Updated Meta-Analysis of VDR FokI and TaqI Variants and Their Association with Melanoma Risk

Nazila Farnoush[1], Mehdi Khosravi-Mashizi[2], Amirhossein Rahmani[3,*], Maedeh Barahman[4], Sepideh Soleymani[2], Fatemeh Asadian[5], Ahmad Shirinzadeh-Dastgiri[6], Mohammad Vakili-Ojarood[7], Seyed Masoud HaghighiKian[2], Amirhosein Naseri[8], Maryam Aghasipour[9], Amirmasoud Shiri[10], Kazem Aghili[11], Hossein Neamatzadeh[12]

ABSTRACT

Background: Research suggests that melanoma patients with low vitamin D levels exhibit a higher risk of tumor ulceration and increased tumor mitotic rates. This has led to investigations into the vitamin D receptor (VDR) gene concerning its potential link to melanoma susceptibility. This meta-analysis aims to explore the association between VDR FokI and TaqI polymorphisms and melanoma risk, with an emphasis on the need for research in diverse populations to enhance our conclusions regarding interactions between skin phenotypes and VDR variations.

Methods: A comprehensive literature search was conducted in databases, including PubMed, Scopus, and Web of Science, for studies linking VDR polymorphisms to melanoma risk, up to February 1, 2024. Keywords used included "Melanoma", "VDR", and various genetic terms. Quantitative synthesis was performed with Comprehensive Meta-Analysis (Version 4.0) and a significance threshold set at $p < 0.05$.

Results: A total of twenty-one case-control studies involving 8,813 melanoma cases and 7,973 controls were included. Twelve studies on FokI had 4,642 cases and 4,534 controls, while nine TaqI studies included 4,171 cases and 3,439 controls. The results show a significant association between the VDR FokI polymorphism and increased melanoma risk across four genetic models (allele model: OR = 1.128, 95% CI 1.026–1.241; P = 0.013; homozygote model: OR = 1.166, 95% CI 1.020–1.332; P = 0.025; heterozygote model: OR = 1.255, 95% CI 1.046–1.507; P = 0.015; dominant model: OR = 1.243, 95% CI 1.052–1.470; P = 0.011). In contrast, the TaqI polymorphism showed no significant association with melanoma risk in the general population.

Conclusions: This meta-analysis suggests that the VDR FokI polymorphism is linked to an increased susceptibility to melanoma, while the TaqI variant does not show a significant association. Future research should explore the interactions between VDR polymorphisms, skin phenotypes, and melanoma risk in diverse populations, with larger and more varied studies needed to confirm these findings and enhance our understanding of genetic factors affecting melanoma susceptibility.

KEYWORDS

melanoma; vitamin D; VDR; polymorphism; genetic susceptibility; meta-analysis

AUTHOR AFFILIATIONS

[1] Department of General Surgery, Babol University of Medical Sciences, Babol, Iran
[2] Department of General Surgery, School of Medicine Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran
[3] Department of Plastic Surgery, Iranshahr University of Medical Sciences, Iranshahr, Iran
[4] Department of Radiation Oncology, Firoozgar Clinical Research Development Center (FCRDC), Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[5] Department of Medical Laboratory Sciences, School of Paramedical Science, Shiraz University of Medical Sciences, Shiraz, Iran
[6] Department of Surgery, School of Medicine, Shohadaye Haft-e Tir Hospital, Iran University of Medical Sciences, Tehran, Iran

Acta Medica (Hradec Králové) 2024; 67(4): 113–124
https://doi.org/10.14712/18059694.2025.8

[7]Department of Surgery, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran
[8]Department of Colorectal Surgery, Imam Reza Hospital, AJA University of Medical Sciences, Tehran, Iran
[9]Department of Cancer Biology, College of Medicine, University of Cincinnati, Ohio, USA
[10]Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[11]Department of Radiology, Shahid Rahnamoun Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[12]Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
* Corresponding author: Department of Plastic Surgery, Iranshahr University of Medical Sciences, Iranshahr, Iran; amirho.rahmani@gmail.com

Received: 6 March 2024
Accepted: 24 February 2025
Published online: 4 April 2025

INTRODUCTION

Melanoma, the most lethal form of skin cancer, arises from transformed melanocytes and affects people of all ages, genders, and ethnicities, with its global incidence rising steadily (1, 2). In 2020, around 325,000 new melanoma cases were reported worldwide, exhibiting significant geographic variation. Australia and New Zealand had the highest rates, with 42 cases per 100,000 person-years for males and 31 for females, while Western and Northern Europe, as well as North America, recorded lower but substantial rates ranging from 17 to 19 for males and 14 to 18 for females. In contrast, many African and Asian countries reported incidence rates below 1 per 100,000 person-years (3, 4). The overall prevalence tends to be higher in males, underscoring the need for continued awareness and prevention efforts. If current trends continue, new cases could surge to 510,000 by 2040, resulting in 96,000 deaths . The World Health Organization noted about 287,723 new cases globally in 2018, projecting a 14% increase in incidence by 2035 (3). Risk factors for melanoma include both environmental and genetic components, such as UV radiation exposure, fair skin, history of sunburns, numerous moles, family history, immunosuppression, specific genetic mutations, and certain occupational exposures to substances like coal tar or arsenic (5–7). Individuals with skin influenced by the melanocortin 1 receptor (MC1R), particularly those with lighter skin or red hair, are more vulnerable to UV damage. A higher number of acquired melanocytic nevi also correlates with increased risk (8, 9). Environmental influences, especially intermittent sun exposure during childhood or adolescence, further elevate melanoma risk, and the use of tanning beds significantly increases this risk among younger individuals (10, 11). Furthermore, a personal history of sunburn raises the likelihood of developing melanoma, and those with immunosuppression due to organ transplants exhibit significantly higher incidence rates compared to the general population. The presence of other skin cancers can also elevate risk, highlighting the intricate relationship between genetic predisposition, environmental factors, and overall health in the development of melanoma (5, 12).

The VDR gene plays a vital role in regulating cell cycle progression, differentiation, and apoptosis, which are all key factors in cancer development (13). Studies suggest that vitamin D deficiency is associated with a higher cancer risk, while elevated vitamin D levels correlate with reduced cancer incidence and mortality (14, 15). Many cancer patients are vitamin D deficient due to factors like impaired physical function, poor diet, chemotherapy, and limited sunlight exposure, prompting increased screenings for deficiencies over the past two decades. Vitamin D interacts with the Vitamin D receptor (VDR), essential for numerous physiological functions, while 25-hydroxyvitamin D [25(OH)D] is the primary marker of vitamin D status (16). As a nuclear macromolecule, the VDR mediates the effects of 1alpha, 25-dihydroxyvitamin D3 [1,25(OH)2D3] and regulates around 2,000 vitamin D-responsive genes involved in cell growth, differentiation, and apoptosis. Research indicates that the VDR gene significantly affects cancer growth and progression. The VDR gene, located on chromosome 12q13.1, has a complex structure with a large promoter region that generates various tissue-specific transcripts (17). It comprises 11 exons over approximately 75 kb: exons 1A, 1B, and 1C are in the 5' upstream non-coding region, while exons 2 to 9 encode the VDR protein, which contains six functional domains. The ligand-binding region interacts with 1,25(OH)2D3 and the retinoic acid X receptor (RXR) (18).

Research indicates that reduced expression of VDR in melanoma is associated with enhanced tumor growth, increased metastatic potential, and poorer survival rates. This suggests that dysregulation of VDR may play a role in the progression of melanoma and could serve as a potential therapeutic target (19, 20). VDR signaling pathways influence key aspects of melanoma biology, such as proliferation, apoptosis, angiogenesis, and invasiveness, highlighting their importance for disease management and treatment outcomes (21, 22). Over 900 genetic variations have been documented in the VDR gene, with polymorphisms like FokI, TaqI, BsmI, and ApaI being the most studied in relation to melanoma (23). However, the precise connection between VDR polymorphisms and melanoma risk is unclear, particularly for FokI (rs2228570) and TaqI (rs731236), which have yielded inconsistent results across studies. In 2020, Birke et al. performed a meta-analysis of 14 studies on VDR polymorphisms and melanoma risk, suggesting that the FokI, ApaI, and BsmI variants may affect susceptibility. Specifically, the BsmI polymorphism was associated with a 15% decrease in malignant melanoma risk, while FokI and ApaI were linked to an increase in risk by 22% and 20%, respectively (24). Other VDR polymorphisms had minimal impact on melanoma risk. Conversely, a meta-analysis by Lee et al. (2015) involving over 8,000 participants found no significant associations between VDR polymorphisms and melanoma risk (25), aligning with earlier findings by Mocellin et al. (2009) on TaqI but differing regarding FokI (26). Similarly, results

for the TaqI polymorphism are inconsistent; some studies suggest that Tt and tt genotypes may reduce melanoma risk by 30%, while others find no significant correlations, complicated by TaqI's strong linkage disequilibrium with other VDR variants (27). These discrepancies highlight the need for further research on ethnic variability in allele frequencies and their effects. To address these inconsistencies, our study undertook a meta-analysis employing systematic review and meta-analysis methodologies, involving comprehensive literature searches, quality assessments, and statistical analyses, to clarify the associations between VDR FokI and TaqI variants and melanoma risk, while also investigating potential ethnic differences.

MATERIALS AND METHODS

SEARCH STRATEGY

The meta-analysis followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to guarantee a transparent and thorough review process. To identify relevant studies investigating the relationship between VDR polymorphisms and melanoma risk, we performed a comprehensive search across various online databases. The databases included PubMed, Web of Science, Elsevier, Europe PMC, ResearchGate, Cochrane Library, EMBASE, SciELO, Chinese Medical Current Contents (CMCC), Google Scholar, Wanfang Data Company, Chaoxing, VIP Information Consulting Company (VIP), Sinomed, Chinese Medical Citation Index (CMCI), Chinese Biomedical Database (CBD), Chinese National Knowledge Infrastructure (CNKI), Scientific Information Database (SID), and ClinicalTrials.gov. The search was restricted to studies published until February 1, 2024. To enhance the breadth of our search, we utilized a diverse array of specific keywords and terms, including "Skin Cancer", "Melanoma", "Cutaneous Melanoma", "Malignant Melanoma", "Cutaneous Malignant Melanoma", "Vitamin D Receptor", "VDR", "Polymorphisms", "FokI", "Taq1", "rs2228570", "rs731236", "Gene", "Genetics", "Single-Nucleotide Polymorphism", "SNPs", "Genotype", "Allelic Variation", "Mutation", "Mutant", "Allele", "Variant", "Risk Factors", "Susceptibility", "Epidemiology", "Molecular Genetics", "Environmental Factors", "Genetic Variation", "Cohort Studies", "Case-Control Studies", "Meta-Analysis", "Gene-Environment Interaction", and "Melanoma Epidemiology". In addition to the electronic search, we manually reviewed the reference lists of all eligible articles and reviews to uncover any pertinent studies that may have been overlooked in the initial search. Importantly, only articles published in English were included to maintain consistency in the meta-analysis framework. Informed consent was not applicable for this study as it did not involve individual participants.

INCLUDING AND EXCLUDING CRITERIA

All studies included in this analysis adhered to predetermined criteria to ensure the relevance and quality of the research. Only case-control or cohort design studies published in English that specifically explored the association between VDR polymorphisms and the risk of cutaneous melanoma in preterm neonates were considered. To qualify, studies needed to provide sufficient and accessible data for calculating odds ratios (ORs) and 95% confidence intervals (CIs). Exclusion criteria included case reports, case series, letters, editorials, comments, reviews, animal studies, in vitro experiments, conference papers, and meta-analyses. Studies that did not present genotype frequency data for VDR polymorphisms, had fewer than 30 participants, or had a follow-up period of less than one year were also excluded, as these factors could compromise the reliability of findings. Additionally, research that lacked appropriate statistical analysis or did not control for potential confounders such as age, sex, and environmental influences was removed. Finally, studies with overlapping data or duplicated analyses were excluded to ensure the uniqueness and validity of the results included in this analysis.

DATA EXTRACTION

Based on the specified inclusion and exclusion criteria, it was determined that two independent authors were responsible for extracting data from the eligible studies. This extraction process was meticulously carried out using a standardized Microsoft Excel spreadsheet. In cases of disagreements or discrepancies during the data extraction, the third author was consulted for resolution. The extracted information from each individual case-control study included the first author's name, year of publication, country of origin, ethnicity, genotyping methods used, source of controls, total number of cases and controls, genotype frequencies of cases and controls for each available VDR polymorphisms, Hardy-Weinberg equilibrium (HWE) test results, and minor allele frequencies (MAFs) observed in the controls. In instances where multiple studies were published by the same investigator(s) and featured duplicated or overlapped data, only the most recent published data or the one with the largest sample size was included in the analysis.

QUALITY SCORE ASSESSMENT

The Newcastle-Ottawa Score (NOS) evaluated the quality of studies in a meta-analysis by examining the methodological aspects of observational research, including case selection, group comparability, and exposure determination, each assessed through eight specific items. Studies with excellent selection and exposure received one star, while comparability could earn up to two stars. Quality was rated on a nine-star scale, with zero indicating poor quality and nine representing high quality. Studies scoring seven or more were considered high quality, while those with at least five points were suitable for meta-analysis. Disagreements were resolved through discussion and consensus.

STATISTICAL ANALYSIS

Quantitative data synthesis was performed using Comprehensive Meta-Analysis (Version 4.0) software developed by Biostat. A two-sided p-value below 0.05 was considered

statistically significant in this study. The study investigated the association between VDR FokI and TaqI polymorphisms and the risk of cutaneous melanoma by calculating ORs with 95% CIs. A Z-test was utilized to assess the statistical significance of pooled data by comparing population means with sample means. The meta-analysis incorporated five genetic models: allelic (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB + BA vs. AA), and recessive (BB vs. BA + AA). A chi-square test evaluated heterogeneity, with significance set at $p < 0.05$. Following Cochrane's guidelines, heterogeneity among studies was measured on a scale from 0 to 100%. If the I^2 value exceeded 50%, random-effect models (DerSimonian-Laird method) were applied; otherwise, fixed-effect models (Mantel-Haenszel method) were used. To ensure the robustness of the findings, sensitivity analysis was conducted by systematically excluding one study at a time to observe its impact on the overall results. Publication bias was assessed using Begg's test, which plotted the standard error (SE) of each study against its corresponding OR, supplemented by Egger's test and visual inspection of the funnel plot for asymmetry. In cases where publication bias was identified, the Duval and Tweedie non-parametric "trim-and-fill" method was employed to adjust the results. The HWE for the control group in each study was evaluated using the chi-square test, assisted by the online software GenePop (http://genepop.curtin.edu.au), which provides functionality for HWE calculations within its genetic data analysis. A p-value below 0.05 was considered significant regarding HWE. Data analysis was conducted using Python, enabling the calculation of ORs, CIs, and metrics for heterogeneity.

RESULTS

CHARACTERISTICS OF SELECTED STUDIES

Figure 1 illustrates the process of selecting appropriate studies. A comprehensive search initially yielded 541 potentially relevant articles. After removing duplicate literature and carefully reviewing titles and abstracts, 318 articles underwent a full-text review. Among these, 190 articles were excluded due to lack of relevance and adequate data. Ultimately, a total of 21 case-control studies, which were derived from eleven publications (28–38), were deemed eligible based on the predefined inclusion criteria. These studies involved a large number of participants, with 8813 individuals identified as melanoma cases and 7973 individuals as controls. A comprehensive overview of the characteristics and genotype distribution of the eligible studies can be found in Table 1. Twelve studies concentrated on FokI, comprising 4642 cases

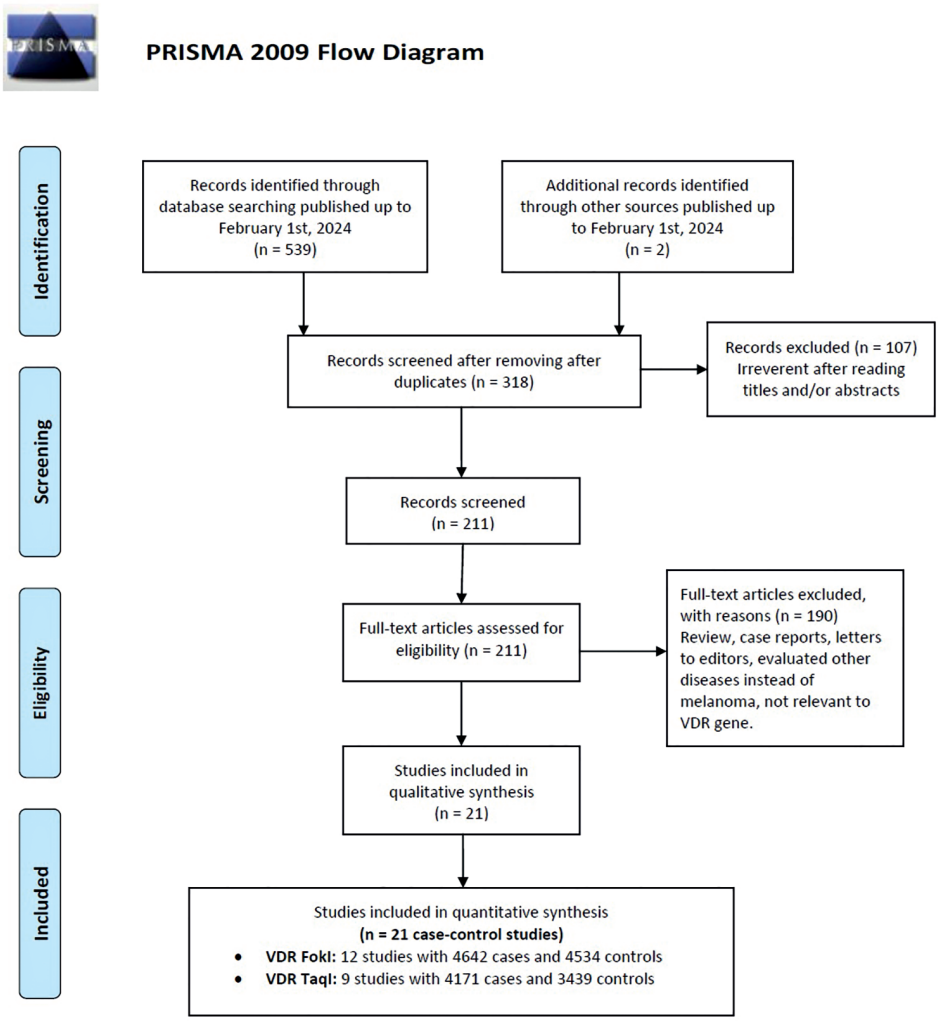

Fig. 1 Flow diagram of the study selection process.

Tab. 1 Characteristics of studies examined in the meta-analysis.

First Author	Country (Ethnicity)	SOC	Genotyping Technique	Case/ Control	Melanoma Cases					Healthy Subjects					MAFs	HWE	NOS
					Genotypes			Allele		Genotypes			Allele				
FokI					CC	TC	TT	C	T	CC	TC	TT	C	T			
Hutchinson 2000	UK (Caucasians)	HB	PCR-RFLP	293/108	105	142	46	352	234	52	44	12	148	68	0.314	0.563	7
Santonocito 2007	Italy (Caucasians)	PB	PCR-RFLP	101/101	47	41	13	135	67	41	46	14	128	74	0.366	0.869	7
Han 2007	USA (Caucasians)	PB	TaqMan	215/854	77	101	37	255	175	325	418	111	1068	640	0.374	0.193	6
Li 2008	USA (Caucasians)	HB	PCR-RFLP	805/841	287	427	91	1001	609	344	396	101	1084	598	0.355	0.424	8
Randerson-Moor 2009	UK (Caucasians)	PB	AS-PCR	1028/402	381	489	158	1251	805	161	176	65	498	306	0.380	0.151	8
Randerson-Moor 2009	UK (Caucasians)	PB	AS-PCR	299/560	96	139	64	331	267	225	255	80	705	415	0.370	0.058	8
Barroso 2008	Spain (Caucasians)	HB	TaqMan	283/245	135	121	27	391	175	110	108	27	328	162	0.330	0.949	7
Gapska 2009	Australia (Caucasians)	HB	TaqMan	763/752	240	377	144	857	665	252	357	143	861	643	0.427	0.408	7
Pena-Chilet 2013	Spain (Caucasians)	HB	AS-PCR	500/309	217	225	58	659	341	140	130	39	410	208	0.336	0.308	6
Zeljic 2014	Serbia (Caucasians)	NA	TaqMan	117/122	40	60	17	140	94	46	62	14	154	90	0.368	0.312	5
Cauci 2017	Italy (Caucasians)	NA	PCR-RFLP	120/120	47	60	13	154	86	54	50	16	158	82	0.341	0.418	6
Aristizábal-Pachón 2022	Colombia (Mixed)	HB	PCR-RFLP	120/120	23	86	11	132	108	65	40	15	170	70	0.292	0.034	6
TaqI					TT	CT	CC	T	C	TT	CT	CC	T	C			
Hutchinson 2000	UK (Caucasians)	HB	PCR-RFLP	261/93	94	127	40	315	207	39	41	13	119	67	0.360	0.674	7
Randerson-Moor 2009	UK (Caucasians)	PB	AS-PCR	1028/402	369	484	175	1222	834	144	194	64	482	322	0.400	0.920	8
Randerson-Moor 2009	UK (Caucasians)	PB	AS-PCR	299/560	107	150	42	364	234	187	273	100	647	473	0.422	0.983	8
Barroso 2008	Spain (Caucasians)	HB	TaqMan	283/245	98	137	48	333	233	91	117	37	299	191	0.389	0.951	7
Li 2008	USA (Caucasians)	HB	PCR-RFLP	805/841	330	355	120	1015	595	269	422	150	960	722	0.429	0.485	7
Gapska 2009	Australia (Caucasians)	HB	TaqMan	760/762	315	351	94	981	539	324	350	88	998	526	0.345	0.656	6
Pena-Chilet 2013	Spain (Caucasians)	HB	AS-PCR	498/294	186	248	64	620	376	109	141	44	359	229	0.389	0.884	5
Zeljic 2014	Serbia (Caucasians)	NA	TaqMan	117/122	33	62	22	128	106	59	48	15	166	78	0.319	0.291	6
Aristizábal-Pachón 2022	Colombia (Mixed)	HB	PCR-RFLP	120/120	106	14	0	226	14	81	39	0	201	39	0.163	0.033	6

Abbreviations: SOC – source of control; PB – population-based; HB – hospital-based; PCR – Polymerase chain reaction; AS – allele-specific; RFLP – restriction fragment length polymorphism; SSP – sequence-specific primers; MAF – minor allele frequency; HWE – Hardy-Weinberg equilibrium; NOS – Newcastle-Ottawa Scale.

and 4534 controls, while nine studies examined TaqI, with 4171 cases and 3439 controls. It is worth mentioning that 19 of the studies included individuals of Caucasian descent, while the rest featured mixed populations. The research, conducted and subsequently published, spanned a considerable timeframe from 2000 to 2022, covering numerous scientific endeavors and inquiries. The study's focus was limited to seven specific countries: the United Kingdom, Italy, the United States of America, Spain, Australia, Serbia, and Colombia. Various genotyping techniques, such as PCR-RFLP, AS-PCR, and TaqMan, were employed throughout these studies. Additionally, it is noteworthy that the genotype distributions among the groups of healthy individuals in a particular FokI study and another TaqI study exhibited deviations from the anticipated proportions according to the HWE principles, as illustrated in Table 1.

QUALITY OF INCLUDED STUDIES

The meta-analysis evaluated the quality of included studies by considering various factors such as sample size, control type, genotyping methods, and Newcastle-Ottawa Scale (NOS) scores. Most studies had substantial sample sizes, notably Li 2008 with 805 melanoma cases and 841 controls, and Randerson-Moor 2009 with 1028 melanoma cases and 402 controls, enhancing data reliability. The studies primarily employed hospital-based (HB) or population-based (PB) controls; while PB controls offer greater generalizability, HB controls may introduce bias if not representative of the general population. MAFs varied within plausible ranges, indicating sufficient power for detecting associations, and compliance with HWE standards was observed, with p-values above 0.05. NOS scores ranged from 5 to 8, with most studies scoring 7 or higher, reflecting sound study design principles. However, the predominance of Caucasian participants may limit generalizability to non-Caucasian populations. Common genotyping methods included PCR-RFLP and TaqMan, noted for their reliability, while allele-specific PCR was effectively used in several studies, showcasing methodological diversity. Variations in genotyping methodologies could lead to differences in sensitivity and specificity, impacting findings' reliability. Addressing these methodological limitations will enrich the discussion and suggest future research directions to enhance genetic assessments. Overall, the studies demonstrate good methodological quality, but biases associated with HB controls and limited ethnic diversity should be taken into account when interpreting results, underscoring their contributions to understanding the genetic basis of melanoma.

DATA SYNTHESIS

Table 2 presents a meta-analysis of the VDR FokI and TaqI polymorphisms and their relationship with melanoma risk. The FokI analysis includes data from 12 studies with 4,642 melanoma cases and 4,534 controls, while the TaqI analysis draws from nine studies with 4,171 cases and 3,439 controls. The findings indicate a significant association between the table and melanoma risk across four genetic models: allele model (T vs. C: OR = 1.128, 95% CI 1.026–1.241; P = 0.013, Figure 2A), homozygote model (TT vs. CC: OR = 1.166, 95% CI 1.020–1.332; P = 0.025, Figure 2B), heterozygote model (TC vs. CC: OR = 1.255, 95% CI 1.046–1.507; P = 0.015, Figure 2C), and dominant model (TT + TC vs. CC: OR = 1.243, 95% CI 1.052–1.470; P = 0.011). In contrast, the TaqI polymorphism shows no significant associations, indicating no increased melanoma risk. Ultimately, the FokI variant appears to have a greater impact on melanoma susceptibility than the TaqI variant, highlighting the importance of VDR polymorphisms in cancer genetics.

EMPLOYING PYTHON FOR AN IN-DEPTH ANALYSIS OF FOKI AND TAQI POLYMORPHISMS

The study employed Python for a comprehensive analysis of FokI and TaqI polymorphisms in relation to melanoma risk, examining twelve studies on FokI with a total of

Tab. 2 Summary of pooled data on the association between VDR polymorphism and melanoma risk.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
FokI										
Overall	T vs. C	Random	49.32	0.027	1.128	1.026–1.241	2.480	0.013	0.837	0.380
	TT vs. CC	Fixed	19.48	0.252	1.166	1.020–1.332	2.248	0.025	1.000	0.553
	TC vs. CC	Random	69.26	≤0.001	1.255	1.046–1.507	2.440	0.015	0.945	0.356
	TT + TC vs. CC	Random	67.19	≤0.001	1.243	1.052–1.470	2.553	0.011	0.631	0.311
	TT vs. TC + CC	Fixed	12.38	0.323	1.054	0.933–1.192	0.850	0.395	0.731	0.937
TaqI										
Overall	C vs. T	Random	77.04	≤0.001	0.973	0.833–1.137	-0.340	0.734	0.602	0.839
	CC vs. TT	Random	59.11	0.017	0.995	0.781–1.267	-0.044	0.965	0.173	0.072
	CT vs. TT	Random	76.33	≤0.001	0.960	0.766–1.204	-0.352	0.725	0.348	0.700
	CC + CT vs. TT	Random	79.14	≤0.001	0.961	0.765–1.207	-0.343	0.732	0.465	0.686
	CC vs. CT + TT	Fixed	9.25	0.359	0.956	0.837–1.093	-0.659	0.510	0.265	0.210

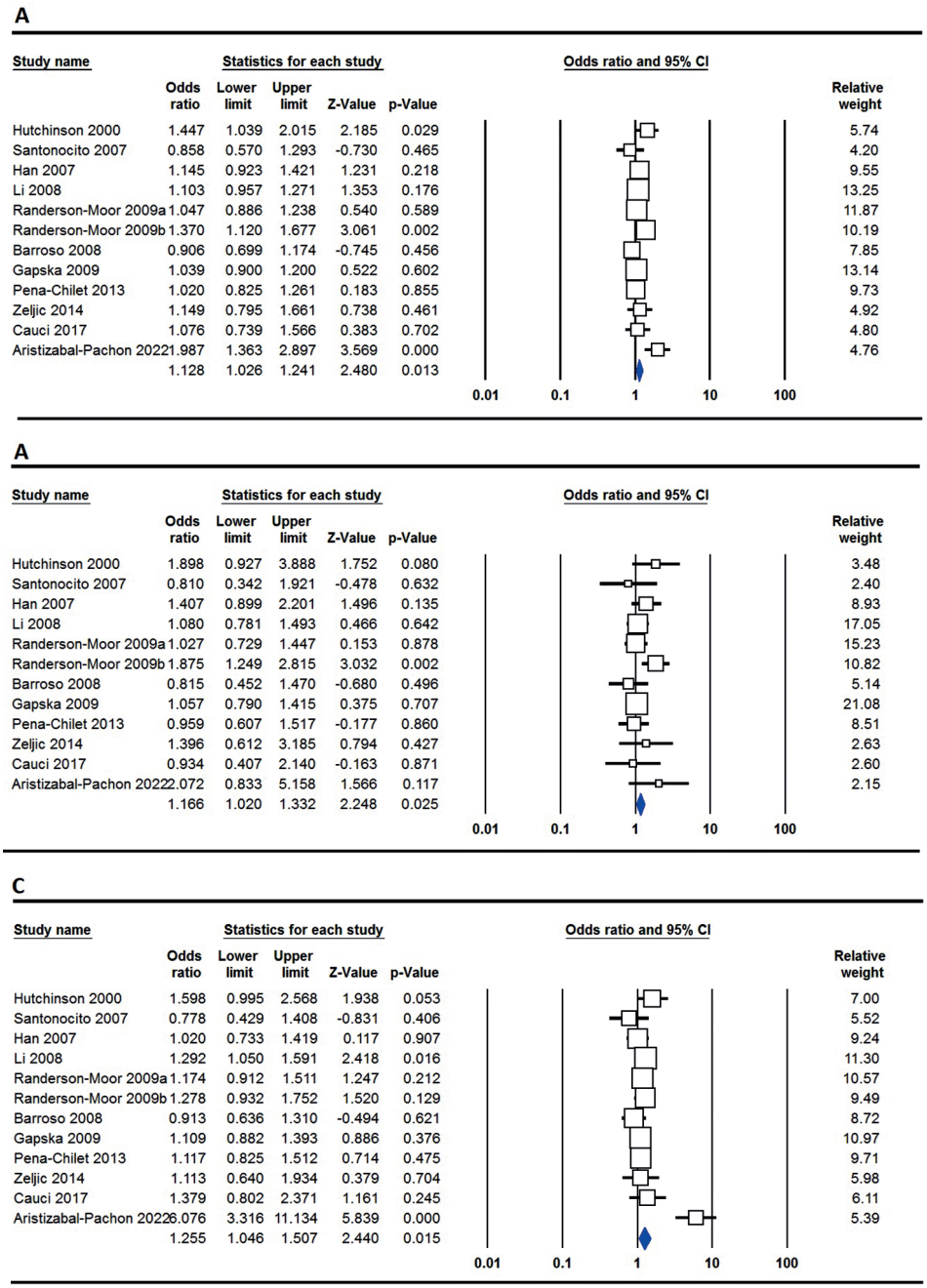

Fig. 2 Forest plots illustrating the correlation between VDR FokI polymorphism and melanoma risk: A: allele model (AA vs. AC + CC); B: homozygote model (AA vs. AC + CC); C: heterozygote model (AA vs. AC + CC).

4,642 cases and 4,534 controls, and nine studies on TaqI involving 4,171 cases and 3,439 controls, leading to a collective analysis of over 9,000 subjects. Significant findings were noted with FokI, particularly in ORs, revealing a 3.37% increase in odds when comparing T vs. C to TT vs. CC, and an 11.29% rise when assessing TC vs. CC relative to T vs. C. Conversely, a decrease of 7.07% was observed when comparing TC vs. CC to TT vs. CC. In contrast, the TaqI subgroup showed no significant association with melanoma risk, as indicated by overlapping CIs, such as for the comparisons of C vs. T (0.833–1.137) and CC vs. TT (0.781–1.267), highlighting a consistent absence of significant difference across various comparisons. The meta-analysis confirmed that nearly 65% of studies investigating TaqI supported similar non-significant results, with high heterogeneity noted for TaqI ($I^2 > 50\%$) indicating variability among studies, whereas moderate heterogeneity for FokI suggested significant overall associations remain. The average OR for FokI was approximately 1.173, suggesting its relevance in melanoma risk, while TaqI's average was around 0.973, indicating no increased risk. This thorough analysis highlights the importance of scrutinizing genetic factors influencing disease risk, as recent data estimates that genetic factors could account for up to 30% of melanoma risk, emphasizing the significance of this research in the broader context of skin cancer studies. Visual representations in Figure 3 illustrate the distinct differences between FokI and TaqI models, with FokI demonstrating strong, statistically significant positive associations across all comparisons, while TaqI exhibited more variability and

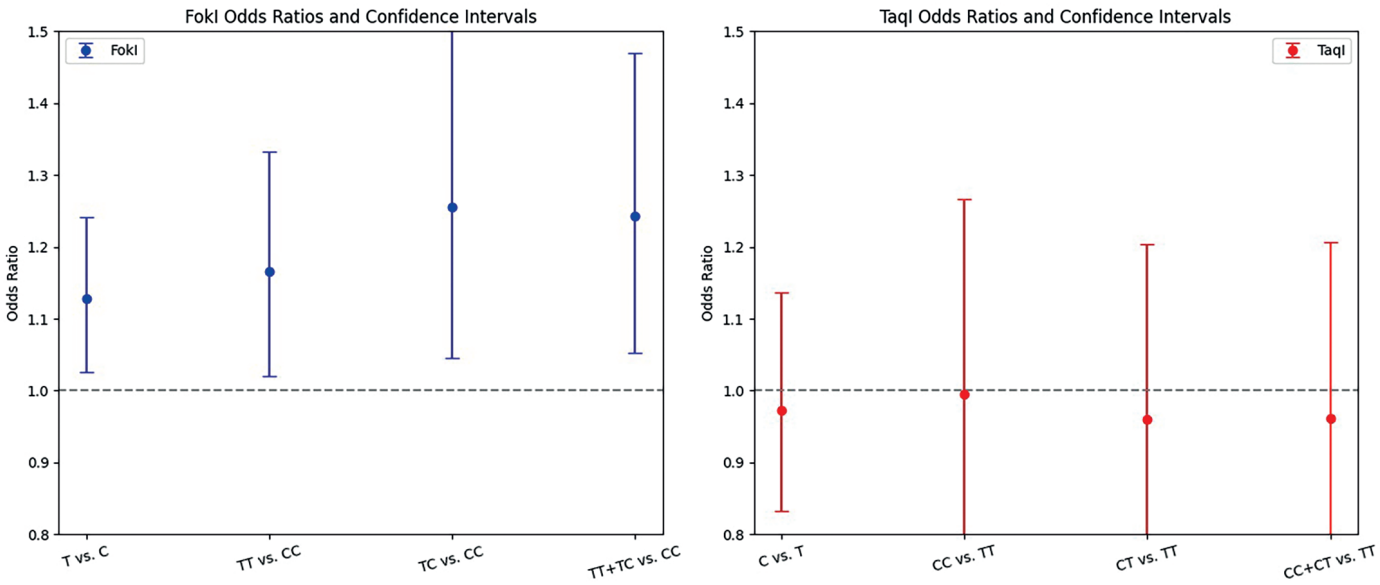

Fig. 3 Comparison of ORs and CIs for FokI and TaqI models. The left plot shows significant positive associations in the FokI model (blue circles), while the right plot indicates greater variability in the TaqI model with some near-significant comparisons (red circles). The dashed line at 1.0 represents no effect.

potential lack of significance in certain areas, suggesting the need for further investigation to better understand these dynamics. Overall, the results indicate that the FokI model provides clearer evidence of beneficial effects, whereas the TaqI model presents a more complex relationship meriting deeper analysis.

HETEROGENEITY

Table 2 highlights significant heterogeneity in research results concerning VDR FokI and TaqI polymorphisms across different genetic models. The I^2 statistic and p-values (P_H) provide valuable insights into these polymorphisms. For the FokI polymorphism, the T vs. C comparison has an I^2 of 49.32, indicating moderate heterogeneity, with a significant p-value of 0.027. In contrast, the TT vs. CC comparison shows low heterogeneity (I^2 = 19.48) and a non-significant p-value of 0.252. The TC vs. CC and TT + TC vs. CC comparisons demonstrate substantial heterogeneity, with I^2 values of 69.26 and 67.19, respectively, both statistically significant ($p \leq 0.001$). The TaqI polymorphism shows considerable heterogeneity in the C vs. T comparison (I^2 = 77.04, $p \leq 0.001$). The CC vs. TT and CT vs. TT comparisons also reveal substantial heterogeneity (I^2 values of 59.11 and 76.33) and are statistically significant (p-values of 0.017 and ≤0.001). The CC vs. CT + TT comparison, however, shows low heterogeneity (I^2 = 9.25, p = 0.359). Overall, the TaqI model exhibits significant heterogeneity across most comparisons, reflecting variability in the studies or populations, while the FokI model shows moderate to substantial heterogeneity in certain comparisons.

PUBLICATION BIAS

The analysis of publication bias regarding the association between VDR polymorphisms and melanoma risk yielded mixed results across different genetic models. For the FokI polymorphism, the Begg's test showed no significant publication bias in overall comparisons (PBeggs = 0.837) or specific contrasts like TT vs. CC (PBeggs = 1.000) and TC vs. CC (PBeggs = 0.945). Similarly, the Egger's test indicated no significant bias, with values ranging from 0.553 for TT vs. CC to 0.937 for TT vs. TC + CC. In the TaqI analysis, the overall genetic model showed no evidence of publication bias per the Begg's test (PBeggs = 0.602), though specific contrasts, such as CC vs. TT and CT vs. TT, exhibited more variable results (PBeggs = 0.173 and 0.348, respectively). The Egger's test for TaqI suggested potential bias in certain contrasts, particularly CC vs. TT (PEggers = 0.072). Figure 4 displays Begg's funnel plots for assessing publication bias in VDR FokI under the allele model (Figure 4A) and VDR TaqI under the recessive model (Figure 4B).

SENSITIVITY ANALYSIS

Sensitivity analyses were conducted by removing each eligible study to evaluate their impact on the overall results. The findings indicated that the statistical significance of the combined ORs for VDR FokI and TaqI polymorphisms remained consistent across all five genetic models, reinforcing the reliability of our results. Furthermore, excluding studies that deviated from HWE did not result in significant changes to the combined ORs. These findings underscore the robustness of our conclusions regarding the association between VDR FokI and TaqI polymorphisms and the risk of the condition investigated. The comprehensive sensitivity analyses enhance the credibility of our research.

HARDY-WEINBERG ANALYSIS

The evaluation of HWE for FokI and TaqI polymorphisms reveals significant variability across studies, countries, and methodologies. For the FokI polymorphism, out of

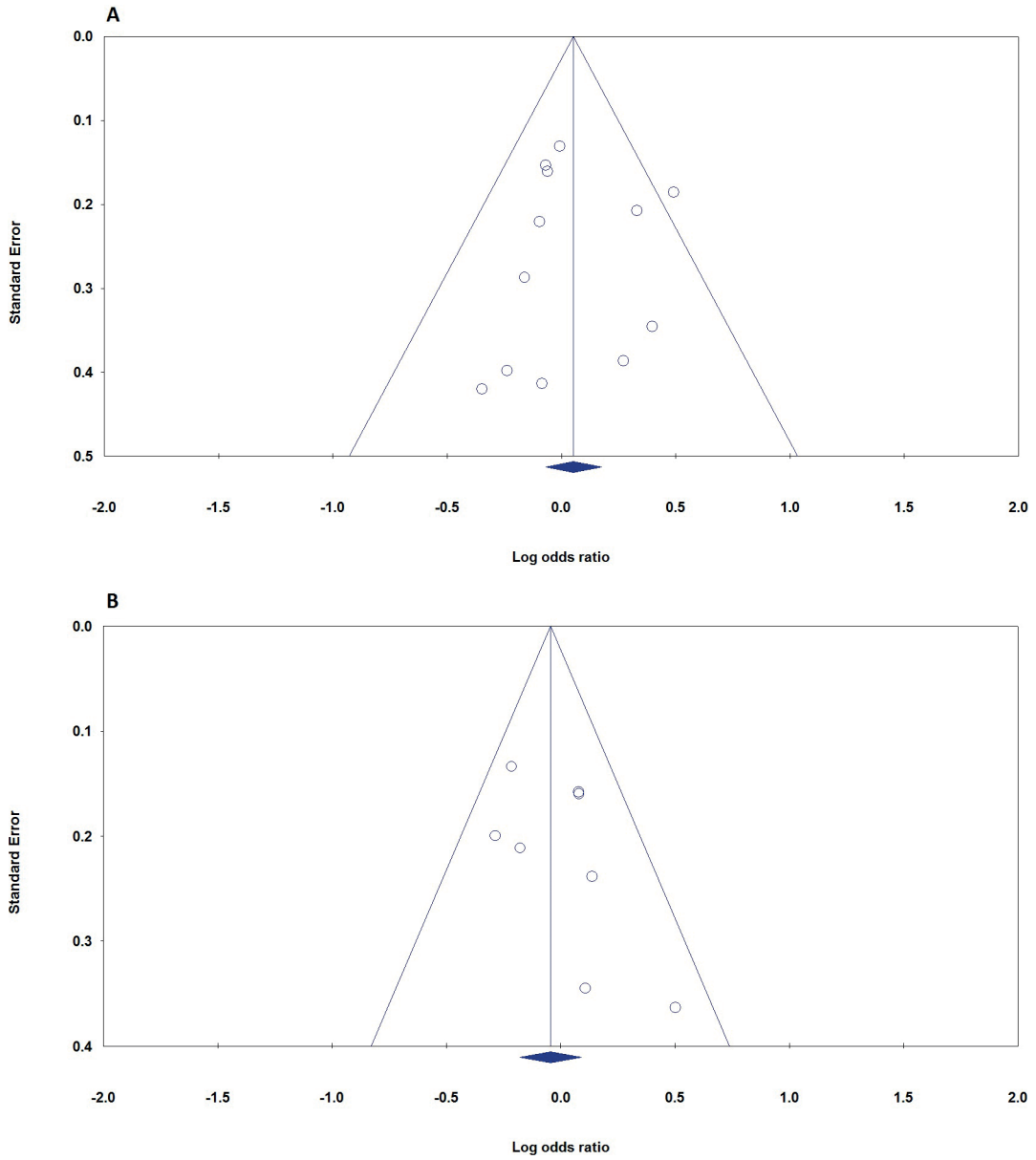

Fig. 4 Begg's funnel plots assessing publication bias in VDR polymorphisms associated with melanoma risk: A: VDR FokI under the allele model (AA vs. AC + CC); B: VDR TaqI under the recessive model (AA vs. AC + CC).

the assessed studies, four demonstrated equilibrium with p-values greater than 0.05 – namely Santonocito (0.869), Barroso (0.949), Gapska (0.408), and Zeljic (0.312) – while seven studies displayed deviations, including Hutchinson (0.563), Han (0.193), and Aristizábal-Pachón (0.034). Geographically, the UK studies generally suggested a lack of HWE, whereas Spain yielded mixed outcomes. Ethnic analysis indicated Caucasian studies showed several deviations from HWE, and genotyping methods like PCR-RFLP were correlated with more departures from equilibrium compared to TaqMan techniques. For the TaqI polymorphism, only two studies were in HWE (Randerson-Moor at 0.920 and Barroso at 0.951), with five studies reporting deviations, including Aristizábal-Pachón at 0.033. Overall, hospital-based controls exhibited greater deviations from HWE than population-based controls, and the data suggests that TaqMan genotyping might perform more favorably in achieving HWE status compared to PCR-RFLP across both polymorphisms.

MINOR ALLELE FREQUENCIES

The evaluation of MAFs for the polymorphisms FokI and TaqI reveals significant variation across different dimensions, including overall averages, by country and ethnicity, genotyping methods, and source of controls. For FokI, the overall average MAF is 0.358, while TaqI has a slightly higher average of 0.366. Country-specific evaluations for FokI show that the USA has the highest MAF at 0.386 among Caucasians, while Colombia, representing a mixed ethnicity, has a lower MAF of 0.292. In contrast, TaqI demonstrates a peak MAF of 0.429 in the USA, with the lowest observed in Colombia at 0.163. Analyzing by genotyping methods indicates that PCR-RFLP provides a consistent MAF for FokI and TaqI, while TaqMan generally yields higher averages. Furthermore, the source of controls impacts MAFs as well, with Population-Based studies often revealing higher frequencies compared to Hospital-Based studies. These evaluations underscore the complexity of genetic diversity linked to FokI and TaqI

polymorphisms, emphasizing the importance of considering multiple variables when interpreting genetic data.

DISCUSSION

Genetic variations, altered expression levels, and dysregulated signaling pathways all contribute to cutaneous melanoma susceptibility and outcomes. The link between VDR FokI and TaqI polymorphisms and melanoma predisposition has been extensively studied. Zeljic et al. conducted research indicating that FokI and TaqI polymorphisms in the VDR gene could serve as potential biomarkers for melanoma susceptibility (37). Similarly, Li et al. discovered a connection between VDR polymorphisms (TaqI and FokI) and cutaneous melanoma risk in a case-control study involving non-Hispanic white patients (39). In contrast, Beysel et al. proposed that the VDR FokI gene polymorphism raises the susceptibility to prostate cancer, while BsmI polymorphism does so for malignant melanoma, and TaqI increases the risk for renal cell carcinoma (40). This indicates that the influence of VDR polymorphisms may vary depending on the type of cancer. Additionally, the study by Marra et al. assessed VDR protein expression and VDR gene polymorphisms, including FokI, BsmI, ApaI, and TaqI, in cutaneous melanoma tissues, offering further proof of the significance of these polymorphisms in melanoma (41). Moreover, the meta-analysis by Rezaiian et al. suggested a potential positive association between VDR FokI and BsmI polymorphisms and non-melanoma skin cancer risks, underscoring the possible role of VDR polymorphisms in skin cancer predisposition (42). Evidence from these studies indicates that VDR FokI and TaqI polymorphisms may indeed influence melanoma predisposition. However, the specific impact of these polymorphisms may differ across various cancer types and populations, highlighting the intricate nature of genetic predisposition to melanoma and the necessity for further research in this domain. By elucidating the intricate relationship between the VDR gene and melanoma, this research paves the way for personalized and effective prevention and management strategies for this lethal disease.

Our analysis investigated the association between the VDR FokI polymorphism and melanoma, synthesizing data from 12 studies involving 4,642 melanoma cases and 4,534 controls. The findings revealed a significant link between the FokI polymorphism and increased melanoma risk, with the mutated allele (T) associated with higher susceptibility, shown by an OR of 1.128 (95% CI 1.026-1.241; P = 0.013). In contrast, a review of nine studies involving 4,171 cases and 3,439 controls found no significant association between the DR TaqI polymorphism and melanoma susceptibility in the general population. In 2020, Birke et al. conducted a meta-analysis of 14 studies assessing the relationship between seven VDR gene polymorphisms and melanoma risk, revealing that VDR variants FokI, ApaI, and BsmI may influence susceptibility. Specifically, the BsmI polymorphism was associated with a 15% reduction in the risk of malignant melanoma, while FokI and ApaI polymorphisms were linked to increased risks of 22% and 20%, respectively. However, no significant associations were found for other VDR gene polymorphisms, suggesting their minimal or non-existent influence on melanoma risk (24). Further investigation by Aristizabal-Pachon et al. focused on two SNPs of the VDR gene in a Colombian cohort of 120 patients and 120 matched healthy controls. Their findings indicated that the FokI polymorphism was associated with a significantly increased melanoma risk (OR: 5.10, 95% CI: 2.85–9.14), whereas the TaqI polymorphism appeared protective (OR: 0.27, 95% CI: 0.14–0.53) in the dominant model analysis. These results suggest that both polymorphisms can influence melanoma risk. Conversely, a meta-analysis by Lee et al. (2015) involving 4,413 patients and 4,072 controls of European descent found no significant associations between FokI, TaqI, ApaI, BsmI, and EcoRV polymorphisms and melanoma risk across 11 studies (25). The recent findings on VDR polymorphisms and melanoma risk reveal both similarities and differences compared to previous meta-analyses. While confirming a significant association between FokI and melanoma risk, the current study reiterates the lack of significant association with TaqI, echoing earlier work by Mocellin et al. (2009) (26) but diverging from Lee et al. (2015) regarding FokI (25). Overall, there is a consensus on the importance of certain VDR polymorphisms, highlighting the complexity of genetic influences on melanoma susceptibility, with varying degrees of association and specific risks attributed to each variant.

LIMITATIONS

The study presents several limitations that need to be acknowledged, starting with the limited number of studies available for inclusion in the meta-analysis, which may impact the overall robustness and reliability of the findings. Significant variations in study designs and methodologies, including participant selection and data collection methods, could introduce bias and affect the validity of the results. Additionally, considerable heterogeneity was revealed during the analysis, particularly in the FokI polymorphism subgroup, where high I^2 values indicated a significant level of inconsistency across studies, raising concerns about the reliability of the pooled results. Many of the included studies had small sample sizes, which led to unstable ORs and reduced statistical power to detect true associations between VDR polymorphisms and melanoma risk. Furthermore, evidence of publication bias was suggested by p-values from Begg's and Egger's tests, indicating that significant findings are more likely to be published, potentially skewing the results toward positive associations and affecting the overall interpretation. The analysis also did not sufficiently control for confounding variables such as environmental exposures, geographical differences, and other genetic variants, which could influence melanoma risk. Moreover, the analysis was primarily restricted to Caucasian populations, limiting the ability to generalize findings to other ethnic groups and raising uncertainties about the applicability of the results across diverse populations. The reliance on single-factor unadjusted ORs due to missing data on important factors such as age, gender, and lifestyle habits may also compromise

the accuracy of the findings. Additionally, the inability to assess the combined effects of VDR FokI and TaqI polymorphisms due to data inadequacy restricts the understanding of their interactions in melanoma pathogenesis. Variations in the time frames of the studies could further affect the detection and reporting of melanoma cases, leading to inconsistencies in outcomes. Lastly, while the study concentrated on VDR polymorphisms, it did not consider other relevant genetic variants that may contribute to melanoma risk, limiting the comprehensiveness of the investigation. The use of different genetic models, such as fixed vs. random effects, may not adequately capture the complexity of the genetic architecture related to melanoma risk, potentially oversimplifying the analysis. Addressing these limitations in future research is essential to enhance the understanding of VDR polymorphisms and their role in melanoma susceptibility, ultimately guiding more effective prevention and treatment strategies.

CLINICAL IMPLICATIONS

The significant association found for certain FokI models, particularly the TC versus CC genotypes, has important clinical implications for genetic screening and risk stratification in melanoma. With varying ORs indicating that individuals with specific FokI polymorphisms may have an elevated risk, this information is vital for genetic counseling and identifying at-risk populations. Additionally, the findings support the concept of personalized medicine, suggesting that high-risk individuals should undergo more proactive monitoring and preventive measures, such as increased dermatological screenings and education on sun protection. However, the inconsistent evidence surrounding the TaqI polymorphism highlights the need for further research to confirm these associations and understand the biological mechanisms involved, potentially leading to new therapeutic targets and preventive strategies. Moreover, these insights can inform the design of clinical trials that explore VDR-targeted therapies or vitamin D supplementation for populations with a higher prevalence of risk alleles, which may influence treatment protocols. Finally, understanding the genetic susceptibility linked to VDR polymorphisms can guide public health initiatives aimed at reducing melanoma incidence in genetically vulnerable groups.

CONCLUSIONS

In summary, this meta-analysis suggests that the VDR FokI polymorphism is linked to melanoma susceptibility, while the VDR TaqI polymorphism does not show a significant correlation with melanoma. Understanding the relationship between VDR gene polymorphisms and melanoma has important clinical implications, especially in personalized medicine. Furthermore, uncovering the mechanisms behind VDR-mediated melanoma risk could lead to novel therapeutic approaches. It is important to note that genetic factors interact with environmental factors to influence melanoma risk. Therefore, further studies with large sample sizes in diverse ethnic groups are needed to enhance our understanding of the role of VDR polymorphisms in melanoma development and to explore interactions among genetic, lifestyle, and environmental factors.

DECLARATIONS

Ethics approval: This article does not involve any studies with human participants or animals conducted by the authors.

Consent to participate: Not applicable for this manuscript.

Availability of data and material: The dataset utilized and/or examined in this study can be obtained from the corresponding author upon reasonable request.

Competing interests: The authors confirm no conflicts of interest.

Funding: No funding was received from any donor organization for this study.

Authors' Contributions: Study concept and design: Nazila Farnoush, Amirhossein Rahmani; Research: Mehdi Khosravi-Mashizi, Fatemeh Asadian; Data analysis and interpretation: Seyed Masoud HaghighiKian; Drafting of the manuscript: Maryam Aghasipour, Kazem Aghili; Critical review of the manuscript: Ahmad Shirinzadeh-Dastgiri, Mohammad Vakili-Ojarood, Amirhosein Naseri; Statistical analysis: Maedeh Barahman, Amirmasoud Shiri; Study supervision: Abolhasan Alijanpour, Hossein Neamatzadeh. All authors consented to submission to the current journal, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

We thank all researchers whose studies contributed to this meta-analysis and appreciate the reviewers for their insightful comments that enhanced the quality of our work.

REFERENCES

1. Wagstaff W, Mwamba RN, Grullon K, et al. Melanoma: Molecular genetics, metastasis, targeted therapies, immunotherapies, and therapeutic resistance. Genes Dis. 2022; 9(6): 1608–23.
2. Asadian F, Niktabar SM, Ghelmani Y, et al. Association of XPC Polymorphisms with Cutaneous Malignant Melanoma Risk: Evidence from a Meta-Analysis. Acta Medica (Hradec Kral). 2020; 63(3): 101–12.
3. Arnold M, Singh D, Laversanne M, et al. Global Burden of Cutaneous Melanoma in 2020 and Projections to 2040. JAMA Dermatology. 2022; 158(5): 495.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424.
5. Wunderlich K, Suppa M, Gandini S, Lipski J, White JM, Del Marmol V. Risk Factors and Innovations in Risk Assessment for Melanoma, Basal Cell Carcinoma, and Squamous Cell Carcinoma. Cancers (Basel). 2024; 16(5): 1016.
6. Lewandowska A, Lewandowski T, Rudzki G, et al. The Risk of Melanoma due to Exposure to Sun and Solarium Use in Poland: A Large-Scale, Hospital Based Case – Control Study. Asian Pac J Cancer Prev. 2023; 24(7): 2259.
7. Gawkrodger DJ. Occupational skin cancers. Occup Med (Chic Ill). 2004; 54(7): 458–463.

8. Roider EM, Fisher DE. Red hair, light skin, and UV-independent risk for melanoma development in humans. JAMA Dermatology. 2016; 152(7): 751.
9. Niktabar SMR, Dastgheib SA, Heiranizadeh N, et al. Association of XPG rs17655G>C and XPF rs1799801T>C Polymorphisms with Susceptibility to Cutaneous Malignant Melanoma: Evidence from a Case-Control Study, Systematic Review and Meta-Analysis. Klin Onkol. 2020; 33(3): 184–94.
10. Raimondi S, Suppa M, Gandini S. Melanoma Epidemiology and Sun Exposure. Acta Derm Venereol. 2020; 100(11): 5746.
11. Hashemzehi A, Ghadyani M, Asadian F, et al. Association of polymorphisms in nucleotide excision repair pathway genes with susceptibility to cutaneous melanoma. Klin Onkol. 2021; 34(5): 350–55.
12. Jiyad Z, Olsen CM, Burke MT, Isbel NM, Green AC. Azathioprine and Risk of Skin Cancer in Organ Transplant Recipients: Systematic Review and Meta-Analysis. Am J Transplant. 2016; 16(12): 3490–503.
13. Carlberg C, Muñoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol. 2022; 79: 217–30.
14. Crew KD. Vitamin D: Are We Ready to Supplement for Breast Cancer Prevention and Treatment? Int Sch Res Not. 2013; 2013(1): 483687.
15. Gallyas Jr F, Alexandru A, Ivan CS, et al. Are Pediatric Cancer Patients a Risk Group for Vitamin D Deficiency? A Systematic Review. Cancers. 2024; 16(24): 4201.
16. Sarathi V, Dhananjaya MS, Karlekar M, Lila AR. Vitamin D deficiency or resistance and hypophosphatemia. Best Pract Res Clin Endocrinol Metab. 2024; 38(2): 101876.
17. Mashhadiabbas F, Neamatzadeh H, Nasiri R, et al. Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case-control studies. Dent Res J. 2018; 15(3): 155–65.
18. Ruiz-Ballesteros AI, Meza-Meza MR, Vizmanos-Lamotte B, Parra-Rojas I, de la Cruz-Mosso U. Association of Vitamin D Metabolism Gene Polymorphisms with Autoimmunity: Evidence in Population Genetic Studies. Int J Mol Sci. 2020; 21(24): 1–24.
19. Slominski AT, Brozyna AA, Zmijewski MA, et al. Vitamin D signaling and melanoma: role of vitamin D and its receptors in melanoma progression and management. Lab Investig. 2017; 97(6): 706–24.
20. Podgorska E, Kim TK, Janjetovic Z, et al. Knocking out the vitamin d receptor enhances malignancy and decreases responsiveness to vitamin d3 hydroxyderivatives in human melanoma cells. Cancers (Basel). 2021; 13(13): 3111.
21. Becker AL, Carpenter EL, Slominski AT, Indra AK. The Role of the Vitamin D Receptor in the Pathogenesis, Prognosis, and Treatment of Cutaneous Melanoma. Front Oncol. 2021; 11: 743667.
22. Campbell MJ, Trump DL. Vitamin D Receptor Signaling and Cancer. Endocrinol Metab Clin North Am. 2017; 46(4): 1009.
23. Usategui-Martín R, De Luis-Román DA, Fernández-Gómez JM, Ruiz-Mambrilla M, Pérez-Castrillón JL. Vitamin D Receptor (VDR) Gene Polymorphisms Modify the Response to Vitamin D Supplementation: A Systematic Review and Meta-Analysis. Nutrients. 2022; 14(2): 360.
24. Birke M, Schope J, Wagenpfeil S, Vogt T, Reichrath J. Association of Vitamin D Receptor Gene Polymorphisms With Melanoma Risk: A Meta-analysis and Systematic Review. Anticancer Res. 2020; 40(2): 583–95.
25. Lee YH, Gyu Song G. Vitamin D receptor FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma: a meta-analysis. J BUON. 2015; 20(1): 235–43.
26. Mocellin S, Nitti D. Vitamin D receptor polymorphisms and the risk of cutaneous melanoma: a systematic review and meta-analysis. Cancer. 2008; 113(9): 2398–407.
27. Vasilovici AF, Grigore LE, Ungureanu L, et al. Vitamin D receptor polymorphisms and melanoma. Oncol Lett. 2019; 17(5): 4162–9.
28. Hutchinson PE, Osborne JE, Lear JT, et al. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. Clin Cancer Res. 2000; 6(2): 498–504.
29. Santonocito C, Capizzi R, Concolino P, et al. Association between cutaneous melanoma, Breslow thickness and vitamin D receptor BsmI polymorphism. Br J Dermatol. 2007; 156(2): 277–82.
30. Aristizábal-Pachón AF, González-Giraldo Y, García AY, Suarez DX, Rodríguez A, Gonzalez-Santos J. Association between VDR Gene Polymorphisms and Melanoma Susceptibility in a Colombian Population. Asian Pac J Cancer Prev. 2022; 23(1): 79–85.
31. Han J, Colditz GA, Hunter DJ. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. Carcinogenesis. 2006; 28(2): 390–7.
32. Li C, Liu Z, Wang LE, et al. Haplotype and genotypes of the VDR gene and cutaneous melanoma risk in non-Hispanic whites in Texas: A case-control study. Int J Cancer. 2008; 122(9): 2077–84.
33. Randerson-Moor JA, Taylor JC, Elliott F, et al. Vitamin D receptor gene polymorphisms, serum 25-hydroxyvitamin D levels, and melanoma: UK case-control comparisons and a meta-analysis of published VDR data. Eur J Cancer. 2009; 45(18): 3271–81.
34. Barroso E, Fernandez LP, Milne RL, et al. Genetic analysis of the vitamin D receptor gene in two epithelial cancers: melanoma and breast cancer case-control studies. BMC Cancer. 2008; 8(1): 385.
35. Gapska P, Scott RJ, Serrano-Fernandez P, et al. Vitamin D receptor variants and the malignant melanoma risk: A population-based study. Cancer Epidemiol. 2009; 33(2): 103–7.
36. Peña-Chilet M, Ibarrola-Villava M, Martin-González M, et al. rs12512631 on the Group Specific Complement (Vitamin D-Binding Protein GC) Implicated in Melanoma Susceptibility. PLoS One. 2013; 8(3): e59607.
37. Zeljic K, Kandolf-Sekulovic L, Supic G, et al. Melanoma risk is associated with vitamin D receptor gene polymorphisms. Melanoma Res. 2014; 24(3): 273–9.
38. Cauci S, Maione V, Buligan C, Linussio M, Serraino D, Stinco G. BsmI (rs1544410) and FokI (rs2228570) vitamin D receptor polymorphisms, smoking, and body mass index as risk factors of cutaneous malignant melanoma in northeast Italy. Cancer Biol Med. 2017; 14(3): 302–18.
39. Li C, Liu Z, Zhang Z, et al. Genetic Variants of the Vitamin D Receptor Gene Alter Risk of Cutaneous Melanoma. J Invest Dermatol. 2007; 127(2): 276–80.
40. Beysel S, Eyerci N, Ulubay M, et al. Maternal genetic contribution to pre-pregnancy obesity, gestational weight gain, and gestational diabetes mellitus. Diabetol Metab Syndr. 2019; 11(1): 37.
41. La Marra F, Stinco G, Buligan C, et al. Immunohistochemical evaluation of vitamin D receptor (VDR) expression in cutaneous melanoma tissues and four VDR gene polymorphisms. Cancer Biol Med. 2017; 14(2): 162–75.
42. Rezaiian F, Davoodi SH, Nikooyeh B, et al. Sun Exposure Makes no Discrimination based on Vitamin D Status and VDR-Foki Polymorphisms for Non-Melanoma Skin Cancers Risk in Iranian Subjects: A Case-Control Study. Asian Pac J Cancer Prev. 2022; 23(6): 1927–33.