

## Review Article

# Vitamin D, Sunlight and Prostate Cancer Risk

Krishna Vanaja Donkena<sup>1</sup> and Charles Y. F. Young<sup>2</sup>

<sup>1</sup> Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

<sup>2</sup> Departments of Urology, Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

Correspondence should be addressed to Charles Y. F. Young, [youngc@mayo.edu](mailto:youngc@mayo.edu)

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Prostate cancer is the second common cancer in men worldwide. The prevention of prostate cancer remains a challenge to researchers and clinicians. Here, we review the relationship of vitamin D and sunlight to prostate cancer risk. Ultraviolet radiation of the sunlight is the main stimulator for vitamin D production in humans. Vitamin D's antiprostata cancer activities may be involved in the actions through the pathways mediated by vitamin D metabolites, vitamin D metabolizing enzymes, vitamin D receptor (VDR), and VDR-regulated genes. Although laboratory studies including the use of animal models have shown that vitamin D has antiprostata cancer properties, whether it can effectively prevent the development and/or progression of prostate cancer in humans remains to be inconclusive and an intensively studied subject. This review will provide up-to-date information regarding the recent outcomes of laboratory and epidemiology studies on the effects of vitamin D on prostate cancer prevention.

## 1. Introduction

The World Health Organization (<http://globocan.iarc.fr/factsheets/cancers/prostate.asp>) indicates that prostate cancer is the second most frequently diagnosed cancer in men (903,000 new cases) and has about 258,000 deaths of this cancer worldwide in 2008. The highest incident rates are among the countries of Australia/New Zealand Western, Northern Europe, and Northern America, and the lowest age-matched incidence rates are those in South-central Asia. In the USA alone, the American Cancer Society (<http://www.cancer.org/Cancer/ProstateCancer/DetailedGuide/prostate-cancer-key-statistics>) estimated death and newly diagnosed cases of prostate cancer were 32,050 and 217,730 men, respectively, in year 2010. Moreover, in USA, the total medical expenditure for prostate cancer treatment was estimated as \$1.3 billion in year 2000, which represents a 30% increase compared to that in 1994. In year 2004, 2.3 billion was estimated for prostate cancer alone [1]. As being a prevalent cancer disease in men, current total cost for PCA prostate cancer treatments in USA would much exceed \$2.3 billion.

Until now, etiology of prostate cancer is still largely unknown. However, it has been suggested that there are

several potential risk factors that may change incidence rates of this cancer, including diet/nutrition, physical activities, and others [2, 3]. Epidemiologic and laboratory studies in nutrition and diet as modifiable risk factors seem to build strong concepts of cancer chemoprevention, a strategy seeking the reduction of cancer risk by the use of chemical agents [3–7]. Conceptually, these agents may be used to prevent, delay, or reverse cancer formation as well as progression. Indeed, due to its long latency of disease onset and high incidence and mortality rates, prostate cancer should be an ideal target for chemoprevention. Proper diets may eventually reduce 50–60% incidence of prostate cancer and many other cancers. Therefore, the potential impact of prostate cancer chemoprevention could be enormous, with respect to prostate cancer patients, in saving life, increasing quality of life and reducing community financial burden.

One such dietary factor having anticancer properties is vitamin D. Vitamin D is very important for normal physiology [8, 9]. The natural way to obtain vitamin D in the body is by exposing skin to sunlight [9, 10]. Avoiding skin carcinogenesis and with many other reasons, skins may not receive sufficient amounts of sunlight exposure for producing enough vitamin D; fortified vitamin D in some commonly consumed foods or supplement forms has been

used for human health purposes. Evidence suggests that vitamin D in our body may be negatively associated with the development and/or progression of several cancers including prostate cancer [10, 11]. As discussed below, although experimental results from *in vitro* and preclinical models showed strong support of antiprostata cancer activities of this vitamin, epidemiological studies and clinical trials on human subjects hardly produce unanimous agreements for the potential of antiprostata cancer efficacy. In this article, we will present recent findings of laboratory results in supporting of vitamin D's antiprostata cancer effects and discuss conflicting epidemiological findings of the vitamin in human subjects.

## 2. Vitamin D Metabolism

Although the previtamin D 7-dehydrocholesterol was thought to be produced in the gut wall cells and transported to skin cells, actually skin cells can synthesize their own 7-dehydrocholesterol, which in turn is converted to a provitamin D, cholecalciferol, or vitamin D<sub>3</sub>, by isomerization upon ultraviolet B (UVB) radiation of sunlight in epidermis [12–14]. Further photoreaction of vitamin D<sub>3</sub> by UVB absorption may generate inactive metabolites. Vitamin D<sub>3</sub> is metabolized to calcidiol 25(OH)D<sub>3</sub> in the liver by the mitochondrial sterol 27-hydroxylase (27-hydroxylase; CYP27A1) and converted to a biologically active vitamin D, calcitriol/1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), by 1 $\alpha$ -hydroxylase (CYP27B1) in the kidney and other tissues including the prostate [15–18]. Usually circulating 25(OH)D<sub>3</sub> level is used to determine vitamin D nutritional status, because it is a predominant form of vitamin D in blood stream and has a much longer half life than that of 1,25(OH)<sub>2</sub>D<sub>3</sub> (i.e., 15 days versus 15 hours) [19]. Importantly, its serum concentrations may be correlated with total vitamin D levels from both endogenous production and dietary uptakes [20–23]. However, 25(OH)D<sub>3</sub> is by no means a perfect marker for active vitamin D<sub>3</sub> status. For example, it is questionable whether measuring 25(OH)D<sub>3</sub> can represent the bioavailability of vitamin D<sub>2</sub> (ergocalciferol, a vitamin D proform derived from fungus products) versus vitamin D<sub>3</sub>. Some studies [24, 25] but not other [26] showed that vitamin D<sub>3</sub> supplementation could increase 25(OH)D<sub>3</sub> to higher levels than the use of vitamin D<sub>2</sub>. In fact, blood 25(OH)D<sub>3</sub> levels can be affected by substrate availability through adiposity sequestration, skin pigmentation, physical activity [20, 27, 28], and the consumption of dietary factors such as genistein and folate [29–32].

As indicated above, 25-hydroxyvitamin D<sub>3</sub> 1 $\alpha$ -hydroxylase or 1 $\alpha$ -hydroxylase (CYP27B1) is also expressed in the prostate, meaning that prostate cells can produce the active form of vitamin D<sub>3</sub>. This enzyme activity has been demonstrated in human primary prostatic cell cultures as well as prostate cancerous cell lines. Obviously, this enzyme may have a role in negatively regulating prostate cell proliferation [33]. Human prostatic cancerous cells seem to have reduced activity or expression levels of 1 $\alpha$ -hydroxylase compared to normal or benign prostatic cells, therefore, losing ability to synthesize 1,25(OH)<sub>2</sub>D<sub>3</sub> [34].

There are not many studies demonstrating intraprostatic concentrations of vitamin D metabolites. One report showed that prostatic 1,25(OH)<sub>2</sub>D<sub>3</sub> levels were higher than that in blood circulation in domestic pigs [35]. Other study found that within 24 hours of intravenous injection of 1,25-dihydroxyvitamin D<sub>3</sub>, less than 1% of the vitamin D in blood was detected in rat prostate tissues [36]. The third study also demonstrated the potential intraprostatic vitamin D metabolism in human prostate [37]. 25OHD<sub>3</sub>, 24,25(OH)<sub>2</sub>D<sub>3</sub>, and 1,25(OH)<sub>2</sub>D<sub>3</sub> were all detected in prostate tissues obtained by prostatectomy. This particular study with a very small sample size seemed to suggest that levels of 24,25(OH)<sub>2</sub>D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub> in the prostate were higher than in serum tested.

One possible mechanism for the reduced expression of 1 $\alpha$ -hydroxylase may be due to hypermethylation or repressive histone modification of its promoter, which could implicate prostate cancer development and progression [38–40]. Other possibility includes posttranslational suppression of enzymatic activity [39, 41].

It was reported that 25(OH)D<sub>3</sub> but not 1,25(OH)<sub>2</sub>D<sub>3</sub> can enhance the expression of 1 $\alpha$ -hydroxylase in cultured prostatic cells [42]. Because of this, the authors of the studies suggested that high concentrations of 25(OH)D<sub>3</sub> might be used as antiprostata cancer agent instead of large doses of 1,25(OH)<sub>2</sub>D<sub>3</sub> to avoid hypercalcemia side-effects.

Opposed to 1 $\alpha$ -hydroxylase, 25-hydroxyvitamin D<sub>3</sub> 24-hydroxylase (CYP24A1) is a catabolic enzyme causing inactivation of 1,25(OH)<sub>2</sub>D<sub>3</sub> that might implicate resistance to antiproliferation effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> [43, 44]. However, some studies suggested that this 24-hydroxylase is downregulated in prostate tumor cells [45]. By examining 30 paired human prostate benign and primary malignant tissues and three prostate cancer cell lines, the study demonstrated that a significant number of malignant tissues had lower mRNA expression and higher promoter methylation levels of the 24-hydroxylase compared to those of benign tissues. In addition, two out of three cancer cell lines tested had high methylation and low expression levels of the enzyme gene. In these two cell lines, that is, PC-3 and LNCaP, treatments with the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine and/or the inhibitor of histone deacetylases trichostatin A can activate the expression of this gene, suggesting that promoter DNA methylation, and repressive histone modifications play roles in repressing its expression [45]. Intriguingly, it has been shown that 1,25(OH)<sub>2</sub>D<sub>3</sub> can induce the expression of the 24-hydroxylase in PC-3, LNCaP, DU145, and primary prostatic stromal cells, perhaps through (VDR) to bind a VDR responsive element (VDRE) [43–45]. A recent study found that a genetic single nucleotide polymorphism in the VDRE of the 24-hydroxylase promoter could reduce the expression and activity of this enzyme [46]. In addition, 1,25(OH)<sub>2</sub>D<sub>3</sub> may modulate the expression of alternative splicing forms of the 24-hydroxylase in prostate cancer cells [47]. The significance of the splicing forms in prostate cells remains unclear. Not surprisingly, the 24-hydroxylase activity in prostate cancer cells could be inversely related to inhibitory proliferation effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> [44]. It was reported that the androgen dihydrotestosterone was

able to inhibit the inducible effect of  $1,25(\text{OH})_2\text{D}_3$  on 24-hydroxylase expression and activity in prostate cancer cells [48, 49]. This seems to indicate that a cross-talk of androgen receptor and VDR was at work. Furthermore, the same group of the authors showed that by suppressing the 24-hydroxylase androgens can largely increase antiproliferative effects of  $1,25(\text{OH})_2\text{D}_3$ . Since prostate stroma may provide an important microenvironment for prostate cancer development, these authors also showed that retinoic acid via retinoic acid receptor alpha inhibited the 24-hydroxylase expression in human prostatic stromal cells P29SN and P32S [50]. When treated with both retinoic acid and  $1,25(\text{OH})_2\text{D}_3$ , synergistic growth inhibitory effects were observed in these cells.

Thus the above studies clearly demonstrated that the 24-hydroxylase is a useful target for increasing anticancer efficacy of vitamin D. Genistein, a soy isoflavone, was shown to be capable of enhancing antiproliferative effect of  $1,25(\text{OH})_2\text{D}_3$  on DU145 cells by repressing the expression of the 24-hydroxylase [51, 52]. Moreover, genistein in nanomolar concentrations was able to inhibit enzymatic activity of the 24-hydroxylase as well as to upregulate the expression of VDR. Recent studies [53, 54] reported that a nonspecific, broad inhibitor of cytochrome P450 enzymes, ketoconazole or a specific 24-hydroxylase inhibitor, RC2204 was used in PC-3 cell culture or xenograft, respectively, to demonstrate that they can suppress 24-hydroxylase activities and enhance antitumor growth potency of  $1,25(\text{OH})_2\text{D}_3$ .

### 3. Action of VDR in Prostate Cancer Cells

Anticancer activities of vitamin D have been suggested to act mainly through its nuclear receptor or VDR. The VDR is a member of nuclear receptor super family, whose functions act as ligand-dependent transcription factor in the nucleus [54–56]. In addition, upon ligand activation, this receptor requires to form a heterodimer with the retinoid X receptor (RXR) in order to bind a specific genomic DNA sequence, that is, a VDRE to activate or repress gene expression [54–56]. RXR of the VDR heterodimer may be subjected to phosphorylation by prolonged activation of the mitogen-activated protein kinase pathway, resulting in the impairment of VDR-mediated prostate cell growth inhibition effects [57]. Recently, a report showed that the vitamin D receptor can form a heterodimer with retinoic acid receptor gamma [58]. Although it has been shown that androgen receptor and VDR may cross talk each other in their pathways [49, 59, 60], the two receptors probably do not have direct interactions. It has been reported that the expression of VDR can be regulated by several hormones including androgens, vitamin D, parathyroid hormone, retinoic acid, and glucocorticoids [55, 56]. However, the regulation of the basal line expression of the receptor is not well studied. Besides, the genomic gene regulation effects, through a so-called nongenomic mechanism, the same receptor activated by vitamin D in the plasma membrane may also have rapid modulation effects on cellular functions [55, 56, 61]. Both genomic and nongenomic effects of VDR have been demonstrated in prostate cells [43, 62, 63]. The question also arises if there is a separate membrane VDR. According to other investigators

[64–66], protein disulfide isomerase family A, member 3 (PDIA3) has been identified as a membrane associated,  $1,25(\text{OH})_2\text{D}_3$  binding protein/receptor that may exhibit some rapid nongenomic actions of  $1,25(\text{OH})_2\text{D}_3$ . PDIA3 with  $1,25(\text{OH})_2\text{D}_3$  binding ability has recently been detected in several human prostate cell lines [66]. The significance of PDIA3-mediated  $1,25(\text{OH})_2\text{D}_3$  action in prostate cancer cells requires further studies.

Vitamin D mainly via VDR's genomic effects may suppress prostate cancer cellular dysfunctions including the inhibition of cell proliferation, cell cycle progression, cell invasiveness, angiogenesis, or induction of cell differentiation and apoptosis [67, 68]. These prostate cancer cellular functions can be altered by the ability of ligand-activated VDR to change the expression and/or functions of many downstream key genes, for example, decrease of c-Myc [69, 70], telomerase [71], *BCL-2* [72],  $\alpha 6$  and  $\beta 4$  integrins [73], cyclin-dependent kinase 2 (*CDK2*) activity [74], and phosphorylation of the retinoblastoma protein [75], and increase of the (CDK) inhibitors *p21<sup>Waf/Cip1</sup>* and *p27<sup>Kip1</sup>* [74, 76–78] and growth arrest and DNA damage-inducible gene gamma (*GADD45 $\gamma$* ) [79]. In addition, active vitamin D<sub>3</sub> and its analogs may increase the expression of E-cadherin [78] and the activity of tissue inhibitor of metalloproteinase-1 (TIMP-1) as well as decrease the expression and activity of MMP-9 [80], thereby decreasing invasive and metastatic potentials of prostate cancer cells studied.

Many angiogenic and proinflammatory regulators may play crucial roles in prostate tumorigenesis and progression [81–84]. It has been shown that  $1\alpha,25$ -dihydroxyvitamin D<sub>3</sub> [ $1,25(\text{OH})_2\text{D}_3$ ] inhibits tumor angiogenesis *in vitro* and *in vivo* [85]. Interleukin 6 (IL-6) is one such molecule that may implicate in prostate cancer progression. Calcitriol was shown to inhibit tumor necrosis factor  $\alpha$  mediated increase of IL-6 in primary prostate cells [86]. Another pro-inflammatory cytokine interleukin 8 (IL-8) may also have angiogenic and tumorigenic potentials in prostate cancer [83]. Calcitriol can lower the IL-8 levels in two immortalized human prostate epithelial cell lines (HPr-1 and RWPE-1) and three prostate cancer cell lines (i.e., LNCaP, PC-3, and DU145) [87], by reducing NF $\kappa$ B p65 nuclear translocation and gene transcription of IL-8. Calcitriol may have radiosensitization effects on prostate cancer cells by suppressing ion radiation-mediated activation of the NF $\kappa$ B related RelB, which subsequently reduces the transcription of manganese superoxide dismutase (MnSOD) [88]. Increased antioxidant activities of MnSOD can cause radiation resistant. It was reported that calcitriol reduces the protein and mRNA expressions of both the hypoxia-inducible factor (HIF)-1 $\alpha$  subunit and the vascular endothelial growth factor (VEGF) in several human cancer cells including prostate cancer cells under hypoxia conditions [89]. Furthermore, using transgenic adenocarcinoma of the mouse prostate (TRAMP)-2 tumors transplanted into either wild-type or VDR knockout (KO) mice with calcitriol treatments, it was found that tumors in the KO mice were larger than that in wild-type mice, suggesting ligand-induced VDR growth inhibitory effects in wild-type mice. Similarly, enlarged blood vessels and increased vessel volume in TRAMP-2 tumors

were found in the VDR knockout mice, suggesting that antitumor angiogenesis was directly affected through VDR and calcitriol at tumor sites. HIF-1 $\alpha$ , VEGF, angiopoietin 1, and platelet-derived growth factor-BB levels were increased in tumors from KO mice [90]. The importance of VDR in negatively regulating prostate cancer progression is further confirmed in the LPB-Tag model of prostate in VDR knockout versus VDR wild-type mice [60].

Vitamin D may also influence genes in the metabolism of prostaglandins (PGs) that can induce the inhibition of the expression of the PG synthesizing cyclooxygenase-2 (COX-2) and the PG receptors EP2 and FP, and increased expression of PG inactivating 15-prostaglandin dehydrogenase [67, 91–93]. The alteration of these gene expressions would decrease the cell proliferative stimulus of PGs in prostate cancer cells.

#### 4. Sunlight Exposure and Prostate Cancer

Vitamin D deficiency or insufficiency has become a public health concern in large proportions of the populations in the United States and Northern European countries especially among ethnic groups with dark skin, and others such as those with physical inactive and little sun exposure. As mentioned above, sunlight exposure may increase vitamin D synthesis in the skin which has been thought to be beneficial to protect from some types of cancer, including prostate cancer. Of course, prolonged sunlight or UVB exposure without adequate skin protection can cause skin cancer. Indeed, there are many ecological and observational studies including case-control and prospective studies [94–106] showing a high degree of consistent results that sunlight exposure is inversely associated with prostate cancer risk. Geographic regions with less sunlight exposure seem to be related to an increased prostate cancer mortality [96, 97]. Studies [102, 103] also showed that patients diagnosed with prostate cancer in summer may have higher survival rates than that of patients in the winter due to seasonal UV irradiance levels. There are epidemiological studies [101, 107–109] suggesting that the ethnic groups with dark skin could be associated with high prostate cancer risk because high skin pigments may reduce the absorption of UV radiation. However, a study reported that black men did not increase their prostate cancer risk in terms of sunlight exposure when compared to white counterparts [110]. There is epidemiological evidence that shows skin cancer patients may have reduced risk for procuring certain types of secondary cancer including prostate cancer [111–113]. However, the result of a study did not support the notion that sunlight induced skin cancer can protect against prostate cancer risk [114]. Although there are overwhelming number of studies indicating that UVB exposure from sunlight consistently reduce risk of prostate cancer development and progression, yet not every study fully supports this idea. For instance, a population-based nested case-control study and meta-analysis [115] only provided a limited support for the effect of sunlight on reducing prostate cancer. Also, a study showed contradictory results that high levels of UVR exposure may be positively associated with the risk of prostate cancer mortality [116].

Another group of investigators [117, 118] used their ecological approach to conduct a multicountry study consisting of 33 countries worldwide to evaluate the effect of residential UV exposure on cancer incidence. The study results did not prove that sunlight/UV exposure could decrease the risk of various cancers including prostate cancer. The investigators of this study emphasized the importance of the control for various confounders that might have been overlooked in other studies.

#### 5. Circulating Vitamin D and Prostate Cancer Risk

Unlike most of sunlight exposure studies, linking circulating vitamin D levels or vitamin D uptakes with the reduction of prostate cancer risk has not been very successful. Of course, there are some studies [119–122] seeming to support the notion that high levels of serum vitamin D have protection effects against prostate cancer. A US study indicated that serum 1,25 vitamin D<sub>3</sub> was negatively associated with prostate cancer restricted to men above median age of 57 years [119]. In a Finnish study with 13 yr followup of about 19,000 men, the authors found that low serum 25(OH)D<sub>3</sub> concentrations were associated with high risk of earlier exposure to and more aggressive prostate cancer [120]. In addition, there are two more recent reports [121, 122] with an 18 yr or a 44.0 month median time followup, respectively, suggesting that both circulating 25(OH)D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub> or 25(OH)D<sub>3</sub> alone at median or higher than medium levels have lower risk for prostate cancer progression.

In fact, there are a good number of studies demonstrating no inverse relationship between circulating vitamin D metabolite levels and risk of prostate cancer [123–129]. For example, a very recent meta-analysis study [127] of relationship of serum 25-hydroxyvitamin D<sub>3</sub> levels with colorectal, breast and prostate cancer and colonic adenoma was reported, showing, although there was a consistent inverse relationship between circulating vitamin D metabolite levels and colorectal cancer, no support for an association for breast and prostate cancer was found. Another recent nested prospective case-cohort study examined older men (65 or >) participating in the multicenter Osteoporotic Fractures in Men study for serum 25-OH vitamin D<sub>3</sub> levels [128]. In this prospective cohort, the authors concluded that there was no association of serum 25-OH vitamin D<sub>3</sub> levels with subsequent prostate cancer risk. A large nested case-control study [119] with a European population [129] indicated no beneficial effects of blood vitamin D levels for reducing prostate cancer risk. Another recent large prospective study [130] also did not show that vitamin D had effects on the reduction of prostate cancer risk. On the other hand, the same report stated that higher blood 25(OH)D<sub>3</sub> levels could be related to increased risk of aggressive prostate cancer. A longitudinal nested case-control study was performed on Nordic men consisting of [131] 622 prostate cancer cases and 1,451 matched controls for serum 25(OH)D<sub>3</sub> levels. Intriguingly, the study revealed a U-shaped relationship of prostate cancer risk and 25(OH)D<sub>3</sub> levels, namely, both



low ( $\leq 19$  nmol/L) and high ( $\geq 80$  nmol/L) 25(OH) $D_3$  serum levels showed positive association with prostate cancer risk, whereas normal average serum concentrations of 25(OH) $D_3$  (40–60 nmol/L) gave the lowest risk of prostate cancer.

It may be worth mentioning that a nested case-control study [132] in the Health Professionals Follow-up Study was designed to determine the relationship of plasma 25(OH) $D_3$  and 1,25(OH) $_2D_3$  with prostate cancer risk. Although it was found that there were no statistically significant differences between the two plasma vitamin D metabolites and the overall prostate cancer risk, a significant inverse association existed between 25-hydroxyvitamin D and advanced prostate cancer when comparing quintile 4 or quintile 5 to the bottom quintile. Moreover, when men who were clinically deficient either vitamin D metabolite compared to those who were not deficient, deficient group showed a 38% lower risk of total prostate cancer, a 58% lower risk of poorly differentiated prostate cancers, and a 49% lower risk of aggressive prostate cancers. An earlier study also reported that only older group ( $>61$  years) with plasma 25(OH) $D_3$  lower than the median showed a 57% reduction of cancer risk [133]. These unexpected results warrant further investigation.

Recent studies also could not find any association of vitamin D uptake with prostate cancer risk [134, 135]. With a mean followup of 8 years, examining men involved in the Multiethnic Cohort Study (1993–2002) using quantitative food frequency questionnaire revealed that there was no significant association between calcium and vitamin D intake and risk of prostate cancer. In the Prostate Cancer Prevention Trial (United States and Canada, 1994–2003) with 9,559 participants, dietary or supplemental intakes of vitamin D as well as many other factors analyzed did not show any significant correlation with prostate cancer risk. A meta-analysis of many observational studies regarding dairy products, calcium, and vitamin D intake and the risk of prostate cancer was also conducted [136]. This study concluded that there was no significant association of dietary vitamin D uptake with the cancer risk.

## 6. Genetic Variations in Vitamin D Signaling Pathways and Prostate Cancer Risk

Since expression and functions of VDR, related vitamin D metabolic enzymes and vitamin D signal downstream genes are associated with vitamin D's action, genetic variation such as the single nucleotide polymorphisms (SNP) in these genes may have impact on vitamin D action in cancer cells. Therefore, analysis of the correlation of these polymorphisms with cancer risk would be highly meaningful. Among more than 470 polymorphisms in the VDR gene [11, 17], there may be six polymorphisms including the Fok1, Cdx2, Bsm1, Apa1, and Taq1 SNPs, and Poly(A) microsatellite to be frequently studied in relation to risk of cancer including prostate cancer.

The five SNPs mentioned above are usually detected by using restriction fragment length polymorphism or direct sequencing, and the PolyA microsatellite at the 3'-untranslated region (3'UTR) of the VDR gene is measured with variable number of tandem repeat. These polymorphisms are located in 5' regulatory, coding, intron, or 3'UTR

of the VDR gene. The functionality of these polymorphisms used in epidemiological and observational studies for cancer risk may have been somewhat demonstrated by experimental approaches yet not completely resolved. For instance, Fok1, located in the exon 2, consists of a T to C change resulting in a longer protein translation (ff versus FF). The short VDR protein (i.e., 424 aa) encoded by the Fok1 FF genotype has a higher transcriptional activity than the long ff protein (i.e., 427 aa) [136–139]. Interestingly, it was also reported that individuals with ff genotype may be associated with lower serum 25(OH) $D_3$  levels than those in individuals with FF genotype [140]. For Cdx2 polymorphism, it has a change from G to A in the binding site for an intestinal-specific transcription factor, CDX2, within the VDR promoter [141], the G allele of the Cdx-2 binding element has a significantly lower electrophoretic gel mobility shift assay activity and a lower transcription assay activity than that of the A allele. Although the PolyA microsatellite polymorphism has been suggested to be important for mRNA stability, studies show inconsistent conclusions, in which a report showed that the length of the UTR has no effect on mRNA stability [142], but other demonstrated that it has stability effects when interacting with Fok1 F allele [139]. Both Bsm1 and Apa1 SNPs are located in the intron near exon 9, and Taq1 SNP is located at exon 9 (which contains the 3'UTR). The potential function roles of these three SNPs in the regulation of VDR mRNA expression were examined briefly, but no conclusive results were produced [142–145].

Indeed, genetic heterogeneity effects of vitamin D signaling related genes, especially the VDR gene, have been attractive research subjects for cancer risk studies and potential applications in cancer prevention strategy. Although there are many of this type of epidemiological analyses [106, 146–172] as listed in Table 1, the apparent question is whether genetic variants of those genes involved in vitamin D pathways have real effects on prostate cancer risk. However, as shown in Table 1, the outcomes remain inconsistent and perhaps conflicting and require further studies.

## 7. Concluding Remarks

Although *in vivo* and *in vitro* laboratory studies provide strong evidence in supporting that vitamin D via VDR possesses antiprostata cancer activities, epidemiological studies have not shown consistent results for vitamin D's antiprostata cancer activities. Among many epidemiological studies, especially those studies with measuring blood vitamin D levels produced the least overall supporting evidence for the antiprostata cancer activities. One drawback of this type of studies is that the designs mainly relied on one measurement of serum/plasma vitamin D metabolites without multiple measurements in an adequate follow-up time. The conclusion from these epidemiologic studies for prostate cancer as well as other cancers are also reflected in the Institute of Medicine's 2011 report on dietary reference intakes for calcium and vitamin D [9] which could not make any conclusion if vitamin D has anticancer activities in humans. However, the inconsistency of outcomes of the epidemiologic studies may still provide a great deal of

TABLE 1: Summary of outcomes of 28 studies on the association of analysis of polymorphisms in vitamin D signal related genes with prostate cancer risk.

Gene(s)	Polymorphism(s)	Case/control	Results
(1) VDR	Taq1	108/170	The tt genotype reduced cancer risk compared to the Tt or TT genotype [146]
(2) VDR & AR	AR CAG repeat and VDR PolyA	57/169	The short CAG or long PolyA increased cancer risk and both increased risk of advanced cancer [147]
(3) VDR	BsmI, ApaI, and Taq1	222/128 A Japanese population	Only BsmI BB or Bb genotype was associated with one-third of the risk of prostate cancer in a Japanese population [148]
(4) VDR	BsmI, ApaI, and Taq1	81 familial cases/105 A Japanese population	No association [149]
(5) VDR	FokI, BsmI, Taq1, and PolyA	A meta-analysis of 14 studies	No association [150]
(6) VDR	FokI, BsmI, ApaI, TaqI, and PolyA	African Americans (113/121) Whites (232/171)	No association but FokI FF genotype was associated with cancer risk in young African American [151]
(7) VDR	Apal and Taq1	165/200 A Brazilian population	No association [152]
(8) VDR	BsmI, FokI, and PolyA	559/523	No association with overall cancer risk, but the BsmI bb was associated with a modest risk increase of localized prostate cancer compared to the BB genotype [153]
(9) VDR	BsmI, ApaI, and TaqI	160/205 A Taiwanese population	No overall cancer risk association with ApaI and TaqI. But the BsmI BB and Bb versus the bb genotypes were negatively associated with risk of cancer [154]
(10) VDR	BsmI and TaqI	428 white men and 310 African-American men	No association with overall cancer risk except that the BsmI B allele was inversely associated with recurrence of locally advanced cancer among white men [155]
(11) VDR	CDX-2, Fok1, and Taq1	368 cancer/243 BPH	CDX-2 GA and AA and Fok1 ff were associated with increased prostate cancer risk in men with UVR exposure above the median, but genotype combinations such as GGTT and FFTT were associated with reduced risk in the higher UVR exposure group [106]
(12) VDR	Cdx2, Fox1, Taq1, and Bgl II	450/455	FokI FF or Ff, TaqI tt, and BglI BB genotypes not Cdx2 genotypes may significantly protect against cancer progression with high sun exposure [156]
(13) VDR	Fok1	128/147 An Indian population	Only the FF genotype showed an increased cancer risk [157]
(14) VDR	FokI and BsmI	812/713 An Australian population	These two SNPs had no effect on prostate cancer risk [158]
(15) VDR, VDBP	Novel sequence variations in the two promoters	165/324 African-American men	A novel VDR-5132 T/C SNP (i.e., CC genotype) was found to increase cancer risk in African-American men [159]
(16) VDR	TaqI, BsmI, ApaI, FokI, and Poly(A)	A meta-analysis of 26 studies	No association [160]
(17) VDR, CYP27A1, CYP24A1	38 SNPs	630/565	Only two VDR SNP loci, rs2107301, and rs2238135, with TT and CC genotypes, respectively, had a 2- to 2.5-fold increased risk of prostate cancer compared with the respective homozygote CC and TT alleles [161]
(18) VDR	Fok1	1,066/1,618	The Fok1 ff genotype was found to increase cancer risk when 25(OH)D levels were lower than the median [162]

TABLE 1: Continued.

Gene(s)	Polymorphism(s)	Case/control	Results
(19) VDR	SNPs in haplotype block subregions C2 and C1	430 cancer/430 BPH UK men	Haplotype block C including G(3436)-A(3944)-C(20965)-C(30056), (G or C)-A-C-C, and G-A-(C or T)-C was found significantly to increase cancer risk in men with very low UVR exposure [163]
(20) VDR	Apa I, BsmI, and Taq I	133/157 a Turkish population	Prostate cancer risk was found to be increased in those whose genotypes were either the Aa or aa compared to those with the AA type [164]
(21) VDR, SRD5A2	Fox1 or Cdx2 and SRD5A2 V89L	444/488 Non-Hispanic White (NHW) men 141/273 Hispanic White (HW) men	Prostate cancer risk was increased by the interaction of the genotype with VDR SRD5A2 V89L VV <i>FokI</i> TT/CT genotypes in NHW men and the interaction of the SRD5A2 V89L VV genotype with VDR CDX2 GG genotypes in HW men [165]
(22) CYP27A1, GC, CYP27B1, CYP24A1, VDR, 7 vitamin D signaling downstream genes	212 SNPs	749/781	No association with overall cancer risk except that the BsmI and rs11574143 were associated with cancer risk only in men with lower 25(OH)D levels [166]
(23) VDR	FokI, Cdx2, BsmI, ApaI, and TaqI	1,604 cases plus a meta-analysis of 13 studies	The BsmI (bb versus BB +Bb), ApaI (aa versus AA+Aa), and TaqI (Tt + tt versus TT) SNPs were determined to be associated with high Gleason scores/cancer progression [167]
(24) VDR		a meta-analysis of several cancers	For prostate cancer, Caucasian men with BsmI Bb would have significant reduction in cancer risk compared with bb genotype. It also concluded that FokI ff would contribute to the increase in cancer risk compared with FF genotype [168]
(25) VDR	TaqI, ApaI, BsmI, FokI, and CDX2	a meta-analysis of 36 studies	The TaqI t and BsmI B alleles were found to be inversely associated with the risk. the ApaI a allele was contributed to the reduction of cancer risk only in Asian populations, and the FokI f allele was contributed to increased cancer risk only in Caucasian populations [169]
(26) VDR, CYP27B1, CYP24A1	48 SNPs	827/787	No significant evidence of association of any of these SNPs (including VDR <i>BsmI</i> , <i>TaqI</i> , <i>ApaI</i> and <i>FokI</i> ) with overall cancer risk or risk for tumor aggressiveness was found [170]
(27) VDR	FokI, BsmI, Tru9I, ApaI, and TaqI	122/130 A Chinese Han population	Only BsmI B allele was found to be inversely associated with cancer risk compared with the b allele [171]
(28) VDR, CYP19A1, CYP17A1, and AR	common SNPs in VDR, CYP17A1 CYP19A1 CAG repeat in AR	95 Italian hereditary familial prostate cancer (HFPC) cases/378 sporadic cancer	Only SNP rs10735810 (VDR1) T/T genotype in exon 4 of and SNP rs731236 (VDR2) T/T genotype in exon 11 of VDR showed positive interaction resulting in increased cancer risk for the HFPC patients compared to sporadic cancer [172]

opportunities for further looking into and understanding very complexed vitamin D pathways for human cancer prevention. For example, some studies indicated that high level of serum vitamin D may, instead of decrease, increase risk of prostate cancer development or progression. The possible explanation seems to involve in local prostatic expression levels of the two vitamin D metabolizing enzymes, CYP27B1 and CYP24A1, as discussed above, which can be regulated by vitamin D, androgens and other dietary compounds. Potentially, overexpression of CYP24A1 could

induce vitamin D resistance and promote risk for prostate cancer. Measuring serum vitamin D may not represent its levels at local tissues. Moreover, there is almost no information about the regulation and activities of these enzymes, as well as vitamin D metabolites in normal and cancerous prostate tissues under the *in vivo* conditions. Similarly, there is lacking of comprehensive information of *in vivo* VDR-mediated pathways in prostate cancer tissues. This could involve the interactions of genetic, epigenetic, and other endogenous and environmental factors at local

tissue levels and will present challenges for developing more sophisticated study designs in the near future.

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## References

- [1] J. Lipscomb, "Estimating the cost of cancer care in the United States: a work very much in progress," *Journal of the National Cancer Institute*, vol. 100, no. 9, pp. 607–610, 2008.
- [2] D. G. Bostwick, H. B. Burke, D. Djakiew et al., "Human prostate cancer risk factors," *Cancer*, vol. 101, supplement 10, pp. 2371–2490, 2004.
- [3] E. A. Klein, "Chemoprevention of prostate cancer," *Annual Review of Medicine*, vol. 57, pp. 49–63, 2006.
- [4] J. F. Lowe and L. A. Frazee, "Update on prostate cancer chemoprevention," *Pharmacotherapy*, vol. 26, no. 3, pp. 353–359, 2006.
- [5] S. M. Lippman and J. J. Lee, "Reducing the "risk" of chemoprevention: defining and targeting high risk—2005 AACR cancer research and prevention foundation award lecture," *Cancer Research*, vol. 66, no. 6, pp. 2893–2903, 2006.
- [6] S. Shukla and S. Gupta, "Dietary agents in the chemoprevention of prostate cancer," *Nutrition and Cancer*, vol. 53, no. 1, pp. 18–32, 2005.
- [7] I. M. Thompson, C. M. Tangen, P. J. Goodman, M. S. Lucia, and E. A. Klein, "Chemoprevention of prostate cancer," *Journal of Urology*, vol. 182, no. 2, pp. 499–508, 2009.
- [8] K. A. Kennel, M. T. Drake, and D. L. Hurley, "Vitamin D deficiency in adults: when to test and how to treat," *Mayo Clinic Proceedings*, vol. 85, no. 8, pp. 752–757, 2010.
- [9] A. C. Ross, J. E. Manson, S. A. Abrams et al., "The 2011 report on dietary reference intakes for calcium and vitamin D from the institute of medicine: what clinicians need to know," *The Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 1, pp. 53–58, 2011.
- [10] M. F. Holick, "Vitamin D and sunlight: strategies for cancer prevention and other health benefits," *Clinical Journal of the American Society of Nephrology*, vol. 3, no. 5, pp. 1548–1554, 2008.
- [11] C. D. Toner, C. D. Davis, and J. A. Milner, "The vitamin D and cancer conundrum: aiming at a moving target," *Journal of the American Dietetic Association*, vol. 110, no. 10, pp. 1492–1500, 2010.
- [12] M. F. Holick, E. Smith, and S. Pincus, "Skin as the site of vitamin D synthesis and target tissue for 1,25-dihydroxyvitamin D<sub>3</sub>: use of calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) for treatment of psoriasis," *Archives of Dermatology*, vol. 123, no. 12, pp. 1677–1683, 1987.
- [13] A. W. Norman, "Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system," *American Journal of Clinical Nutrition*, vol. 67, no. 6, pp. 1108–1110, 1998.
- [14] H. H. Glossmann, "Origin of 7-dehydrocholesterol (provitamin D) in the skin," *Journal of Investigative Dermatology*, vol. 130, no. 8, pp. 2139–2141, 2010.
- [15] B. A. Ingraham, B. Bragdon, and A. Nohe, "Molecular basis of the potential of vitamin D to prevent cancer," *Current Medical Research and Opinion*, vol. 24, no. 1, pp. 139–149, 2008.
- [16] D. Gupta, C. A. Lammersfeld, K. Trukova, and C. G. Lis, "Vitamin D and prostate cancer risk: a review of the epidemiological literature," *Prostate Cancer and Prostatic Diseases*, vol. 12, no. 3, pp. 215–226, 2009.
- [17] M. L. McCullough, R. M. Bostick, and T. L. Mayo, "Vitamin D gene pathway polymorphisms and risk of colorectal, breast, and prostate cancer," *Annual Review of Nutrition*, vol. 29, pp. 111–132, 2009.
- [18] L. A. Mucci and D. Spiegelman, "Vitamin D and prostate cancer risk—a less sunny outlook?" *Journal of the National Cancer Institute*, vol. 100, no. 11, pp. 759–761, 2008.
- [19] G. Jones, "Pharmacokinetics of vitamin D toxicity," *American Journal of Clinical Nutrition*, vol. 88, no. 2, pp. 582S–586S, 2008.
- [20] S. A. Talwar, J. F. Aloia, S. Pollack, and J. K. Yeh, "Dose response to vitamin D supplementation among postmenopausal African American women," *American Journal of Clinical Nutrition*, vol. 86, no. 6, pp. 1657–1662, 2007.
- [21] R. P. Heaney, K. M. Davies, T. C. Chen, M. F. Holick, and M. J. Barger-Lux, "Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol," *American Journal of Clinical Nutrition*, vol. 77, no. 1, pp. 204–210, 2003.
- [22] J. F. Aloia, M. Patel, R. DiMaano et al., "Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1952–1958, 2008.
- [23] K. D. Cashman, T. R. Hill, A. J. Lucey et al., "Estimation of the dietary requirement for vitamin D in healthy adults," *American Journal of Clinical Nutrition*, vol. 88, no. 6, pp. 1535–1542, 2008.
- [24] H. M. Trang, D. E. Cole, L. A. Rubin, A. Pierratos, S. Siu, and R. Vieth, "Evidence that vitamin D<sub>3</sub> increases serum 25-hydroxyvitamin D more efficiently than does vitamin D<sub>2</sub>," *American Journal of Clinical Nutrition*, vol. 68, no. 4, pp. 854–858, 1998.
- [25] L. A. G. Armas, B. W. Hollis, and R. P. Heaney, "Vitamin D<sub>2</sub> is much less effective than vitamin D<sub>3</sub> in humans," *Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 11, pp. 5387–5391, 2004.
- [26] M. F. Holick, R. M. Biancuzzo, T. C. Chen et al., "Vitamin D<sub>2</sub> is as effective as vitamin D<sub>3</sub> in maintaining circulating concentrations of 25-hydroxyvitamin D," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 3, pp. 677–681, 2008.
- [27] A. C. Looker, "Do body fat and exercise modulate vitamin D status?" *Nutrition Reviews*, vol. 65, no. 8, pp. S124–S126, 2007.
- [28] L. B. Yanoff, S. J. Parikh, A. Spitalnik et al., "The prevalence of hypovitaminosis D and secondary hyperparathyroidism in obese black Americans," *Clinical Endocrinology*, vol. 64, no. 5, pp. 523–529, 2006.
- [29] S. Chennaiah, V. Vijayalakshmi, and C. Suresh, "Effect of the supplementation of dietary rich phytoestrogens in altering the vitamin D levels in diet induced osteoporotic rat model," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 21, no. 1–2, pp. 268–272, 2010.
- [30] H. S. Cross and E. Kallay, "Regulation of the colonic vitamin D system for prevention of tumor progression: an update," *Future Oncology*, vol. 5, no. 4, pp. 493–507, 2009.
- [31] A. Hossein-nezhad, K. Mirzaei, Z. Maghbooli, A. Najmafshar, and B. Larijani, "The influence of folic acid supplementation on maternal and fetal bone turnover," *Journal of Bone and Mineral Metabolism*, vol. 29, no. 2, pp. 186–192, 2010.



- [32] H. S. Cross, T. Nittke, and M. Peterlik, "Modulation of vitamin D synthesis and catabolism in colorectal mucosa: a new target for cancer prevention," *Anticancer Research*, vol. 29, no. 9, pp. 3705–3712, 2009.
- [33] T. C. Chen, "25-hydroxyvitamin D-1 alpha-hydroxylase (CYP27B1) is a new class of tumor suppressor in the prostate," *Anticancer Research*, vol. 28, no. 4A, pp. 2015–2017, 2008.
- [34] L. W. Whitlatch, M. V. Young, G. G. Schwartz et al., "25-hydroxyvitamin D-1alpha-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 81, no. 2, pp. 135–140, 2002.
- [35] J. Rungby, L. Mortensen, K. Jakobsen, A. Brock, and L. Mosekilde, "Distribution of hydroxylated vitamin D metabolites [25(OH)<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub>] in domestic pigs: evidence that 1,25(OH)<sub>2</sub>D<sub>3</sub> is stored outside the blood circulation?" *Comparative Biochemistry and Physiology*, vol. 104, no. 3, pp. 483–484, 1993.
- [36] B. R. Konety, G. Somogyi, A. Atan, J. Muindi, M. B. Chancellor, and R. H. Getzenberg, "Evaluation of intraprostatic metabolism of 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol) using a microdialysis technique," *Urology*, vol. 59, no. 6, pp. 947–952, 2002.
- [37] Y. R. Lou, S. Qiao, R. Talonpoika, H. Syväla, and P. Tuohimaa, "The role of vitamin D3 metabolism in prostate cancer," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 92, no. 4, pp. 317–325, 2004.
- [38] T. C. Chen, L. Wang, L. W. Whitlatch, J. N. Flanagan, and M. F. Holick, "Prostatic 25-hydroxyvitamin D-1alpha-hydroxylase and its implication in prostate cancer," *Journal of Cellular Biochemistry*, vol. 88, no. 2, pp. 315–322, 2003.
- [39] J. F. Ma, L. Nonn, M. J. Campbell, M. Hewison, D. Feldman, and D. M. Peehl, "Mechanisms of decreased Vitamin D 1alpha-hydroxylase activity in prostate cancer cells," *Molecular and Cellular Endocrinology*, vol. 221, no. 1-2, pp. 67–74, 2004.
- [40] M. Khorchide, D. Lechner, and H. S. Cross, "Epigenetic regulation of vitamin D hydroxylase expression and activity in normal and malignant human prostate cells," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 93, no. 2-5, pp. 167–172, 2005.
- [41] L. Wang, K. S. Persons, D. Jamieson et al., "Prostate 25-hydroxyvitamin D-1alpha-hydroxylase is up-regulated by suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor," *Anticancer Research*, vol. 28, no. 4A, pp. 2009–2013, 2008.
- [42] Y. R. Lou, I. Laaksi, H. Syväla et al., "25-hydroxyvitamin D3 is an active hormone in human primary prostatic stromal cells," *The FASEB journal*, vol. 18, no. 2, pp. 332–334, 2004.
- [43] R. J. Skowronski, D. M. Peehl, and D. Feldman, "Vitamin D and prostate cancer: 1,25 dihydroxyvitamin D3 receptors and actions in human prostate cancer cell lines," *Endocrinology*, vol. 132, no. 5, pp. 1952–1960, 1993.
- [44] G. J. Miller, G. E. Stapleton, T. E. Hedlund, and K. A. Moffatt, "Vitamin D receptor expression, 24-hydroxylase activity, and inhibition of growth by 1alpha,25-dihydroxyvitamin D3 in seven human prostatic carcinoma cell lines," *Clinical Cancer Research*, vol. 1, no. 9, pp. 997–1003, 1995.
- [45] W. Luo, A. R. Karpf, K. K. Deeb et al., "Epigenetic mechanisms of promigratory chemokine CXCL14 regulation in human prostate cancer cells," *Cancer Research*, vol. 70, no. 14, pp. 5953–5962, 2010.
- [46] A. Roff and R. T. Wilson, "A novel SNP in a vitamin D response element of the CYP24A1 promoter reduces protein binding, transactivation, and gene expression," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 112, no. 1–3, pp. 47–54, 2008.
- [47] J. R. Muindi, A. Nganga, K. L. Engler, L. J. Coignet, C. S. Johnson, and D. L. Trump, "CYP24 splicing variants are associated with different patterns of constitutive and calcitriol-inducible CYP24 activity in human prostate cancer cell lines," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 103, no. 3–5, pp. 334–337, 2007.
- [48] Y. R. Lou and P. Tuohimaa, "Androgen enhances the antiproliferative activity of vitamin D3 by suppressing 24-hydroxylase expression in LNCaP cells," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 99, no. 1, pp. 44–49, 2006.
- [49] Y. R. Lou, N. Nazarova, R. Talonpoika et al., "5alpha-dihydrotestosterone inhibits 1alpha,25-dihydroxyvitamin D3-induced expression of CYP24 in human prostate cancer cells," *Prostate*, vol. 63, no. 3, pp. 222–230, 2005.
- [50] Y. R. Lou, S. Miettinen, H. Kagechika, H. Gronemeyer, and P. Tuohimaa, "Retinoic acid via RARalpha inhibits the expression of 24-hydroxylase in human prostate stromal cells," *Biochemical and Biophysical Research Communications*, vol. 338, no. 4, pp. 1973–1981, 2005.
- [51] H. Farhan, K. Wähälä, and H. S. Cross, "Genistein inhibits vitamin D hydroxylases CYP24 and CYP27B1 expression in prostate cells," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 84, no. 4, pp. 423–429, 2003.
- [52] S. Swami, A. V. Krishnan, D. M. Peehl, and D. Feldman, "Genistein potentiates the growth inhibitory effects of 1,25-dihydroxyvitamin D3 in DU145 human prostate cancer cells: role of the direct inhibition of CYP24 enzyme activity," *Molecular and Cellular Endocrinology*, vol. 241, no. 1-2, pp. 49–61, 2005.
- [53] J. R. Muindi, Y. u. WD, Y. Ma et al., "CYP24A1 inhibition enhances the antitumor activity of calcitriol," *Endocrinology*, vol. 151, no. 9, pp. 4301–4312, 2010.
- [54] A. V. Krishnan, D. L. Trump, C. S. Johnson, and D. Feldman, "The role of vitamin D in cancer prevention and treatment," *Endocrinology and Metabolism Clinics of North America*, vol. 39, no. 2, pp. 401–418, 2010.
- [55] J. W. Pike and M. B. Meyer, "The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D<sub>3</sub>," *Endocrinology and Metabolism Clinics of North America*, vol. 39, no. 2, pp. 255–269, 2010.
- [56] M. T. Mizwicki and A. W. Norman, "The vitamin D sterol-vitamin D receptor ensemble model offers unique insights into both genomic and rapid-response signaling," *Science Signaling*, vol. 2, no. 75, p. re4, 2009.
- [57] Z. Zhang, P. Kovalenko, M. Cui, M. Desmet, S. K. Clinton, and J. C. Fleet, "Constitutive activation of the mitogen-activated protein kinase pathway impairs vitamin D signaling in human prostate epithelial cells," *Journal of Cellular Physiology*, vol. 224, no. 2, pp. 433–442, 2010.
- [58] N. J. Koszewski, J. Herberth, and H. H. Malluche, "Retinoic acid receptor gamma 2 interactions with vitamin D response elements," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 120, no. 4-5, pp. 200–207, 2010.
- [59] S. Murthy, I. U. Agoulnik, and N. L. Weigel, "Androgen receptor signaling and vitamin D receptor action in prostate cancer cells," *Prostate*, vol. 64, no. 4, pp. 362–372, 2005.

- [60] S. Mordan-McCombs, T. Brown, W. L. Wang, A. C. Gaupel, J. Welsh, and M. Tenniswood, "Tumor progression in the LPB-Tag transgenic model of prostate cancer is altered by vitamin D receptor and serum testosterone status," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 121, no. 1-2, pp. 368-371, 2010.
- [61] L. P. Zanello and A. W. Norman, "Rapid modulation of osteoblast ion channel responses by  $1\alpha,25(\text{OH})_2$ -vitamin  $\text{D}_3$  requires the presence of a functional vitamin D nuclear receptor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 6, pp. 1589-1594, 2004.
- [62] C. Crescioli, M. Maggi, G. B. Vannelli et al., "Effect of a vitamin  $\text{D}_3$  analogue on keratinocyte growth factor-induced cell proliferation in benign prostate hyperplasia," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 7, pp. 2576-2583, 2000.
- [63] T. E. Hedlund, K. A. Moffatt, and G. J. Miller, "Stable expression of the nuclear vitamin D receptor in the human prostatic carcinoma cell line JCA-1: evidence that the antiproliferative effects of  $1\alpha, 25$ -dihydroxyvitamin  $\text{D}_3$  are mediated exclusively through the genomic signaling pathway," *Endocrinology*, vol. 137, no. 5, pp. 1554-1561, 1996.
- [64] H. A. Pedrozo, Z. Schwartz, S. Rimes et al., "Physiological importance of the  $1,25(\text{OH})_2\text{D}_3$  membrane receptor and evidence for a membrane receptor specific for  $24,25(\text{OH})_2\text{D}_3$ ," *Journal of Bone and Mineral Research*, vol. 14, no. 6, pp. 856-867, 1999.
- [65] I. Nemere, M. C. Farach-Carson, B. Rohe et al., "Ribozyme knockdown functionally links a  $1,25(\text{OH})_2\text{D}_3$  membrane binding protein ( $1,25\text{D}_3$ -MARRS) and phosphate uptake in intestinal cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 19, pp. 7392-7397, 2004.
- [66] S. Karlsson, J. Olausson, D. Lundh et al., "Vitamin D and prostate cancer: the role of membrane initiated signaling pathways in prostate cancer progression," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 121, no. 1-2, pp. 413-416, 2010.
- [67] A. V. Krishnan and D. Feldman, "Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemoprevention and treatment," *Endocrine-Related Cancer*, vol. 17, no. 1, pp. R19-R38, 2010.
- [68] E. Gocek and G. P. Studzinski, "Vitamin D and differentiation in cancer signaling differentiation," *Critical Reviews in Clinical Laboratory Sciences*, vol. 46, no. 4, pp. 190-209, 2009.
- [69] J. N. Rohan and N. L. Weigel, " $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  reduces c-Myc expression, inhibiting proliferation and causing  $\text{G}_1$  accumulation in C4-2 prostate cancer cells," *Endocrinology*, vol. 150, no. 5, pp. 2046-2054, 2009.
- [70] S. Toropainen, S. Väisänen, S. Heikkinen, and C. Carlberg, "The down-regulation of the human MYC gene by the nuclear hormone  $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  is associated with cycling of corepressors and histone deacetylases," *Journal of Molecular Biology*, vol. 400, no. 3, pp. 284-294, 2010.
- [71] N. Ikeda, H. Uemura, H. Ishiguro et al., "Combination treatment with  $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  and 9-cis-retinoic acid directly inhibits human telomerase reverse transcriptase transcription in prostate cancer cells," *Molecular Cancer Therapeutics*, vol. 2, no. 8, pp. 739-746, 2003.
- [72] S. E. Blutt, T. J. McDonnell, T. C. Polek, and N. L. Weigel, "Calcitriol-induced apoptosis in LNCaP cells is blocked by overexpression of Bcl-2," *Endocrinology*, vol. 141, no. 1, pp. 10-17, 2000.
- [73] V. Sung and D. Feldman, " $1,25$ -Dihydroxyvitamin  $\text{D}_3$  decreases human prostate cancer cell adhesion and migration," *Molecular and Cellular Endocrinology*, vol. 164, no. 1-2, pp. 133-143, 2000.
- [74] E. S. Yang and K. L. Burnstein, "Vitamin D inhibits  $\text{G}_1$  to S progression in LNCaP prostate cancer cells through p27Kip1 stabilization and Cdk2 mislocalization to the cytoplasm," *Journal of Biological Chemistry*, vol. 278, no. 47, pp. 46862-46868, 2003.
- [75] S. S. Jensen, M. W. Madsen, J. Lukas, L. Binderup, and J. Bartek, "Inhibitory effects of  $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  on the  $\text{G}_1$ -S phase-controlling machinery," *Molecular Endocrinology*, vol. 15, no. 8, pp. 1370-1380, 2001.
- [76] M. Liu, M. H. Lee, M. Cohen, M. Bommakanti, and L. P. Freedman, "Transcriptional activation of the Cdk inhibitor p21 by vitamin  $\text{D}_3$  leads to the induced differentiation of the myelomonocytic cell line U937," *Genes and Development*, vol. 10, no. 2, pp. 142-153, 1996.
- [77] S. E. Blutt, E. A. Allegretto, J. W. Pike, and N. L. Weigel, " $1,25$ -dihydroxyvitamin  $\text{D}_3$  and 9-cis-acid act synergistically to inhibit the growth of LNCaP prostate cells and cause accumulation of cells in  $\text{G}_1$ ," *Endocrinology*, vol. 138, no. 4, pp. 1491-1497, 1997.
- [78] M. J. Campbell, E. Elstner, S. Holden, M. Uskokovic, and H. P. Koeffler, "Inhibition of proliferation of prostate cancer cells by a 19-nor-hexafluoride vitamin  $\text{D}_3$  analogue involves the induction of p21waf1, p27kip1 and E-cadherin," *Journal of Molecular Endocrinology*, vol. 19, no. 1, pp. 15-27, 1997.
- [79] O. Flores and K. L. Burnstein, "GADD45gamma: a new vitamin D-regulated gene that is antiproliferative in prostate cancer cells," *Endocrinology*, vol. 151, no. 10, pp. 4654-4664, 2010.
- [80] B. Y. Bao, S. D. Yeh, and Y. F. Lee, " $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  inhibits prostate cancer cell invasion via modulation of selective proteases," *Carcinogenesis*, vol. 27, no. 1, pp. 32-42, 2006.
- [81] Z. Culig, H. Steiner, G. Bartsch, and A. Hobisch, "Interleukin-6 regulation of prostate cancer cell growth," *Journal of Cellular Biochemistry*, vol. 95, no. 3, pp. 497-505, 2005.
- [82] B. Wegiel, A. Bjartell, Z. Culig, and J. L. Persson, "Interleukin-6 activates PI3K/Akt pathway and regulates cyclin A1 to promote prostate cancer cell survival," *International Journal of Cancer*, vol. 122, no. 7, pp. 1521-1529, 2008.
- [83] S. Araki, Y. Omori, D. Lyn et al., "Interleukin-8 is a molecular determinant of androgen independence and progression in prostate cancer," *Cancer Research*, vol. 67, no. 14, pp. 6854-6862, 2007.
- [84] S. Vasto, G. Carruba, G. Candore, E. Italiano, D. Di Bona, and C. Caruso, "Inflammation and prostate cancer," *Future Oncology*, vol. 4, no. 5, pp. 637-645, 2008.
- [85] D. J. Mantell, P. E. Owens, N. J. Bundred, E. B. Mawer, and A. E. Canfield, " $1\alpha,25$ -dihydroxyvitamin  $\text{D}_3$  inhibits angiogenesis in vitro and in vivo," *Circulation Research*, vol. 87, no. 3, pp. 214-220, 2000.
- [86] L. Nonn, L. Peng, D. Feldman, and D. M. Peehl, "Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D," *Cancer Research*, vol. 66, no. 8, pp. 4516-4524, 2006.
- [87] B. Y. Bao, J. Yao, and Y. F. Lee, " $1\alpha, 25$ -dihydroxyvitamin  $\text{D}_3$  suppresses interleukin-8-mediated prostate cancer cell angiogenesis," *Carcinogenesis*, vol. 27, no. 9, pp. 1883-1893, 2006.

- [88] Y. Xu, F. Fang, D. K. Clair et al., "Suppression of RelB-mediated manganese superoxide dismutase expression reveals a primary mechanism for radiosensitization effect of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> in prostate cancer cells," *Molecular Cancer Therapeutics*, vol. 6, no. 7, pp. 2048–2056, 2007.
- [89] M. Ben-Shoshan, S. Amir, D. T. Dang, L. H. Dang, Y. Weisman, and N. J. Mabeesh, "1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells," *Molecular Cancer Therapeutics*, vol. 6, no. 4, pp. 1433–1439, 2007.
- [90] I. Chung, G. Han, M. Seshadri et al., "Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis *in vivo*," *Cancer Research*, vol. 69, no. 3, pp. 967–975, 2009.
- [91] J. Moreno, A. V. Krishnan, S. Swami, L. Nonn, D. M. Peehl, and D. Feldman, "Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cell," *Cancer Research*, vol. 65, no. 17, pp. 7917–7925, 2005.
- [92] A. V. Krishnan, J. Moreno, L. Nonn et al., "Novel pathways that contribute to the anti-proliferative and chemopreventive activities of calcitriol in prostate cancer," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 103, no. 3–5, pp. 694–702, 2007.
- [93] A. V. Krishnan, S. Srinivas, D. Feldman et al., "Inhibition of prostaglandin synthesis and actions contributes to the beneficial effects of calcitriol in prostate cancer," *Dermato-Endocrinology*, vol. 1, no. 1, pp. 7–11, 2009.
- [94] H. van der Rhee, J. W. Coebergh, and E. D. Vries, "Sunlight, vitamin D and the prevention of cancer: a systematic review of epidemiological studies," *European Journal of Cancer Prevention*, vol. 18, pp. 458–475, 2009.
- [95] E. M. John, J. Koo, and G. G. Schwartz, "Sun exposure and prostate cancer risk: evidence for a protective effect of early-life exposure," *Cancer Epidemiology Biomarkers and Prevention*, vol. 16, no. 6, pp. 1283–1286, 2007.
- [96] C. L. Hanchette and G. G. Schwartz, "Geographic patterns of prostate cancer mortality. evidence for a protective effect of ultraviolet radiation," *Cancer*, vol. 70, no. 12, pp. 2861–2869, 1992.
- [97] G. G. Schwartz and C. L. Hanchette, "UV, latitude, and spatial trends in prostate cancer mortality: all sunlight is not the same (United States)," *Cancer Causes and Control*, vol. 17, no. 8, pp. 1091–1101, 2006.
- [98] W. B. Grant, "An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation," *Cancer*, vol. 94, no. 6, pp. 1867–1875, 2002.
- [99] C. J. Luscombe, A. A. Fryer, M. E. French et al., "Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer," *The Lancet*, vol. 358, no. 9282, pp. 641–642, 2001.
- [100] E. M. John, D. M. Dreon, J. Koo et al., "Residential sunlight exposure is associated with a decreased risk of prostate cancer," *Journal of Steroid Biochemistry & Molecular Biology*, vol. 89–90, no. 1–5, pp. 549–552, 2004.
- [101] D. Bodiwala, C. J. Luscombe, M. E. French et al., "Susceptibility to prostate cancer: studies on interactions between UVR exposure and skin type," *Carcinogenesis*, vol. 24, no. 4, pp. 711–717, 2003.
- [102] Z. Lagunova, A. C. Porojnicu, A. Dahlback, J. P. Berg, T. M. Beer, and J. Moan, "Prostate cancer survival is dependent on season of diagnosis," *Prostate*, vol. 67, no. 12, pp. 1362–1370, 2007.
- [103] T. E. Robsahm, S. Tretli, A. Dahlback, and J. Moan, "Vitamin D<sub>3</sub> from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway)," *Cancer Causes and Control*, vol. 15, no. 2, pp. 149–158, 2004.
- [104] J. L. Colli and A. Colli, "International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels," *Urologic Oncology*, vol. 24, no. 3, pp. 184–194, 2006.
- [105] Y. Ben-Shlomo, S. Evans, F. Ibrahim et al., "The risk of prostate cancer amongst black men in the United Kingdom: the process cohort study," *European Urology*, vol. 53, no. 1, pp. 99–105, 2008.
- [106] D. Bodiwala, C. J. Luscombe, M. E. French et al., "Polymorphisms in the vitamin D receptor gene, ultraviolet radiation, and susceptibility to prostate cancer," *Environmental and Molecular Mutagenesis*, vol. 43, no. 2, pp. 121–127, 2004.
- [107] S. Moon, S. Holley, D. Bodiwala et al., "Associations between G/A1229, A/G3944, T/C30875, C/T48200 and C/T65013 genotypes and haplotypes in the vitamin D receptor gene, ultraviolet radiation and susceptibility to prostate cancer," *Annals of Human Genetics*, vol. 70, pp. 226–236, 2006.
- [108] C. J. Luscombe, M. E. French, S. Liu et al., "Outcome in prostate cancer associations with skin type and polymorphism in pigmentation-related genes," *Carcinogenesis*, vol. 22, no. 9, pp. 1343–1347, 2001.
- [109] N. Rukin, M. Blagojevic, C. J. Luscombe et al., "Associations between timing of exposure to ultraviolet radiation, T-stage and survival in prostate cancer," *Cancer Detection and Prevention Journal*, vol. 31, no. 6, pp. 443–449, 2007.
- [110] J. L. Colli and W. B. Grant, "Solar ultraviolet B radiation compared with prostate cancer incidence and mortality rates in United States," *Urology*, vol. 71, no. 3, pp. 531–535, 2008.
- [111] E. de Vries, I. Soerjomataram, S. Houterman et al., "Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation?" *American Journal of Epidemiology*, vol. 165, no. 8, pp. 966–972, 2007.
- [112] N. J. Rukin, M. P. Zeegers, S. Ramachandran et al., "A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma," *British Journal of Cancer*, vol. 96, no. 3, pp. 523–528, 2007.
- [113] P. Tuohimaa, E. Pukkala, G. Scélo et al., "Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation," *European Journal of Cancer*, vol. 43, no. 11, pp. 1701–1712, 2007.
- [114] F. Levi, L. Randimbison, V. C. Te, M. M. Conconi, and C. La Vecchia, "Risk of prostate, breast and colorectal cancer after skin cancer diagnosis," *International Journal of Cancer*, vol. 123, no. 12, pp. 2899–2901, 2008.
- [115] R. Gilbert, C. Metcalfe, S. E. Oliver et al., "Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis," *International Journal of Cancer*, vol. 125, no. 6, pp. 1414–1423, 2009.
- [116] W. B. Grant, "Geographic variation of prostate cancer mortality rates in the United States: implications for prostate cancer risk related to vitamin D," *International Journal of Cancer*, vol. 111, no. 3, pp. 470–471, 2004.
- [117] P. Waltz and G. Chodick, "International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels," *Urologic Oncology*, vol. 25, no. 1, p. 85, 2007.
- [118] P. Waltz and G. Chodick, "Assessment of ecological regression in the study of colon, breast, ovary, non-Hodgkin's lymphoma, or prostate cancer and residential UV," *European Journal of Cancer Prevention*, vol. 17, no. 3, pp. 279–286, 2008.



- [119] E. H. Corder, H. A. Guess, B. S. Hulka et al., "Vitamin D and prostate cancer: a prediagnostic study with stored sera," *Cancer Epidemiology Biomarkers and Prevention*, vol. 2, no. 5, pp. 467–472, 1993.
- [120] M. H. Ahonen, L. Tenkanen, L. Teppo, M. Hakama, and P. Tuohimaa, "Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland)," *Cancer Causes and Control*, vol. 11, no. 9, pp. 847–852, 2000.
- [121] H. Li, M. J. Stampfer, J. B. Hollis et al., "A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer," *PLoS Medicine*, vol. 4, no. 3, article e103, 2007.
- [122] S. Tretli, E. Hernes, J. P. Berg, U. E. Hestvik, and T. E. Røksahm, "Association between serum 25(OH)D and death from prostate cancer," *British Journal of Cancer*, vol. 100, no. 3, pp. 450–454, 2009.
- [123] M. M. Braun, K. J. Helzlsouer, B. W. Hollis, and G. W. Comstock, "Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States)," *Cancer Causes and Control*, vol. 6, no. 3, pp. 235–239, 1995.
- [124] P. H. Gann, J. Ma, C. H. Hennekens et al., "Circulating vitamin D metabolites in relation to subsequent development of prostate cancer," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 5, no. 2, pp. 121–126, 1996.
- [125] A. M. Nomura, G. N. Stemmermann, J. Lee et al., "Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States)," *Cancer Causes and Control*, vol. 9, no. 4, pp. 425–432, 1998.
- [126] E. A. Platz, M. F. Leitzmann, B. W. Hollis, W. C. Willett, and E. Giovannucci, "Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer," *Cancer Causes and Control*, vol. 15, no. 3, pp. 255–265, 2004.
- [127] S. Gandini, M. Boniol, J. Haukka et al., "Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma," *International Journal of Cancer*, vol. 128, no. 6, pp. 1414–1424, 2011.
- [128] C. M. Barnett, C. M. Nielson, J. Shannon et al., "Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men," *Cancer Causes and Control*, vol. 21, no. 8, pp. 1297–1303, 2010.
- [129] R. C. Travis, F. L. Crowe, N. E. Allen et al., "Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European prospective investigation into cancer and nutrition (EPIC)," *American Journal of Epidemiology*, vol. 169, no. 10, pp. 1223–1232, 2009.
- [130] J. Ahn, U. Peters, D. Albanes et al., "Serum vitamin D concentration and prostate cancer risk: a nested case-control study," *Journal of the National Cancer Institute*, vol. 100, no. 11, pp. 796–804, 2008.
- [131] P. Tuohimaa, L. Tenkanen, M. Ahonen et al., "Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the nordic countries," *International Journal of Cancer*, vol. 108, no. 1, pp. 104–108, 2004.
- [132] B. Mikhak, D. J. Hunter, D. Spiegelman, E. A. Platz, B. W. Hollis, and E. Giovannucci, "Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk," *Prostate*, vol. 67, no. 9, pp. 911–923, 2007.
- [133] J. Ma, M. J. Stampfer, P. H. Gann et al., "Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians," *Cancer Epidemiology Biomarkers and Prevention*, vol. 7, no. 5, pp. 385–390, 1998.
- [134] S. Y. Park, S. P. Murphy, L. R. Wilkens, D. O. Stram, B. E. Henderson, and L. N. Kolonel, "Calcium, vitamin D, and dairy product intake and prostate cancer risk: the multiethnic cohort study," *American Journal of Epidemiology*, vol. 166, no. 11, pp. 1259–1269, 2007.
- [135] A. R. Kristal, K. B. Arnold, M. L. Neuhouser et al., "Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial," *American Journal of Epidemiology*, vol. 172, no. 5, pp. 566–577, 2010.
- [136] M. Huncharek, J. Muscat, and B. Kupelnick, "Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies," *Nutrition and Cancer*, vol. 60, no. 4, pp. 421–441, 2008.
- [137] A. G. Uitterlinden, Y. Fang, J. B. Van Meurs, H. A. P. Pols, and J. P. T. M. Van Leeuwen, "Genetics and biology of vitamin D receptor polymorphisms," *Gene*, vol. 338, no. 2, pp. 143–156, 2004.
- [138] L. Gennari, V. De Paola, D. Merlotti, G. Martini, and R. Nuti, "Steroid hormone receptor gene polymorphisms and osteoporosis: a pharmacogenomic review," *Expert Opinion on Pharmacotherapy*, vol. 8, no. 5, pp. 537–553, 2007.
- [139] G. K. Whitfield, L. S. Remus, P. W. Jurutka et al., "Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene," *Molecular and Cellular Endocrinology*, vol. 177, no. 1-2, pp. 145–159, 2001.
- [140] S. M. Orton, A. P. Morris, B. M. Herrera et al., "Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis," *American Journal of Clinical Nutrition*, vol. 88, no. 2, pp. 441–447, 2008.
- [141] H. Arai, K. I. Miyamoto, M. Yoshida et al., "The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene," *Journal of Bone and Mineral Research*, vol. 16, no. 7, pp. 1256–1264, 2001.
- [142] L. K. Durrin, R. W. Haile, S. A. Ingles, and G. A. Coetzee, "Vitamin D receptor 3'-untranslated region polymorphisms: lack of effect on mRNA stability," *Biochimica et Biophysica Acta*, vol. 1453, no. 3, pp. 311–320, 1999.
- [143] T. Carling, J. Rastad, G. Akerström, and G. Westin, "Vitamin D receptor (VDR) and parathyroid hormone messenger ribonucleic acid levels correspond to polymorphic VDR alleles in human parathyroid tumors," *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 7, pp. 2255–2259, 1998.
- [144] W. Verbeek, A. F. Gombart, M. Shiohara et al., "Vitamin D receptor: no evidence for allele-specific mRNA stability in cells which are heterozygous for the Taq I restriction enzyme polymorphism," *Biochemical and Biophysical Research Communications*, vol. 238, no. 1, pp. 77–80, 1997.
- [145] N. A. Morrison, J. C. Qi, A. Tokita et al., "Prediction of bone density from vitamin D receptor alleles," *Nature*, vol. 387, no. 6628, p. 106, 1994.
- [146] J. A. Taylor, A. Hirvonen, M. Watson, G. Pittman, J. L. Mohler, and D. A. Bell, "Association of prostate cancer with vitamin D receptor gene polymorphism," *Cancer Research*, vol. 56, no. 18, pp. 4108–4110, 1996.
- [147] S. A. Ingles, R. K. Ross, M. C. Yu et al., "Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor," *Journal of the National Cancer Institute*, vol. 89, no. 2, pp. 166–170, 1997.



- [148] T. Habuchi, T. Suzuki, R. Sasaki et al., "Association of vitamin D receptor gene polymorphism with prostate cancer and benign prostatic hyperplasia in a Japanese population," *Cancer Research*, vol. 60, no. 2, pp. 305–308, 2000.
- [149] K. Suzuki, H. Matsui, N. Ohtake et al., "Vitamin D receptor gene polymorphism in familial prostate cancer in a Japanese population," *International Journal of Urology*, vol. 10, no. 5, pp. 261–266, 2003.
- [150] C. Ntais, A. Polycarpou, and J. P. Ioannidis, "Vitamin D receptor gene polymorphisms and risk of prostate cancer: a meta-analysis," *Cancer Epidemiology Biomarkers and Prevention*, vol. 12, no. 12, pp. 1395–1402, 2003.
- [151] I. Oakley-Girvan, D. Feldman, T. R. Eccleshall et al., "Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor," *Cancer Epidemiology Biomarkers and Prevention*, vol. 13, no. 8, pp. 1325–1330, 2004.
- [152] S. Maistro, I. Snitcovsky, A. S. Sarkis, I. A. da Silva, and M. M. Brentani, "Vitamin D receptor polymorphisms and prostate cancer risk in Brazilian men," *International Journal of Biological Markers*, vol. 19, no. 3, pp. 245–249, 2004.
- [153] M. B. Cheteri, J. L. Stanford, D. M. Friedrichsen et al., "Vitamin D receptor gene polymorphisms and prostate cancer risk," *Prostate*, vol. 59, no. 4, pp. 409–418, 2004.
- [154] S. P. Huang, Y. H. Chou, W. S. Wayne Chang et al., "Association between vitamin D receptor polymorphisms and prostate cancer risk in a Taiwanese population," *Cancer Letters*, vol. 207, no. 1, pp. 69–77, 2004.
- [155] H. Williams, I. J. Powell, S. J. Land et al., "Vitamin D receptor gene polymorphisms and disease free survival after radical prostatectomy," *Prostate*, vol. 61, no. 3, pp. 267–275, 2004.
- [156] E. M. John, G. G. Schwartz, J. Koo et al., "Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer," *Cancer Research*, vol. 65, no. 12, pp. 5470–5479, 2005.
- [157] D. K. Mishra, H. K. Bid, D. S. Srivastava, A. Mandhani, and R. D. Mittal, "Association of vitamin D receptor gene polymorphism and risk of prostate cancer in India," *Urologia Internationalis*, vol. 74, no. 4, pp. 315–318, 2005.
- [158] V. M. Hayes, G. Severi, E. J. Padilla et al., "Genetic variants in the vitamin D receptor gene and prostate cancer risk," *Cancer Epidemiology Biomarkers and Prevention*, vol. 14, no. 4, pp. 997–999, 2005.
- [159] L. C. Kidd, D. N. Paltoo, S. Wang et al., "Sequence variation within the 5' regulatory regions of the vitamin D binding protein and receptor genes and prostate cancer risk," *Prostate*, vol. 64, no. 3, pp. 272–282, 2005.
- [160] S. I. Berndt, J. L. Dodson, W. Y. Huang, and K. K. Nicodemus, "Systematic review of vitamin D receptor gene polymorphisms and prostate cancer risk," *Journal of Urology*, vol. 175, no. 5, pp. 1613–1623, 2006.
- [161] C. N. Holick, J. L. Stanford, E. M. Kwon et al., "Comprehensive association analysis of the vitamin D pathway genes, VDR, CYP27B1, and CYP24A1, in prostate cancer," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 16, no. 10, pp. 1990–1999, 2007.
- [162] H. Li, M. J. Stampfer, J. B. Hollis et al., "A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer," *PLoS Medicine*, vol. 4, no. 3, article e103, 2007.
- [163] N. J. Rukin, C. Luscombe, S. Moon et al., "Prostate cancer susceptibility is mediated by interactions between exposure to ultraviolet radiation and polymorphisms in the 5' haplotype block of the vitamin D receptor gene," *Cancer Letters*, vol. 247, no. 2, pp. 328–335, 2007.
- [164] I. H. Onen, A. Ekmekci, M. Eroglu et al., "Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer," *Experimental Biology and Medicine*, vol. 233, no. 12, pp. 1608–1614, 2008.
- [165] K. C. Torkko, A. van Bokhoven, P. Mai et al., "VDR and SRD5A2 polymorphisms combine to increase risk for prostate cancer in both non-hispanic white and hispanic white men," *Clinical Cancer Research*, vol. 14, no. 10, pp. 3223–3229, 2008.
- [166] J. Ahn, D. Albanes, S. I. Berndt et al., "Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk," *Carcinogenesis*, vol. 30, no. 5, pp. 769–776, 2009.
- [167] L. Chen, G. D. Smith, D. M. Evans et al., "Genetic variants in the vitamin D receptor are associated with advanced prostate cancer at diagnosis: findings from the prostate testing for cancer and treatment study and a systematic review," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 18, no. 11, pp. 2874–2881, 2009.
- [168] S. Raimondi, H. Johansson, P. Maisonneuve, and S. Gandini, "Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk," *Carcinogenesis*, vol. 30, no. 7, pp. 1170–1180, 2009.
- [169] M. Yin, S. Wei, and Q. Wei, "Vitamin D receptor genetic polymorphisms and prostate cancer risk: a meta-analysis of 36 published studies," *International Journal of Clinical and Experimental Medicine*, vol. 2, no. 2, pp. 159–175, 2009.
- [170] S. K. Holt, E. M. Kwon, U. Peters, E. A. Ostrander, and J. L. Stanford, "Vitamin D pathway gene variants and prostate cancer risk," *Cancer Epidemiology Biomarkers and Prevention*, vol. 18, no. 6, pp. 1929–1933, 2009.
- [171] Y. Bai, Y. Yu, B. Yu et al., "Association of vitamin D receptor polymorphisms with the risk of prostate cancer in the Han population of Southern China," *BMC Medical Genetics*, vol. 10, article 125, 2009.
- [172] M. Risio, T. Venesio, E. Kolomoets et al., "Genetic polymorphisms of CYP17A1, vitamin D receptor and androgen receptor in Italian heredo-familial and sporadic prostate cancers," *Cancer Epidemiology*. In press.



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