to identify available articles in which VDR polymorphisms were analyzed in melanoma patients (until March 2014). Combinations of keywords, such as 'vitamin D receptor,' 'VDR,' 'polymorphism,' and 'melanoma' were entered as Medical Subject Headings (MeSH) or text words. References in the identified studies were also investigated to identify additional studies not indexed by MEDLINE and EMBASE.

No language or country restrictions were applied. Studies were included if: (1) they were case-control studies; (2) the data were original (independent of other studies); and (3) they provided enough data to calculate OR. Studies were excluded if: (1) they contained overlapping data; (2) the number of genotypes or alleles could not be ascertained; or (3) the family members were also included in the study, because these analyses are based on linkage considerations.

Following the specified selection criteria, data were extracted from the original studies and assessed by 2 independent reviewers. Any discrepancies between reviewer-observations were resolved by consulting a third reviewer. The extracted information from each study included the author, year of publication, ethnicity of study population, demographics, and number of cases and controls for each of the FokI, BsmI, ApaI, TaqI, and EcoRV genotypes. Allele frequencies were calculated from the corresponding distribution of genotypes.

Evaluations of statistical associations

We performed meta-analyses using: (1) allelic contrast; (2) homozygote contrast; (3) recessive models; and (4) dominant models. Point estimates of risk, ORs, and 95% CIs were estimated for each study. Moreover, within- and between-study variations or heterogeneities were assessed using Cochran's Q-statistic. This heterogeneity test assesses the null hypothesis that all studies evaluated have the same effect. The effect

Table 1. Characteristics of individual studies included in the meta-analysis.

Study [Ref]	*Country*	*Ethnicity*	*Numbers*		*Polymorphism(s)*	*Association findings*
			Cases	*Controls*		
Zeljic, 2014 [10]	Serbia	European	117	122	FokI, TaqI, ApaI*, EcoRV	FokI (p<0.001), TaqI (p=0.006), ApaI, EcoRV (NS)
Pena-Chilet, 2013 [11]	Spain	European	530	314	FokI, TaqI, EcoRV	NS
Randerson-Moor-1, 2009 [12]	UK	European	1028	402	FokI, BsmI, TaqI, ApaI, EcoRV	NS
Randerson-Moor-2, 2009 [12]	UK	European	299	560	FokI, BsmI, TaqI, ApaI, EcoRV	FokI (p=0.003), others (NS)
Barroso, 2008 [13]	Spain	European	283	245	FokI, TaqI, EcoRV	NS
Li, 2008 [19]	USA	European	805	841	FokI, BsmI, TaqI	FokI (p=0.03), BsmI (p<0.01), TaqI (p<0.01)
Santonocito, 2007 [14]	Italy	European	101	101	FokI, BsmI, EcoRV	FokI (NS), BsmI (p=0.01), EcoRV (NS)
Povey, 2007 [15]	UK	European	596	441	FokI, EcoRV	NS
Han, 2007 [16]	USA	European	219	873	FokI, BsmI	NS
Halsall, 2004 [17]	UK	European	174	80	EcoRV	EcoRV (p=0.03)
Hutchinson, 2000 [18]	UK	European	261	93	FokI, TaqI	FokI (p=0.026), TaqI (NS)

Ref: reference, NS: not significant, UK: United Kingdom, USA: United States of America; *control genotypes not in Hardy-Weinberg equilibrium

of heterogeneity was quantified using I^2, which ranges between 0 and 100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than chance [23]. I^2 values of 25, 50, and 75% were nominally assigned as low, moderate, and high estimates, respectively.

The fixed effects model assumes that the effect of genetic factors on melanoma susceptibility across all studies investigated is similar, and that the observed variations among studies are caused by chance alone [24]. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance [25]. When study groups are homogeneous, the use of fixed or random effects models generates similar results, and when this is not the case, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is used when there is significant between-study heterogeneity [25]. Statistical analyses were conducted using a comprehensive meta-analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by omitting each individual study to investigate the statistical robustness of these results and to examine the potential source of the observed heterogeneity. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which includes a required range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test [26], which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included

One hundred thirty four studies were identified by electronic and manual search, and 14 were selected for a full-text review based on the details in their titles and abstracts. Of these 14 studies, 4 were excluded because 2 contained duplicate data and 2 did not include VDR polymorphism data. Thus, 10 studies met the inclusion criteria [10-19] (Figure 1). Of the eligible studies, 1 contained data on 2 different groups [12], and these were treated independently. Thus, a total of 11 separate comparisons were considered for meta-analysis, which included 4,413 patients and 4,072 controls in total (Table 1), all of whom were of European ethnicity. All studies provided genotype data of the VDR polymorphisms except for one study, which only provided allele data. The VDR FokI polymorphism was examined by 9 studies, BsmI by 5, TaqI by 7, ApaI by 3, and EcoRV by 9. Selected characteristics of these studies with respect to the association between the VDR polymorphisms and melanoma are summarized in Table 1.

Table 2. Meta-analysis of the association between melanoma incidence and the VDR FokI and BsmI polymorphisms

Polymorphism	*Population*	*No. of studies*	*Numbers*		*Test of association*			*Test of heterogeneity*		
			Cases	*Controls*	*OR*	*95% CI*	*p value*	*Model*	*p value*	I^2
FokI F vs f	Overall	10	4787	3314	1.016	0.869–1.189	0.839	R	0.000	79.7
FF vs Ff + ff (recessive)	Overall	9	4504	3069	0.954	0.771–1.180	0.662	R	0.000	74.7
FF + Ff vs ff (dominant)	Overall	9	4504	3069	1.093	0.853–1.400	0.483	R	0.002	67.7
FF vs ff	Overall	9	4504	3069	1.074	0.763–1.511	0.684	R	0.000	79.2
BsmI B vs b	Overall	5	3073	2076	0.901	0.783–1.036	0.144	R	0.049	57.9
BB vs Bb + bb (recessive)	Overall	5	3073	2076	0.871	0.677–1.120	0.282	R	0.074	53.0
BB + Bb vs bb (dominant)	Overall	5	3073	2076	0.868	0.767–0.982	0.025	F	0.121	45.1
BB vs bb	Overall	5	3073	2076	0.810	0.601–1.092	0.167	R	0.044	59.1

VDR: vitamin D receptor, OR: odds ratio, CI: confidence interval, R: random effects models, F: fixed effects model

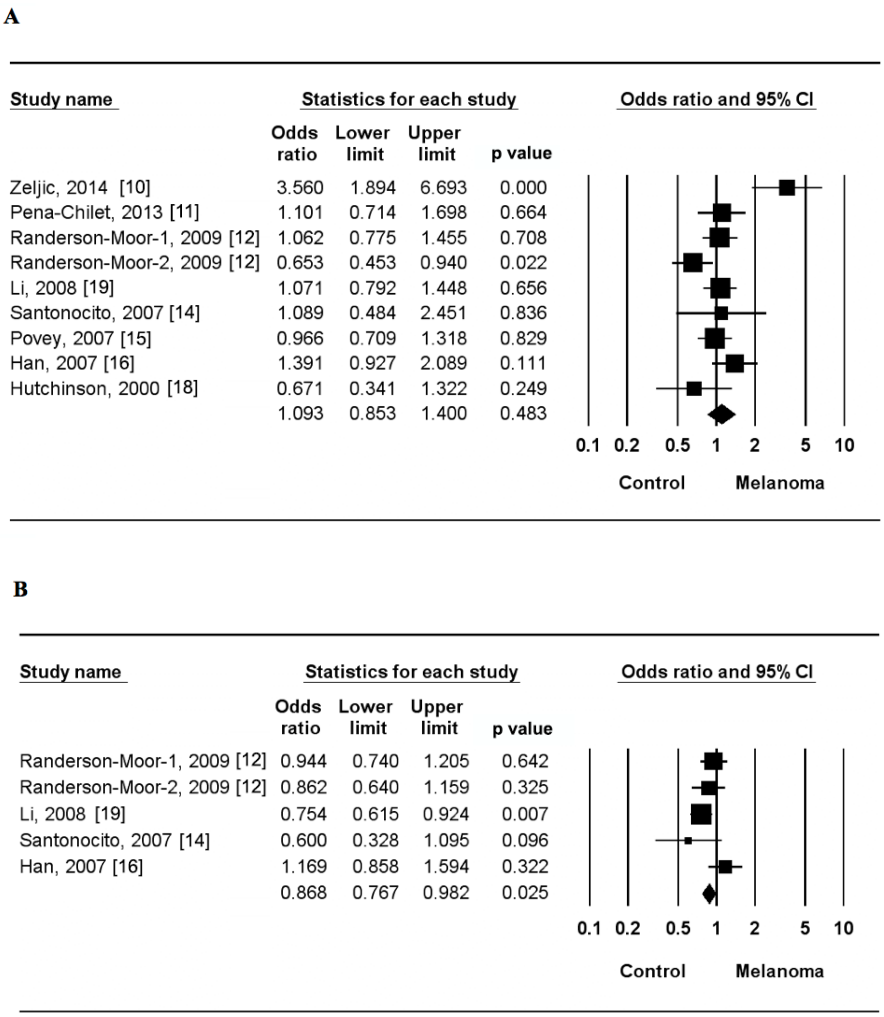


Figure 2. ORs and 95% CIs of individual studies and pooled data for the association between melanoma incidence and the VDR FokI **(A)** and BsmI **(B)** polymorphisms under the dominant model.

Table 3. Meta-analysis of the association between melanoma incidence and the VDR TaqI, ApaI, and EcoRV polymorphisms

Polymorphism	*Population*	*No. of studies*	*Numbers*		*Test of association*			*Test of heterogeneity*		
			Cases	*Controls*	*OR*	*95% CI*	*p value*	*Model*	*p value*	I^2
TaqI T vs t	Overall	7	3291	2557	0.986	0.842–1.156	0.864	R	0.001	72.7
TT vs Tt + tt (recessive)	Overall	6	3008	2312	0.963	0.734–1.265	0.788	R	0.000	78.6
TT + Tt vs tt (dominant)	Overall	6	3008	2312	1.101	0.942–1.286	0.226	F	0.296	18.1
TT vs tt	Overall	6	3008	2312	1.041	0.760–1.427	0.801	R	0.013	65.4
ApaI A vs a	Overall	3	1444	1086	0.949	0.842–1.069	0.388	F	0.150	47.3
AA vs Aa + aa (recessive)	Overall	3	1444	1086	0.895	0.745–1.076	0.239	F	0.440	0
AA + Aa vs aa (dominant)	Overall	3	1444	1086	0.982	0.801–1.205	0.863	F	0.129	51.2
AA vs aa	Overall	3	1444	1086	0.912	0.719–1.155	0.444	F	0.138	49.4
EcoRV E vs e	Overall	8	2803	2221	0.993	0.875-1.126	0.911	R	0.038	52.8
EE vs Ee + ee (recessive)	Overall	7	2520	1976	1.018	0.770–1.346	0.902	R	0.000	75.7
EE + Ee vs ee (dominant)	Overall	7	2520	1976	1.001	0.766–1.309	0.993	R	0.017	61.2
EE vs ee	Overall	7	2520	1976	1.002	0.767–1.310	0.988	R	0.059	50.6

For abbreviations see footnote of Table 2

Association between FokI polymorphism and melanoma

A summary indicating the association between VDR FokI and BsmI polymorphisms and melanoma is presented in Table 2. Meta-analysis revealed no association between melanoma and the FokI F allele in all study subjects (OR=1.016, 95% CI=0.869–1.189, p=0.839) (Table 2). The recessive and dominant models and homozygote contrast failed to reveal an association between the FokI polymorphism and susceptibility to melanoma (Table 2, Figure 2).

Association between BsmI, TaqI, and ApaI polymorphisms and melanoma

The meta-analysis revealed no association between melanoma and the BsmI B allele (OR=0.901, 95% CI=0.783–1.036, p=0.144) (Table 2). However, there was an association between the incidence of melanoma and the Bb+bb genotype in Europeans (OR=0.868, 95% CI=0.767–0.982, p=0.025) (Table 2, Figure 2). The recessive model and homozygote contrast did not reveal an association between the BsmI polymorphism and melanoma (Table 2). There was no association between melanoma and the TaqI T allele (OR=0.986, 95% CI=0.842–1.156, p=0.864) (Table 3). The recessive and dominant models and homozygote contrast failed to reveal an association between the TaqI polymorphism and melanoma (Table 3, Figure 3). Moreover, the ApaI polymorphism showed no association between melanoma and the A allele (OR=0.949, 95% CI=0.842–1.069, p=0.388) (Table 3). Furthermore, no association was found between melanoma and the ApaI polymorphism using other genetic models (Table 3, Figure 3).

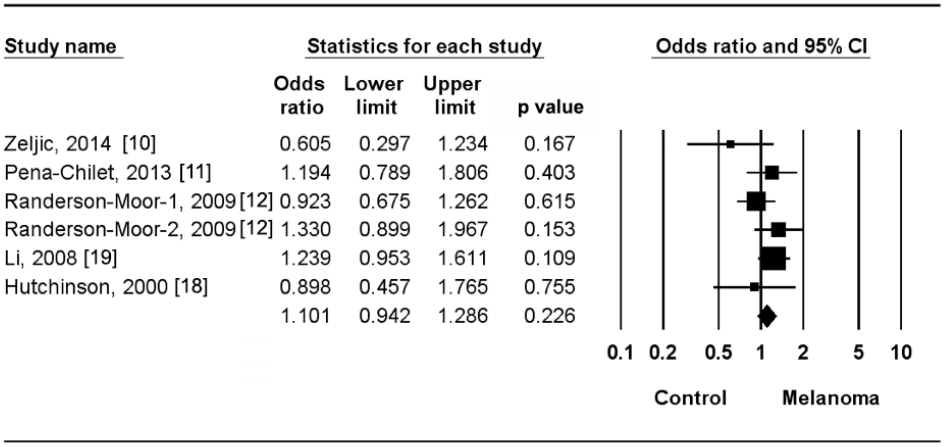
Association between the EcoRV polymorphism and melanoma

Meta-analysis revealed no association between melanoma and the EcoRV E allele (OR=0.993, 95% CI=0.875–1.126, p=0.911) (Table 3). The recessive and dominant models and homozygote contrast revealed no association between the EcoRV polymorphism and melanoma (Table 3, Figure 3).

Heterogeneity, sensitivity analysis, and publication bias

Some heterogeneity was observed in the VDR polymorphisms except for in the ApaI polymorphism (Tables 2 and 3). However, there was no

A



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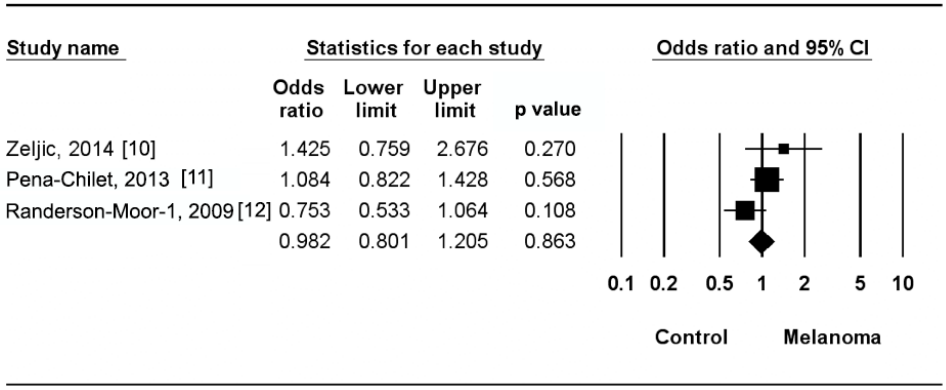

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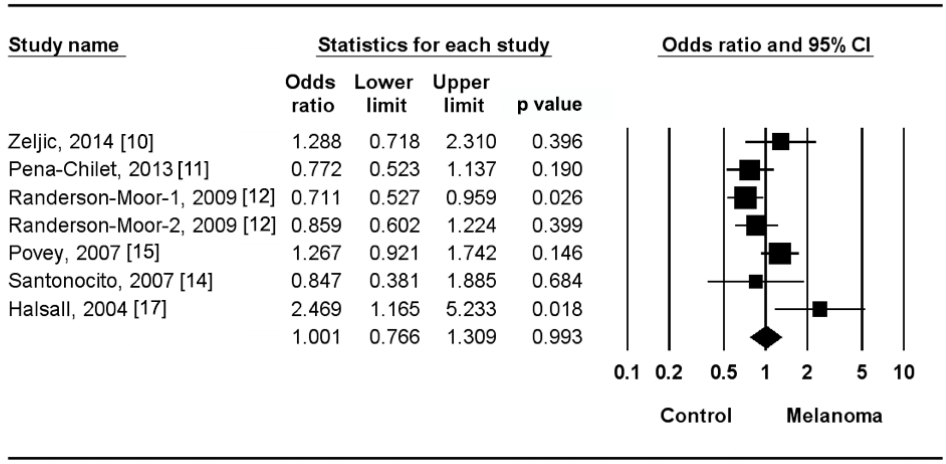

Figure 3. ORs and 95% CIs of individual studies and pooled data for the association between melanoma incidence and the VDR TaqI **(A)**, ApaI **(B)**, and EcoRV **(C)** polymorphisms under the dominant model.

significant heterogeneity of the BsmI Bb+bb genotype. Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating statistically robust results of the FokI, TaqI, and EcoRV polymorphisms.

The distributions of genotypes in normal control groups were not consistent with the Hardy-Weinberg (H-W) equilibrium in one study of the ApaI polymorphism [10]. Deviation from the H-W equilibrium among controls implies potential bias during control selection or from genotyping errors; however, excluding the study did not affect our ApaI-polymorphism result.

It was difficult to correlate the funnel plot, which is usually used to detect publication bias, because the number of studies included in this analysis was relatively small. However, Egger's regression test showed no evidence of publication bias (Egger's regression test p-values > 0.1).

Discussion

Although the multifactorial nature of melanoma is well recognized, genetic factors are considered strong determinants of melanoma; thus, researchers have been encouraged to search for the responsible genes. Many genes have been studied in this context, including the VDR gene [1]. Vitamin D plays a key role in calcium homeostasis and also contributes to immune system regulation [3]. Given the immunosuppressive effects of vitamin D and a potential link between vitamin D deficiency and cancer, VDR polymorphisms, which may influence VDR activity, have been studied as potential causes of certain cancers, including melanoma [4]. Vitamin D regulates cellular proliferation, differentiation, and apoptosis processes, which influence cancer development [4]. Since VDR polymorphisms have been reported to be associated with the development of several cancers [27], they could be considered as risk factors for melanoma development.

In this meta-analysis, we combined data from published studies to evaluate the genetic association between the most commonly studied polymorphisms of the VDR gene, namely, the FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms, and susceptibility to melanoma. The FokI, TaqI, ApaI, and EcoRV polymorphisms showed no association with melanoma in the European population. In contrast, the BsmI polymorphism revealed an association between melanoma and the Bb+Bb genotype (OR=0.868, 95% CI=0.767–0.982, p=0.025). These results suggest that carrying the VDR BsmI B allele may be a protective factor for melanoma development in Europeans. However, the functional significance of the BsmI polymorphism remains unclear. If the BsmI polymorphism has a functional role, our findings may support a protective role of vitamin D against melanoma. We also cannot rule out the possibility that the BsmI polymorphism may be in LD with a causative polymorphism of melanoma.

The functional effects of the BsmI, ApaI, and TaqI polymorphisms, which are all located near the 3'-UTR region, are unclear. However, some studies suggest that these polymorphisms may alter polyadenylation of the VDR mRNA transcript, and thus affect mRNA stability [28]. The BsmI, ApaI, and TaqI polymorphisms are in regions of strong LD. Our meta-analysis did not identify any association between melanoma and the ApaI and TaqI polymorphisms. The reason for this lack of association could be explained with further haplotype studies.

Our results should be interpreted with caution because of the limited number of the studies included, which restricted further subgroup analyses. Furthermore, the relative importance of the VDR polymorphisms during the development of melanoma may be dependent on ethnicity. However, we were unable to perform ethnicity-specific meta-analysis in various populations because of limited data. It is important to substantially increase this number so that subgroup analysis for various ethnic populations can be performed. Furthermore, the BsmI polymorphism OR was very modest and only found to be significant in the recessive model.

The FokI polymorphism is located in a start codon that creates an alternative start site, resulting in the synthesis of a protein of an alternate length [29]. The long variant f allele is transcriptionally less active and associated with lower transactivation of the VDR gene than the short F allele [29]. The variant protein may have decreased capacity to inhibit cellular growth after the administration of vitamin D [29]. However, our findings are inconsistent with that functional analysis of the VDR FokI polymorphism. Genetic association results sometimes do not coincide with the results of functional studies, because the disease is complex. Multiple genes, genetic backgrounds, and environmental factors contribute to melanoma development. Moreover, it is possible that our meta-analysis results may be also due to type II error (false-negative).

The present study has some limitations that need to be taken into account during interpretation. First, patient heterogeneity and confounding

factors may have distorted the analysis. Second, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Furthermore, LD was found for the BsmI, TaqI, and ApaI polymorphisms [9]; however, no meta-analysis of haplotypes was possible because of inadequate haplotype data. Third, the VDR polymorphisms may be associated with melanoma severity, but the limited amount of available data did not allow us to investigate this association.

In conclusion, this meta-analysis demonstrated that the BsmI polymorphism is associated with susceptibility to melanoma in the European population, because the VDR BsmI B allele may play a protective role in the development of melanoma. However, a similar association was not found between the FaqI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma. Large-scale studies of populations that include different ethnicities are necessary to explore the roles of VDR gene polymorphisms in the pathogenesis of melanoma.

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