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The Association Between the Genetic *VDR* SNP c.907+75C>T and Prostate Cancer Risk Is Modified by Tanning Potential

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Abstract. *Background: Prostate cancer (PCa) is a multifactorial disease involving complex interactions between genetic and physiological/environmental factors. Vitamin D receptor (VDR) plays a role in numerous cellular pathways and it has been suggested that VDR genetic variants influence individual susceptibility to PCa. Materials and Methods: Logistic regression analysis was used to assess the association of six VDR single nucleotide polymorphisms (SNPs) and factors such as tanning potential and UV sunlight exposure with PCa risk. Results: Marginal significant interactions were found, with a 2-fold increase risk of PCa between SNP 1 (c.278-69G>A) and sunlight UV exposure [odds ratio (OR)=2.02, 95% confidence intervaI (CI)=1.036-4.36; p=0.05]; and a 4-fold increase risk of PCa between SNP 4 (c.907+75C>T) and tanning potential (OR=4.40, 95% CI=0.89-29.12; p=0.0591). In contrast, SNP 5 (rs731236, TaqI) and tanning potential interaction had a protective effect by reducing the risk of PCa by 55% (β=−0.804; OR=0.448, 95% CI=0.197-9.42; p=0.0427). SNPs 2 (rs61614328) and 6 (rs533037428) did not show any association with PCa even in the presence of UV sunlight exposure. Conclusion: The protective effect of SNP 4 from PCa is lost and modified by tanning potential in African Americans. This finding needs to be verified by larger studies in different ethnic populations.*

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Prostate cancer (PCa) has high incidence as well as high mortality, which makes it an important worldwide health issue (1, 2). Furthermore, PCa etiology is complex, involving many risk factors such as age, vitamin D status, ethnic origin, and family history of PCa (3, 4). Epidemiological studies suggest that PCa risk may at least partly be determined by interactions between the environment and genetic predisposition (5-7). PCa rates are higher in African American men compared to other ethnic groups in the United States (4, 5, 8). Additionally, this group of men are more likely to be diagnosed at a later stage of disease development.

PCa risk has been inversely associated with sun exposure. In most individuals, about 90% of circulating levels of 25-hydroxyvitamin D are derived from casual sun exposure (9). In the United States, high residential sun exposure has been associated with lower mortality rates and reduced risk for PCa (10, 11). A case–control study by Luscombe *et al*. found a 3-fold increased risk with low lifetime sun exposure (12). Vitamin D is an important candidate implicated in PCa risk and its deficiency has been hypothesized to be a risk factor for PCa (13, 14). Reduced vitamin D levels correlate with established risk factors such as increasing age, African American ethnicity, and residence in northern latitudes (15). Cordera *et al*. also used diagnostic serum samples from blood to show that the risk of PCa decreased with higher levels of 1,25-dihydroxyvitamin D (6). The physiological and environmental factors that modify the supply of cutaneous vitamin D are levels of UV exposure, skin pigmentation, and polymorphism in the vitamin D receptor (*VDR*) gene (16).

VDR polymorphisms have been studied as candidates for PCa susceptibility by many investigators (17-20). The expression or function of *VDR* may be influenced by polymorphisms in the 3' end. Polymorphisms in *VDR* might

alter receptor function and affect PCa susceptibility. More than 60 *VDR* polymorphisms are located in the promoter, in and around exons 2-9, and in the 3'UTR region (21, 22). Several genetic studies have reported conflicting results on the associations between *VDR* polymorphisms and PCa risk (17). The significant effects of *VDR* polymorphisms and sunlight exposure on PCa have been reported in our previous study (23). As a follow-up to this, we investigated the specific interactions between individual single nucleotide polymorphisms (SNPs) and other physiological/environmental factors (UV sunlight exposure, tanning potential, vitamin D level) with PCa risk.

Materials and Methods

Study subjects. Ninety-one African American men with histologically diagnosed adenocarcinoma of the prostate and 92 African American controls were recruited from Howard University Hospital. The Howard University Institutional Review Board (IRB-02-MED-42) approved the study protocol, and informed consent was obtained from the study participants. Demographics and medical history details were previously described (7, 24). A blood sample was collected prior to treatment from each participant using vacutainers containing EDTA anticoagulant.

Serum 25-hydroxyvitamin D measurement. Enzyme immunoassay from Immunodiagnostic Systems Ltd. (Immunodiagnostic Systems, Fountain Hills, AZ, USA) was used for the quantitative determination of 25-hydroxyvitamin D in serum (25, 26).

Polymerase chain reaction (PCR). Genomic DNA extraction was performed using QIAmp DNA Blood Maxi Kit (Qiagen Inc., Valencia, CA, USA) according to the manufacturer's instructions. List of *VDR* primers and PCR conditions were as previously described by Copeland *et al*. (27).

Denaturing high-performance liquid chromatography (DHPLC) and DNA sequencing. The entire *VDR* gene was screened for germline mutations by DHPLC instrument (WAVE® DNA Fragment Analysis System; Transgenomics, Omaha, NE, USA) as previously described (27). Genomic DNA was amplified using GeneAmp 9700 thermal cycler (27) and purified by Qiagen column (QIAquick PCR purification Kit 50; Qiagen, Inc., Valencia, CA, USA). The amplified samples were sequenced using ABI 377 DNA sequencer (Applied Biosystems, Foster City, CA, USA), and fluorescently labeled Big-dye terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA). For further confirmation, samples were also sequenced commercially by ACGT Incorporation (Wheeling, IL, USA). Sequencher Version 4.8 software (Gene Codes Corporation, Ann Arbor, MI, USA) was used to analyze the generated data, and SNPs were identified using the International Hapmap project (http//: www.hapmap.org; https://www.ncbi.nlm.nih.gov/projects/SNP/). Nomenclature for the identified SNPs was assigned according to den Dunnen and Antonarakis (28), and the Reference SNP accession ID (rs ID) was assigned for all previously reported SNPs using BLAST SNP (http://www.ncbi.nlm.nih.gov/SNP/snp_blastByOrg.cgi).

Assessment of UVR exposure. Each participant answered questions from the validated UV questionnaire (29). This questionnaire is designed to calculate the total amount of exposure (hours/year) to UV light from childhood until the time of the interview. The cumulative sunlight exposure for each participant was assessed by a combination of his history of occupational and non-occupational sunlight exposure as described previously (24).

Assessment of tanning potential. A computerized narrow-band reflectometer (Mexameter®MX 18, Courage+Khazaka electronic GmbH, Cologne, Germany) was used to measure the skin color (24). The quantitative index of sun exposure (tanning potential) that is related to cumulative lifetime sun exposure was calculated as previously described (30, 31).

Statistical analyses. We employed several statistical methods to determine the association of *VDR* SNPs and factors with PCa. Student's *t*-test and Mann–Whitney were used to determine if there were differences in the mean of age, outdoor UV exposure, serum vitamin D level, supplemental vitamin D, and dietary vitamin D between PCa cases and controls before and after adjusting for age. Since the *t*-test showed age to be a significant factor, logistic regression analysis was carried out on the other factors by adjusting for age.

Furthermore, logistic regression was used to select the best predictors among the detected SNPs and their interactions with the physiological/environmental factors. The physiological/environmental variables were standardized for logistic regression in determining the effect of the interaction between the SNPs, factors, and PCa. The association of SNPs, UV sunlight exposure, and tanning potential with PCa risk were demonstrated using interaction plots.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated, adjusting for age. Estimates were considered statistically significant for two-tailed values of $p<0.05$. All analyses were carried out using SPSS version 26.0 (IBM, Armonk, NY, USA).

Results

Previously, we conducted a case–control study to investigate the association of vitamin D, UV sunlight exposure, and tanning potential with PCa. At the same time, we screened the *VDR* gene for mutations/SNPs. We identified seven distinct polymorphisms [SNP 1 (c.278-69G>A), SNP 2 (rs61614328), SNP 3 (rs11574114), SNP 4 (c.907+75 C>T), SNP 5 (rs731236, *TaqI*), SNP 6 (rs533037428), and SNP 7 (rs7975232, *ApaI*)] (23). However, SNP 3 was detected in only one case, therefore, this SNP was excluded from this study. In this article, we further investigated the gene-physiological/environmental interaction relating to PCa risk.

Before age-matching, Mann–Whitney test and Student's *t*-test showed significant differences between the cases and controls for age and outdoor sunlight exposure ($p=0.001$), while being marginally significant for supplemental vitamin D intake ($p=0.079$). Men 60 years and older were found to have a higher incidence of PCa compared to those younger than 50 years, and the mean UV sunlight exposure was higher in controls (5,017.2 h) than in cases (1,786.6 h). The mean serum vitamin D levels for cases (26.8 ng/ml) and controls (29.1 ng/ml) were both below the normal range (30-74 ng/ml) (Table I). To ensure the difference in mean of outdoor UV sun

Table I. *The mean values for physiological/environmental factors in unmatched cases and controls (N=182).*

Characteristic	Cases		Controls		*p*-Value	
	Mean	Standard error	Mean	Standard error	Student's *t*-test	Mann–Whitney
Age, years	64.53	0.940	58.67	0.991	**0.001**	**0.0001**
UV sunlight exposure, h	1786.57	227.828	5017.18	857.055	**0.001**	**0.0007**
Serum vitamin D, ng/ml	26.75	1.612	29.06	1.475	0.291	0.2079
Supplemental vitamin D, mg/day	129.70	20.637	169.51	20.427	0.174	0.0791
Dietary vitamin D, mg/day	140.32	11.978	155.00	13.838	0.42	0.4157
Tanning potential, %	30.32	2.658	36.51	3.4813	0.16	0.3982

Statistically significant *p*-values are shown in bold.

Table II. *The mean values for physiological/environmental factors in age-matched cases and controls (N=106).*

Characteristic	Cases		Controls		*p*-Value	
	Mean	Standard error	Mean	Standard error	Student's *t*-test	Mann–Whitney
Age, years	60.9	1.146	60.9	1.1460	0.990	0.997
UV sunlight exposure, h	1846.98	373.131	6117.44	1360.832	**0.003**	**0.044**
Serum vitamin D, ng/ml	28.27	2.138	29.72	1.918	0.618	0.7
Supplemental vitamin D, mg/day	147.25	27.889	171.99	25.367	0.516	3.16
Dietary vitamin D, mg/day	156.67	17.538	146.06	20.538	0.689	0.857
Tanning potential, %	24.77	3.069	39.5	4.699	**0.010**	**0.026**

Statistically significant *p*-values are shown in bold.

Table III. *Association of age, UV sunlight exposure, vitamin D levels, and prostate cancer risk using logistic regression.*

Variable	β	Standard error	Odds ratio[a]	95% CI	*p*-Value
Intercept	−1.5252	0.6051			**0.011**
Age, years					
40-49			1		(Ref)
50-59	0.697	0.678	2.008	0.531-7.592	0.304
60-69	2.211	0.676	9.126	2.422-34.382	**0.001**
≥70	2.167	0.714	8.734	2.154-35.416	**0.002**
UV sunlight exposure[b]	−1.170	0.373	0.310	0.149-0.645	**0.001**
Serum vitamin D[b]	−0.093	0.177	0.911	0.643-1.289	0.598
Supplemental vitamin D[b]	−0.050	0.180	0.950	0.667-1.355	0.778
Dietary vitamin D[b]	0.091	0.196	1.096	0.746-1.609	0.640
Tanning potential[b]	−0.346	0.186	0.707	0.491-1.018	0.062

[a]Adjusted for age. [b]Variables are standardized. Statistically significant *p*-values are shown in bold.

exposure was not influenced by imbalances in ages of controls and cases, we reanalyzed the data in pairs of men matched for age. Significant differences were found only for UV sunlight exposure (p=0.003) and tanning potential (p=0.01) (Table II). Furthermore, significant associations were found between PCa risk and age older than 60 years as well as tanning potential (p=0.06) and outdoor UV sun exposure (p=0.001) (Table III).

The interactions between the individual *VDR* SNPs and factors for PCa risk were analyzed using logistic regression (Tables IV, V, and VI). *VDR* SNPs 4 and 5 showed a significant protective effect by reducing PCa risk (β=−3.23, OR=0.039, 95% CI=0.0005-0.274, p=0.01670; and β=−1.884, OR=0.152, 95% CI=0.075-0.295, $p=6.05\times10^{-8}$, respectively). Notable interactions with a 2-fold increase risk of PCa between SNP 1

Table IV. *Assessment of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 1 (c.278-69G>A) interaction with outdoor UV sunlight exposure concerning prostate cancer risk using logistic regression analysis.*

Variable	β	Standard error	Odds ratio	95% CI	*p*-Value
Intercept	–0.98	0.193	0.907	0.619-1.32	0.612
VDR SNP 1	0.237	0.311	1.27	0.690-2.34	0.446
UV sunlight exposure	–0.48	0.279	0.619	0.348-1.049	0.0850
VDR SNP 1 × sunlight	0.702	0.361	2.02	1.036-4.361	0.0520

Table V. *Assessment of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 4 (c.907+75C>T) interaction with tanning potential (TP) concerning prostate cancer risk using logistic regression analysis.*

Variable	β	Standard error	Odds ratio	95% CI	*p*-Value
Intercept	0.277	0.185	1.319	0.919-1.905	0.135
VDR SNP 4	–3.23	1.354	0.039	0.0005-0.274	**0.0167**
TP	–0.54	0.203	0.584	0.385-0.855	**0.00785**
VDR SNP 5 × TP	1.482	0.785	4.40	0.891-29.12	0.0591

Statistically significant *p*-values are shown in bold.

Table VI. *Assessment of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 5 (rs731236) interaction with tanning potential (TP) concerning prostate cancer risk using logistic regression analysis.*

Variable	β	Standard error	Odds ratio	95% CI	*p*-Value
Intercept	1.082	0.260	2.95	1.816-5.062	**2.964×10^{-5}**
VDR SNP 5	–1.884	0.348	0.152	0.0750-0.295	**6.05×10^{-8}**
TP	0.381	0.314	1.463	0.817-2.848	0.2256
VDR SNP 5 × TP	–0.804	0.397	0.448	0.197-0.942	**0.0427**

Statistically significant *p*-values are shown in bold.

and sunlight UV exposure (OR=2.02, 95% CI=1.036-4.36; p=0.052); and a 4-fold increase risk of PCa between SNP 4 and tanning potential (OR=4.40, 95% CI=0.89-29.12; $p=0.0591\times10^{-2}$) were found. In contrast, potential interaction between SNP 5 and tanning had a protective effect by reducing the risk of PCa by 55% (β=–0.804; OR=0.448, 95% CI=0.197-9.42; p=0.0427). SNPs 2 and 6 did not show any association with PCa even in the presence of UV sunlight exposure. Furthermore, the significant interactions of the SNPs, UV sunlight exposure, tanning potential with PCa risk were also demonstrated using the interaction plot (Figures 1-3). An increased risk of PCa was found with increase of UV sunlight exposure and in the presence of SNP 1.

Discussion

Most of the emerging epidemiological evidence has shown that *VDR* polymorphisms and vitamin D from sunlight exposure play a role in the development of PCa. Liu *et al.* reported the association of six variants with PCa and their cumulative effect (32). This relationship suggested that men who carried any combination of 1, 2, or >3 risky genotypes had a gradually increased PCa risk. However, Berndt *et al.* did not find evidence to support an association between any of the *VDR* polymorphisms and the risk of PCa (33). We recently reported that *VDR* SNPs 4 (c907+75C>T) and 7 (rs7975232) play a significant role in the development of PCa in African Americans (7, 23).

The cumulative effects of *VDR* polymorphism, UV sunlight exposure, and vitamin D level on PCa risk has also been investigated by other researchers (34, 35). North American-based studies linking latitude with PCa mortality have shown that UV radiation (UVR) has a protective effect against the development of PCa (11, 34) and suggested that the impact of *VDR* genotype might be evident in men with certain levels of UVR exposure. Bodiwala *et al.* used a median value of cumulative UVR exposure per year (1,100 h/year) and found no association below the median, while

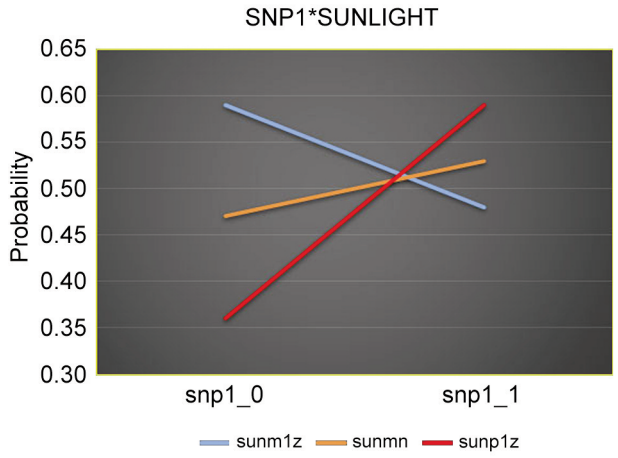

Figure 1. *Demonstration of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 1 (c.278-69G>A) interaction with UV sunlight exposure concerning prostate cancer risk using the interaction plot.*

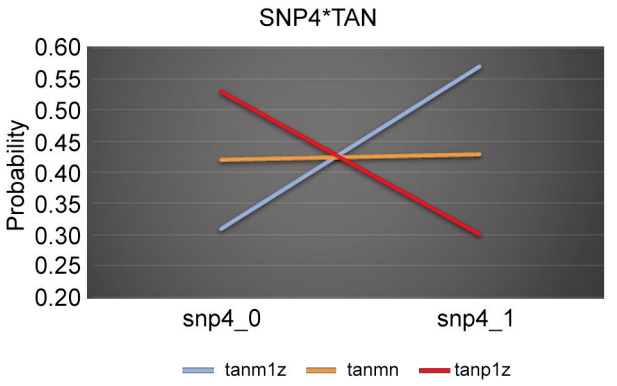

Figure 2. *Demonstration of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 4 (c.907+75C>T) interaction with tanning potential concerning prostate cancer risk using interaction plot.*

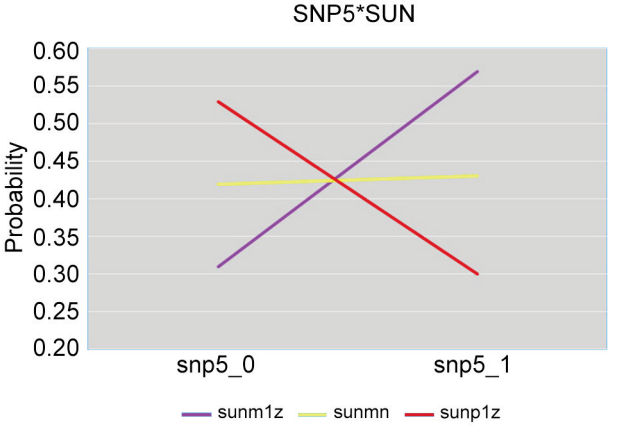

Figure 3. *Demonstration of the most predictive vitamin D receptor (VDR) single nucleotide polymorphism (SNP) 5 (rs731236) interaction with UV sunlight exposure concerning prostate cancer risk using the interaction plot.*

VDR polymorphisms were associated with PCa risk in men with UVR exposure levels above the median (19). In our study, the mean sunlight UV exposure levels for the cases (1,787 h/year) and the controls (5,017 h/year) were much higher than that reported by Bodiwala *et al*. (19). The mean UV sunlight exposure for the controls was almost three times that of the cases, indicating the protective effect of UV sunlight exposure against PCa. This is reflected by the negative regression coefficient (β=–1.1704) between UV sunlight exposure and PCa. Bodiwala *et al*. (16) and Luscombe *et al*. (12) showed that the pathogenesis of PCa in men with low levels of UVR exposure is different from that in men with higher levels. Thus, *VDR* variants are not associated with PCa risk in the group with a relatively low UVR exposure. Levels of UVR exposure below the median may be associated with PCa that develops because of relative vitamin D deficiency, which appears to have been the case in the present study (levels below 30 ng/ml).

Conflicting results have been reported on the effect of the vitamin D level on PCa risk. Recent studies by Park *et al*. (30) and Kristal *et al*. (36) did not find any association of vitamin D uptake with PCa risk. Huncharek *et al*. found no significant association in a meta-analysis in observational studies regarding diet, calcium, and vitamin D intake and the risk of PCa (37). On the other hand, Bahar *et al*. showed that plasma vitamin D <26 ng/ml was associated with a threefold risk for PCa (38). A study by Murphy *et al*. showed that vitamin D deficiency was associated with higher Gleason score and tumor stage in both Caucasians and African Americans (39). This means that vitamin D deficiency may play a role in influencing the relationship between UV sunlight exposure and PCa risk. Nevertheless, the inverse relationship between UV sunlight exposure and PCa risk has been reported by Liu *et al*. (32). In the United States, high levels of UV sun exposure were associated with lower mortality rates and reduced risk of PCa (34). Moreover, a case–control study from England revealed a 3-fold increased risk to be associated with a low lifetime UV sunlight exposure (12). Results from our previous studies (23, 24) have shown that outdoor UV sunlight exposure was associated with reduced PCa risk.

Conclusion

This study showed that the association of *VDR* SNPs with PCa risk may be dependent on the level of UV sunlight exposure

and the level of serum vitamin D. *VDR* variants are not associated with PCa risk in men with relatively low UV sunlight exposure and high serum vitamin D level. As sunlight exposure increases, the risk of PCa decreases, which indicates an inverse relationship between the two. Similarly, the risk of PCa decreases with a diminution in tanning potential. Results from this study also showed that UV sunlight exposure has a protective effect against PCa when the vitamin D level is not limiting. Overall, these findings provide additional information for future epidemiological and functional studies in African Americans. The generated data of gene–physiological/environmental factors interaction from this study is important for discovery of novel genetic risk factors, risk prediction, and identification of certain high-risk populations to outline public health strategies for targeted prevention.

Conflicts of Interest

Authors have no personal or financial conflicts of interest to report.

Authors' Contributions

DB and MD conducted the laboratory analyses, and writing-original draft preparation. VA performed the statistical analyses. TN collected the clinical data and contributed to data analyses. OOK contributed to the data analyses and article writing-reviewing and editing. RLC and YK were responsible for the experimental design and contributed to the data analyses and article writing.

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