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ORIGINAL ARTICLE

Genetic polymorphisms of vitamin D receptor and the risk of prostate cancer: A meta-analysis

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Summary

Purpose: *Vitamin D receptor (VDR) polymorphisms are considered to be risk factors for prostate cancer. However, previous case-control studies on the association between the variants of VDR and prostate cancer have shown contradictory results. Therefore, the role of VDR in prostate cancer remains unresolved. To investigate a potential correlation between VDR polymorphisms and prostate cancer risk, a meta-analysis of case-control and cohort studies was conducted.*

Methods: *Eligible studies were retrieved via both computerized searches and review of references. The association of VDR polymorphisms to prostate cancer was evaluated for 4 well-known VDR polymorphisms (FokI, BsmI, ApaI and TaqI) separately. Stratified analyses on ethnic characteristics (Caucasians or Asians), cancer stage (localized or advanced) and Gleason score (<7 or >7) were performed. Fixed- or random-effect models were used to summarize the estimates of odds ratio (OR) with 95%CI according to the heterogeneity. Sensitivity analyses were conducted.*

Results: *A total of 40 studies met the inclusion criteria of the meta-analysis. The FF genotype illustrated a protective effect on prostate cancer in the Caucasian subgroup (OR=0.905, 95%CI 0.823, 0.995). Conversely, the bb and the TT genotypes were associated with increased risk of prostate cancer (OR=0.838, 95%CI 0.709,0.990; OR=1.127, 95%CI 1.023,1.242, respectively).*

Conclusion: *Our analysis supported the hypothesis that several different VDR polymorphisms may increase the risk of prostate cancer. However, others illustrated a protective effect on carcinogenesis. Further efforts should be made to establish the mechanisms between VDR polymorphisms and prostate cancer.*

Key words: *meta-analysis, polymorphism, prostate cancer, vitamin D receptor*

Introduction

Prostate cancer is the most commonly diagnosed type of cancer among men and it remains the second leading cause of cancer deaths worldwide [1]. Siegel et al. reported that 241,740 men were diagnosed with prostate cancer, among which 12% were predicted to die in 2012 [1]. Both genetic and environmental factors are considered to play important roles in the occurrence of prostate cancer [2]. Smoking and drinking are well-established environmental risk factors for prostate cancer [3]. The etiology of prostate cancer remains unresolved, although genetic polymorphisms may play important roles in the genesis of prostate cancer.

Vitamin D, the active form of which is 1, 25-dihydroxyvitamin D3, plays a central role in the control of mineral metabolism [4]. Moreover, it has been associated with proliferation, differentiation, angiogenesis and apoptosis [5]. Several studies have reported that 1,25-dihydroxyvitamin D3 exhibited prominent antiproliferative effects on malignant cells such as prostate [6], breast [7], and colon [8] cell lines. 1,25-dihydroxyvitamin D3 is largely mediated by the vitamin D receptor (VDR) [5,9]. VDR is a ligand-dependent transcription factor, which is expressed in a large number of cell types, including prostate cells [10,11]. Consequently, any change in VDR may cause differences in the incidence of prostate cancer.

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Located on chromosome 12q12-14 (21,22) [12] the VDR gene includes several allelic variations that have been epidemiologically involved in the etiology of prostate cancer [13-15]. The most common single nucleotide polymorphisms (SNPs), including FokI [15], BsmI [16], ApaI [13], and TaqI [4] were considered to impact the expression and function of the VDR protein, which was associated with prostate cancer [4,17].

Two alleles can be distinguished in exon 2 at the 5` end of VDR by RFLP (restriction fragment length polymorphism) using endonuclease FokI. The FokI polymorphism was associated with the transactivation of the 1,25-dihydroxyvitamin D3 signal [17]. Alternatively, BsmI, ApaI and TaqI, which cut the 3' UTR region of the VDR gene, did not change the translation product of the VDR gene. However, the SNPs in the 3' UTR region are thought to be related to mRNA stability and may therefore alter the activity of vitamin D via translation regulation [18].

With the development of RFLP, additional studies have explored the relationship between prostate cancer and polymorphisms in the VDR gene, using FokI, BsmI, ApaI and TaqI. However, the results among studies have been inconsistent. For example, Onen [19] reported that the AA genotype in ApaI polymorphism was associated with the development of sporadic prostate cancer in Turkish population. Huang [15] suggested that the VDR FokI FF genotype increased the risk of early-onset prostate cancer, especially its more aggressive forms. Nevertheless, studies conducted by Bai [20] and Mikhak [21] found no significant association between prostate cancer and VDR gene polymorphisms.

Given the differing results reported in studies regarding the correlation between VDR gene polymorphisms and prostate cancer, some systematic reviews and meta-analyses have been conducted [22-24]. However, the latter were either restricted to the whole population or lacked stratified analyses. We therefore performed a comprehensive meta-analysis of all published studies that investigated associations between prostate cancer and the 4 most common VDR gene polymorphisms (FokI, BsmI, ApaI and TaqI). Furthermore, we stratified our analyses on ethnic characteristics (Caucasians or Asians), cancer stage (localized or advanced) and Gleason score (<7 or >7).

Methods

Literature search

To get a comprehensive view of VDR gene polymorphisms and prostate cancer risk, we undertook a systematic literature search strategy. We identified publications updated to October 2012 using Pubmed, Embase and Web of Science. "VDR", "Vitamin D receptor", "polymorphism" and "prostate cancer" were used as keywords to identify the publications. Additional publications were identified either by cited references in the retrieved articles or from previous meta-analyses on VDR gene polymorphisms and prostate cancer. Each publication identified was reviewed and evaluated against the following criteria: (1) cohort or case-control study assessing the association between VDR gene polymorphisms and prostate cancer; (2) at least one of the 4 polymorphic sites mentioned above were included; (3) articles were published between 1998 and October 2012 regardless of the written language; (4) exact data in both case and control groups were determined. Studies with overlapping or insufficient data were excluded. Figure 1 demonstrates the process used to select articles.

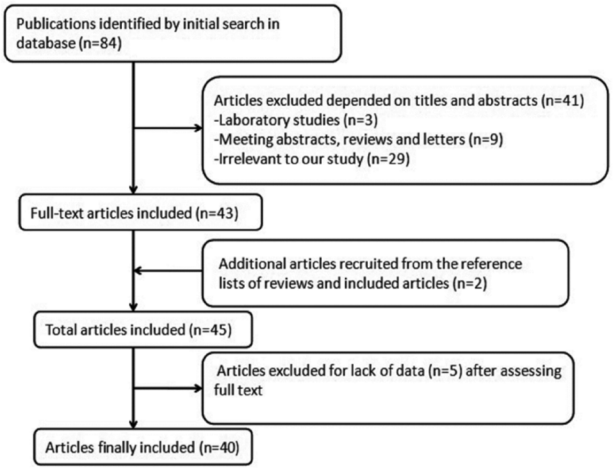

Figure 1. Process of article selection.

Data extraction

The data extracted from the publications included name of the first author, year of publication, number of cases and controls, ethnicity, polymorphic sites and subgroups of the study. Investigators, divided in two groups, extracted data from all the potentially qualified articles in case of mistakes and omissions.

Statistics

A fixed-effect model following the method of Mantel-Haenszel was applied to provide a summary estimation of the VDR gene polymorphisms associated with prostate cancer when no heterogeneity was found [25], otherwise a random-effect model following the method of DerSimonian and Laird was applied for pooling instead [26].

We selected OR and 95% CI to evaluate the strength of the association between the 4 gene poly-

morphisms and prostate cancer risk, respectively [27]. For each locus, stratified analyses were performed on ethnic characteristics (Caucasians or Asians), cancer stage (localized or advanced) and Gleason score (<7 or >7).

The extent of heterogeneity across the eligible studies was quantified via the Q test and I^2 test [28,29] with the statistical significance level set at 0.05. A sensitivity analysis was conducted to assess the value of a single study on the overall estimate.

All statistical analyses were performed using STATA version 11 (StataCorp, College Station, Texas, USA).

Results

Eligible studies

A total of 45 studies were evaluated [15,19-21,30-69]. Five studies that had neither a case group nor a healthy control group were excluded [55-57,60] and one study was excluded due to lacking data [59]. A total of 40 studies were thus included in our analysis (Table 1). Because prostate cancer is a common disease, relative risk (RR) is considered the same as OR. Therefore, we selected OR as the result to estimate the correlation between VDR polymorphisms and risk of prostate cancer.

Simultaneously, sensitivity analysis was performed to evaluate the effect of a single study on the total estimate by sequentially excluding each study in one turn. In this meta-analysis, we determined that no individual study affected the summary of risk estimate significantly (data not shown).

Polymorphism site FokI

Of the 45 studies reviewed, 16 were associated with FokI. Heterogeneity among these 16 studies was noticed in the Asian subgroup of the dominant gene model (p=0.076 I^2=52.7%), thus the method of DerSimonian and Laird for random-effect model was performed in the subgroup analysis. The method of Mantel-Haenszel for the fixed-effect model was used for all other data analyzed.

No significant relationship between the FokI gene polymorphism and prostate cancer risk was found in the 16 studies under either the dominant model (OR=0.959, 95%CI 0.881,1.043) or the recessive model (OR=1.021, 95%CI 0.914,1.140) that included the whole population. Furthermore, no specific association was detected between the FokI gene polymorphism and prostate cancer risk in either the dominant model (OR=0.979, 95%CI 0.837,1.144) or the recessive model (OR=0.932, 95%CI 0.770,1.127) according to TNM stage. No analysis based on Gleason score was performed due to the limited number of studies. For the stratified analysis on ethnicity, the FF genotype showed a protective effect for prostate cancer risk in the Caucasian subgroup of the dominant model (OR=0.905, 95%CI 0.823,0.995). Publication bias was assessed by Egger`s test. We found no publication bias for FokI gene polymorphism in the above models (Table 2).

Polymorphism site BsmI

19 studies were included in the analysis. No significant relationship was found between the BsmI gene polymorphism and prostate cancer in the dominant model of overall studies (OR=1.037, 95%CI 0.932,1.153). However, in the recessive model of overall studies, the bb genotype increased the risk of prostate cancer compared to the BB genotype (OR=0.838, 95%CI 0.709,0.990). In the stratified analyses by ethnicity, TNM stage, and Gleason score, no significant association was detected in either the dominant or recessive model (Table 3). Publication bias was assessed by Egger`s test. No publication bias for BsmI gene polymorphism was observed in any model (dominant model: p=0.324, recessive model: p=0.249).

Polymorphism site TaqI

For the relationship between the TaqI gene polymorphism and the incidence of prostate cancer, 28 studies were included in the analyses. No heterogeneity was observed according to Q test and I^2 test for the overall studies (Table 4). For the overall analysis of the dominant model, the TT genotype was associated with an increased risk factor for prostate cancer (OR=1.127, 95%CI 1.023,1.242, p=0.197, I^2=20.8%), whereas in the recessive model there was no such an association (OR=1.066, 95%CI 0.930,1.222, p=0.436, I^2=1.5%). For the ethnicity subgroup analysis the Asian subgroup showed a statistically positive correlation between the TT genotype and increased risk of prostate cancer both in the dominant model (OR=1.291, 95%CI 1.030,1.617) and the recessive model (OR=2.199, 95%CI 1.036,4.671), which further supported our previous results. The stratified analyses of TNM stage and Gleason score, however, showed no significant correlation in either the dominant model or recessive model. No bias was found in Egger`s test for publication bias of the overall analysis (Table 4).

Table 1. Description of the eligible studies included in the meta-analysis

Year	*First author [Ref.no]*	*Ethnicity*	*Cases*	*Controls*	*Polymorphic sites*	*Cancer evaluation*
1998	Ma [30]	Caucasians	372	591	BsmI TaqI	No[a]
1998	Kibel [68]	Caucasians	41	41	TaqI	No
1999	Watanabe [32]	Asians	100	202	TaqI	TNM[b]
1999	Correa-Cerro [31]	Caucasians	132	105	TaqI FokI	No
2000	Blazer [33]	Caucasians	77	183	TaqI	TNM
2000	Habuchi [69]	Asians	222	128	BsmI TaqI ApaI	No
2001	Chokkalingam [35]	Asians	191	304	BsmI FokI	TNM
2001	Hamasaki [34]	Asians	115	133	TaqI	TNM Gleason[c]
2002	Gsur [38]	Caucasians	190	190	TaqI	Gleason
2002	Hamasaki [37]	Asians	110	90	TaqI	TNM Gleason
2002	Medeiros [36]	Caucasians	163	211	TaqI	No
2003	Suzuki [39]	Asians	81	105	BsmI TaqI ApaI	TNM Gleason
2003	Nam [62]	Caucasians	483	804	BsmI	No
2003	Tayeb [58]	Caucasians	21	379	TaqI	No
2004	Cheteri [43]	Caucasians	559	523	BsmI FokI	TNM Gleason
2004	Maistro [40]	Caucasians	165	200	TaqI ApaI	TNM Gleason
2004	Yang [42]	Asians	80	96	FokI	No
2004	Liu [44]	Asians	112	190	BsmI TaqI	No
2004	Oakley-Girvan [41]	Caucasians	232	171	BsmI TaqI ApaI FokI	No
2004	Huang [45]	Asians	160	205	BsmI TaqI ApaI	TNM Gleason
2004	Bodiwala [61]	Caucasians	368	243	FokI TaqI	No
2005	Mishra [47]	Asians	128	147	FokI	No
2005	John [46]	Caucasians	450	455	FokI TaqI	TNM
2005	Forrest [48]	Caucasians	288	700	TaqI	No
2005	Hayes [54]	Caucasians	812	713	FokI BsmI	No
2006	Huang [15]	Asians	416	502	FokI	TNM Gleason
2006	Cicek [49]	Caucasians	439	479	BsmI TaqI ApaI FokI	TNM Gleason
2006	Andersson [50]	Caucasians	124	176	TaqI	No
2006	Chaimuangraj [51]	Asians	28	30	BsmI TaqI ApaI	No
2007	Rukin [65]	Caucasians	430	320	FokI	No
2007	Holick [52]	Caucasians	630	565	TaqI BsmI	No
2007	Li [72]	Caucasians	1066	1618	FokI BsmI	No
2007	Mikhak [21]	Caucasians	688	689	FokI BsmI	TNM Gleason
2008	Torkko [53]	Caucasians	444	488	FokI	No
2008	Onen [19]	Caucasians	133	157	BsmI TaqI ApaI	No
2008	Onsory [64]	Asians	100	100	TaqI	No
2009	Bai [20]	Asians	122	130	BsmI TaqI ApaI FokI	TNM Gleason
2009	Holt [67]	Caucasians	827	787	TaqI BsmI	No
2011	Risio [63]	Caucasians	95	378	TaqI	No
2011	Szendroi [66]	Caucasians	204	102	BsmI	No

a: Indicates the study was neither stratified by Gleason stage nor by TNM stage.
b: T1-2N0M0 considered to be localized stage; T3-4NM0-1, T1-4NM1 considered to be advanced stage. Only the statistics of the advanced stage group were extracted.
c: Only the statistics of the Gleason score >7 group were extracted.

Table 2. Results of the analysis for FokI gene polymorphism

Group	*OR (95% CI)*	$P_{heterogeneity}$	I^2 (%)
Dominant model (FF vs Ff+ff)			
Overall	0.959 (0.881, 1.043)	0.147	30.5
Asians	1.203 (0.997, 1. 452)	0.076	52.7
Caucasians	0.905 (0.823, 0.995)	0.999	0
TNM stage	0.979 (0.837, 1.144)	0.605	0
Gleason score	-	-	-
Recessive model (FF+Ff vs ff)			
Overall	1.021 (0.914, 1.140)	0.370	7.6
Asians	1.214 (0.977, 1.509)	0.292	19.2
Caucasians	0.960 (0.844, 1.092)	0.692	0
TNM stage	0.932 (0.770, 1.127)	0.328	13.6
Gleason score	-	-	-

Table 3. Results of the analysis for BsmI gene polymorphism

Group	*OR (95% CI)*	$P_{heterogeneity}$	I^2 (%)
Dominant model (BB vs Bb+bb)			
Overall	1.037 (0.932, 1.153)	0.341	10.3
Asians	0.945 (0.523, 1.707)	0.316	15.3
Caucasians	1.040 (0.933, 1.159)	0.299	16.7
TNM stage	0.980 (0.752, 1.278)	0.960	0
Gleason score	1.046 (0.763, 1.434)	0.524	0
Recessive model (BB+Bb vs bb)			
Overall	0.838 (0.709, 0.990)	0	64.2
Asians	0.675 (0.398, 1.147)	0.001	74.1
Caucasians	0.937 (0.855, 1.026)	0.544	0
TNM stage	0.701 (0.425, 1.156)	0.04	57.2
Gleason score	0.791 (0.445, 1.407)	0.006	72.6

Table 4. Results of the analysis for TaqI gene polymorphism

Group	*OR (95% CI)*	$P_{heterogeneity}$	I^2 (%)
Dominant model (TT vs Tt+tt)			
Overall	1.127 (1.023, 1.242)	0.197	20.8
Asians	1.291 (1.030, 1.617)	0.294	16.7
Caucasians	1.093 (0.982, 1.217)	0.239	21.5
TNM stage	1.432 (0.981, 2.090)	0.02	60.1
Gleason score	1.629 (0.882,3.009)	0.001	75.9
Recessive model (TT+Tt vs tt)			
Overall	1.066 (0.930, 1.222)	0.436	1.5
Asians	2.199 (1.036, 4.671)	0.7	0
Caucasians	1.037 (0.903, 1.192)	0.457	0
TNM stage	1.205 (0.938, 1.547)	0.411	2.5
Gleason score	0.891 (0.654,1.215)	0.193	32.4

Table 5. Results of the analysis for ApaI gene polymorphism

Group	*OR (95% CI)*	$P_{heterogeneity}$	I^2 (%)
Dominant model (AA vs Aa+aa)			
Overall	1.027 (0.769, 1.371)	0.031	52.6
Asians	1.424 (1.048, 1.935)	0.461	0
Caucasians	0.825 (0.668, 1.019)	0.119	53.1
TNM stage	1.280 (0.617, 2.655)	0.028	72.1
Gleason score	0.891 (0.686, 1.157)	0.602	0
Recessive model (AA+Aa vs aa)			
Overall	0.942 (0.808, 1.098)	0.797	0
Asians	1.047 (0.849, 1.293)	0.891	0
Caucasians	0.836 (0.668, 1.046)	0.644	0
TNM stage	0.913 (0.692, 1.205)	0.428	0
Gleason score	-	-	-

Polymorphism site ApaI

The heterogeneity test indicated a significant heterogeneity in the dominant model of 10 studies (p=0.031, I^2=52.6%) evaluated for the ApaI polymorphism site. As a result, the random-effect model was applied. No significant association was found between the ApaI gene polymorphism and prostate cancer risk in either the dominant model (OR=1.027, 95%CI 0.769,1.371) or the recessive model (OR=0.942, 95%CI 0.808,1.098) of overall studies. In the stratified analyses for ethnicity, TNM stage, and Gleason score, no specific relationship was found between the ApaI gene polymorphism and prostate cancer in either the dominant or recessive model (Table 5).

Discussion

Prostate cancer is considered a multi-factor-induced disease, which can only ultimately be diagnosed by pathological examination (prostate biopsy). PSA is widely applied for prostate cancer screening. Nevertheless, neither biopsy nor PSA are suitable for detecting the early-stage prostate cancer. Therefore, a new diagnostic method that can illustrate an individual's susceptibility to prostate cancer is eagerly needed. With the introduction of new genetic technology, it may be possible to find a genetic biomarker to use for early detection of prostate cancer [70]. Many genetic epidemiological studies have therefore been conducted to assess the association between genetic polymorphisms and prostate cancer, including variants in the androgen receptor (AR) gene [71] and the angiotensin I-converting enzyme gene [2]. The VDR gene has earned

special attention because abundant evidence has clearly demonstrated a potential effect of vitamin D on antiproliferation, prodifferentiation and proapoptosis [5]. Numerous individual epidemiological studies have illustrated a potential relationship between the VDR gene polymorphisms and prostate cancer risk, however, the results across studies have been equivocal. Therefore, identifying a new genetic biomarker such as the VDR gene polymorphism to detect prostate cancer remains a challenging topic.

We searched all the epidemiological studies for the results on the relationship between the VDR gene polymorphisms and prostate cancer risk to provide an evidence-based analysis. Compared with previous analyses, our meta-analysis included the 4 main polymorphisms of the VDR gene and also included subgroup analyses consisting of ethnicity, TNM stage and Gleason score. In addition, our study examined both the dominant model and the recessive model for each polymorphic site.

The FokI data yielded conflicting results in the ethnic subgroup analysis. In the Asian subgroup of the dominant model, the FF genotype showed a marginally positive correlation between the FokI gene polymorphism and prostate cancer (OR=1.203, 95%CI 0.997,1.452), whereas a negative correlation was observed in Caucasians (OR=0.905, 95%CI 0.823,0.995). The data therefore suggest that the FF genotype may increase the risk of prostate cancer in individuals of Asian ethnicity. Conversely the FF genotype may be protective in Caucasians. These divergent results indicated that the distribution of FF genotype differed by ethnicity. Between-study heterogeneity was found in the Asian subgroup (I^2=52.7%), which was acceptable according to our knowledge. One potential causal factor contributing to such a heterogeneity was an inadequate number of cases. Bai et al. [20] found no relationship between the FokI polymorphism and prostate cancer (number of cases 122), while Huang et al. [15] found a positive correlation between the FF genotype and prostate cancer (number of cases 416). Further studies of individuals of Asian ethnicity are needed to better clarify the relationship between FokI polymorphism and prostate cancer risk.

When BsmI was analyzed, we found that the BB+Bb genotype were negatively correlated with prostrate cancer for the recessive model of overall studies, which suggests that the bb genotype may play an important part in the carcinogensis of prostate cancer (OR=0.838, 95%CI 0.709,0.990, I^2=64.2%). It is important to point out, however, that severe heterogeneity among the studies was detected. Moreover, when the analysis was stratified by ethnicity, no such relationship was observed. We therefore suggest that these data be interpreted cautiously considering the heterogeneity of the Asian subgroup of the recessive model (OR=0.675, 95%CI 0.398, 1.147, p=0.001, I^2=64.2%). We cannot simply exclude the relationship between the bb genotype and increased risk of prostate cancer in Asians. We found no correlation between the BsmI polymorphism and prostate cancer on TNM stage or Gleason score. As previously stated, because of the severity of heterogeneity, we cannot exclude a relationship between the bb genotype and the risk of prostate cancer. A key reason could be the diversity of the genotype distribution of BsmI in the included studies. Another important factor related to the heterogeneity was the different inclusion criteria in different studies.

When TaqI was analyzed, for the overall analysis of dominant model, we found a statistically significant positive correlation between the TT genotype and prostate cancer (OR=1.127, 95%CI 1.023,1.242, p=0.197, I^2=20.8%). For the ethnicity subgroup analysis the Asian subgroup was positively correlated in both the dominant model (OR=1.291, 95%CI 1.030,1.617) and recessive model (OR=2.199, 95%CI 1.036,4.671) as well. Moreover, no heterogeneity was detected according to Q test and I^2 test for the overall studies. Therefore, the TT genotype could dramatically increase the risk of prostate cancer, especially in individuals of Asian ethnicity. Although the TaqI polymorphism does not change the translation product of the VDR gene, it is thought to be related to mRNA stability and therefore to altered activity of vitamin D via translation regulation [18]. Further research is needed to discover a potential mechanism. The stratified analyses of TNM stage and Gleason score found no significant correlation in either the dominant model or the recessive model. Similar result was found when ApaI was analyzed.

There were several limitations in this meta-analysis, which might affect the final results. First, studies with insufficient data were excluded according to our inclusion criteria. Nevertheless, some of these studies illustrated definite association between VDR polymorphisms and prostate cancer. Second, although no publication bias was detected in this analysis, the strategy of including only pub-

lished studies and the exclusion of studies without sufficient information could result in possible publication bias. Third, although the stratified analysis on ethnicity was conducted, the actual population composition of the included investigations was unavailable, which could cause potential bias in our analysis. Finally, the limited number of studies, especially for the stratified analyses on TNM stage and Gleason score, reduced the power of our analysis. More well-designed studies, including case-control and cohort ones, are needed to improve the confidence of the meta-analysis.

In conclusion, the results from our meta-analysis illustrated that some VDR gene polymorphisms when stratified by ethnicity were related with the risk of prostate cancer, while others remained equivocal. Therefore, further studies with more systematic designs and involving larger populations are needed to undertand the relation between the VDR gene polymorphisms and prostate cancer.

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