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# The double disparity: Vitamin D deficiency and lethal prostate cancer in black men

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## Abstract

Epidemiological data from as early as the 1930s documented a dramatic racial disparity in prostate cancer incidence, survival, and mortality rates among Black men—a trend that persists to this day. Black men are disproportionately burdened by prostate cancer, developing the disease at younger ages, facing more aggressive and lethal forms, and ultimately experiencing double the mortality rate of men of European descent. Investigating the multifactorial contributors to this racial disparity has been extensive, but results have often been inconsistent or inconclusive, making it difficult to pinpoint clear correlations. However, there is strong evidence suggesting that vitamin D deficiency is significantly associated with lethal forms of prostate cancer. This is particularly important given that Black men are at a higher risk for both vitamin D deficiency and developing aggressive, lethal prostate cancer, presenting a double disparity. The disparity in prostate cancer and vitamin D extends to Black men outside the US, but most of the studies have been done in African American men. Understanding the available evidence on vitamin D deficiency and its influence on prostate cancer biology may reveal new opportunities for prevention and therapeutic intervention.

### Keywords

Prostate cancer; Disparities; Vitamin D



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Declaration of Competing Interest

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CRediT authorship contribution statement

**Kirsten D. Krieger:** Writing – original draft. **Adriana Duraki:** Writing – original draft, Writing – review & editing. **Larisa Nonn:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jsbmb.2025.106675.

## 1. Introduction

With 1.5 million new cases globally in 2022, prostate cancer (PCa) stands as the second most common cancer and the fifth leading cause of cancer mortality among men [102]. Although prevalence is high, PCa cases typically have some of the best prognoses with 5-year survival ranging from 70 % to 100 % [70]. PCa mortality rates in Black men are approximately two to four times higher than those in every other racial and ethnic group [102]. Among all cancer types, PCa presents the most significant racial health disparity, with African American men facing an increased risk of lethal PCa compared to individuals of other racial backgrounds in the US [65]. One factor that may partially explain this disparity is vitamin D deficiency, as the higher levels of melanin in the skin of Black men reduce their ability to synthesize vitamin D from sunlight exposure. Vitamin D is a steroid hormone precursor known for its essential roles in maintaining bone health, supporting immune function, regulating cell differentiation and proliferation, and exhibiting anti-inflammatory and anticancer properties.

In this review, we provide a comprehensive and up-to-date summary of dietary intake, case-control, and epidemiological studies investigating the role of vitamin D in PCa. This synthesis provides an overview of the current understanding of vitamin D's influence on PCa risk, progression, aggressiveness, and mortality, including a dedicated section focusing on research involving Black men to address the double disparity in PCa outcomes. Finally, we explore why nearly half of the compiled studies report null findings, discussing inherent study design limitations that complicate the control of vitamin D intake and status, potentially obscuring true associations and underestimating its impact.

### 1.1. The biological importance of vitamin D

Vitamin D, often called the "sunshine vitamin," is a steroid hormone rather than a true vitamin, as it can be synthesized in the skin upon exposure to sunlight [69]. It's primarily recognized for maintaining calcium homeostasis and bone health, but its role extends to regulating cell fate, proliferation, and differentiation [34]. The cutaneous precursor, vitamin D3, undergoes UV exposure-induced hydroxylation to form 25-hydroxyvitamin D (25(OH)D), the primary circulating metabolite and the clinical standard for assessing vitamin D status. Additional hydroxylation produces the active ligand, 1,25-dihydroxyvitamin D (1,25 (OH)2D), which binds to the vitamin D receptor (VDR) to regulate the transcription of hundreds of genes. Vitamin D can also directly affect the epigenome and regulate over 1000 genes, either through VDR binding or indirect pathways (Carlberg 2019).

Vitamin D deficiency affects individuals across all age groups, with prevalence varying based on factors such as geographical location, season, and population demographics (Holick 2006a). Certain groups are at a higher risk, including those with limited sun exposure, low dietary intake, and individuals with darker skin tones, as melanin reduces the skin's ability to synthesize vitamin D (Holick 2006a; Institute of Medicine (US) 2011). To maintain healthy serum levels, individuals in these at-risk groups must ensure adequate vitamin D intake through diet or supplements. Vitamin D status is determined by serum concentrations of 25(OH)D, which reflect both endogenous production and dietary intake

(EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2016). Although the ideal serum 25(OH)D levels and specific thresholds for deficiency, insufficiency, and sufficiency remain subjects of debate, a general consensus holds that serum levels of 50 nmol/L (20 ng/mL) or higher are adequate for bone and overall health in individuals without risk factors for deficiency.

### 1.2. The role of vitamin D in prostate health and cancer risk

Accumulated evidence from cellular, molecular and developmental studies suggests that vitamin D plays a significant role in maintaining prostate health, with emerging research exploring whether insufficient levels of vitamin D could influence PCa development. Like other organs, prostate cells express VDR and is responsive to 1,25(OH)2D (Miller et al., 1992; Skowronski et al., 1993; Peehl et al., 1994; Barreto et al., 2000). In normal human prostate tissue, VDR is expressed in both the epithelial and stromal cell types [57,58]. VDR levels vary with both age and prostate zone, with the highest expression observed in middle-aged men (ages 20–50), while younger and older individuals show a decline in expression [58], suggesting that vitamin D plays a critical role in maintaining prostate homeostasis throughout adulthood. This emphasizes the importance of the vitamin D axis in prostate biology and supporting the hypothesis that vitamin D deficiency—modulated by factors such as age and race—may increase the risk of developing PCa (Schwartz & Hulka 1990).

Beyond its essential roles in bone health, vitamin D has profound effects on cellular functions that are critical in PCa biology. Vitamin D regulates cell proliferation by modulating cell cycle and promoting apoptosis [119,34]. It also has a crucial role in immune regulation, impacting both innate and adaptive immunity, which likely contribute to benefits in cancer prevention activities [119,34]. In PCa cells, vitamin D has a prodifferentiating effect, that supports a less malignant and more normal phenotype [34], inducing differentiation markers such as PSA, cytokeratins, and E-cadherin (Gocek and Studzinski 2009a), further underscoring its influence on cellular behavior. The regulation of various physiological processes, including cell proliferation, immune modulation, and differentiation, highlights the non-calcemic functions of vitamin D [108,119] are summarized in Fig. 1.

### 1.3. Implications of vitamin D in prostate cancer

In the 1990s an hypothesis emerged, linking vitamin D deficiency to increased PCa risk, thus factors such as age, race, and residence in regions associated with reduced sunlight exposure—could contribute to vitamin D deficiency and, consequently, PCa risk (Schwartz & Hulka 1990). This hypothesis gained support from observations that men in the United States experienced higher rates of PCa mortality based on their geographic location, particularly their distance from the equator (Hanchette and Schwartz 1992). Furthermore, men diagnosed with PCa during the summer or fall, when circulating vitamin D levels are higher, tended to have better prognoses (Robsahm et al., 2004). Following the initial study that connected reduced sunlight exposure to increased PCa mortality (Hanchette and Schwartz 1992), there has been three decades, of epidemiological research on this topic has encompassed a wide array of studies, including prospective cohort studies, case-control

studies, clinical trials, Mendelian randomization studies, and meta-analyses. We performed a comprehensive literature review of these studies and they are summarized in Supplemental TABLE I and discussed in this review.

## 2. Method

A literature search was performed to identify various studies and clinical trials examining the relationship between vitamin D and prostate cancer. We focused on studies that reported serum levels of vitamin D or dietary intake in relation to prostate cancer incidence, mortality, or advancement. The NCBI PubMed database was used to retrieve relevant articles through a search strategy incorporating the following combination of terms: (vitamin D or 25(OH)D or 1,25(OH)2D) AND (prostate cancer or prostate) AND (prospective cohort or cohort or case-control or meta-analyses or pilot studies or clinical trials). Only articles written in or translated to English were included. Duplicate articles were ignored. Each article was reviewed if title and abstract appeared relevant. Reviewing included confirmation that the study reported an association between vitamin D and prostate cancer. Comprehensive cross-referencing was utilized in addition to the database search strategy to identify additional studies that were not captured in the initial search. For eligible studies, the following data was extracted: author(s); publication year; characteristics of study population including age, race, location, health, cohort/case number; percentage of vitamin D deficient population (if reported); overall findings/conclusions of the relationship between vitamin D and prostate cancer; study type/design; and overall role of vitamin D in relation to prostate cancer.

## 3. Results

### 3.1. Human studies on vitamin D and prostate cancer

Many epidemiological studies have explored the relationship between vitamin D status and PCa. Geographic and seasonal variations in sunlight exposure, which affect cutaneous vitamin D synthesis, provided early links to PCa mortality (Hanchette & Schwartz 1992). Since that seminal finding, there have been observational studies that examine associations between PCa risk and/or mortality by vitamin D dietary intake or blood levels of vitamin D metabolites, which are summarized in Table 1.

### 3.2. Dietary intake studies

To evaluate the relationship between vitamin D dietary intake and PCa risk, Tseng et al. found a weak inverse association, indicating that higher dietary vitamin D intake was weakly linked to a reduced risk of PCa [116]. However, most other diet-focused cohort studies reported no significant associations [15,22,45,50,59,90]. Case-control studies showed a similar pattern, with Deneo-Pellegrini et al. noting a weak association between high dietary vitamin D intake and decreased PCa risk [28], while several other case-control studies found no such link [120,56,21,60,109,51,88]. More recently, Batai et al. identified a protective effect of high dietary vitamin D in reducing the risk of aggressive PCa [10]. In addition to cohort and case-control studies, two meta-analyses [42,52] and one Mendelian randomization study [25] also reported null associations. The lack of agreement among these

diet-focused studies may stem from differences in study design, low vitamin D in most diets, and population characteristics such as location, race, and age, which will be discussed in greater detail later.

### 3.3. Serum vitamin D and prostate cancer incidence and risk

Numerous investigations examine the influence of circulating serum vitamin D metabolite levels on PCa incidence and risk. The findings from prospective cohort studies of men are mixed, with some reporting a protective effect of 25(OH)D serum levels on overall PCa risk [24,74, 91], and others indicating a U-shaped curve [123] or no significant association at all [103,107,86,9]. Given the high prevalence of PCa, it is unlikely that vitamin D levels alone are modifiers of incidence.

More than 35 case-control studies have investigated the relationship between serum vitamin D levels and PCa. While most of these studies show no association between vitamin D status and PCa risk [2,8,18,26,33,39,43,48,54,62,66,82,88,89,93,94,95,101,111,114,126], characteristics such as location, race, and age, which will be a few studies have reported inverse associations indicating protective effects of vitamin D on PCa risk [3,5,6,30,75,117,118] or positive associations suggesting harmful effects of vitamin D status [122,16,4,53,72]. Meta-analyses investigating the relationship between PCa risk and vitamin D tend to align with the null associations [127,38,42] or indicate harmful associations [125,40]. These discrepancies may arise from variations in how vitamin D levels are standardized across studies based on factors like the season of blood collection, geographic location, age, and other variables, along with the exclusion of dietary vitamin D intake and sun exposure data.

### 3.4. Epidemiological studies on vitamin D and prostate cancer aggressiveness and mortality

Although modulation of overall PCa risk by vitamin D is unclear, a protective effect is more consistently observed when examining the risk of metastatic or aggressive PCa [32,44,49,79,80,83]. The majority of case-control studies focusing on the risk of aggressive or advanced PCa lean toward supporting a protective role [2,3,43,63,75,95,128], rather than a harmful one [4,94].

When examining the relationship between vitamin D status and PCa mortality, findings from prospective cohort studies are inconsistent. Some studies indicate that sufficient vitamin D levels are associated with lower PCa mortality [113,17,29,32,74], while others report no significant associations [36,47,49,100]. Notably, case-control studies focusing on PCa mortality consistently show that higher serum 25(OH)D levels are linked to a reduced risk of lethal PCa [101,128,73]. Meta-analyses also support the protective effect of adequate vitamin D levels in reducing PCa mortality [104,27].

### 3.5. Case-control studies

Case-control studies have found evidence supporting a protective effect of vitamin D against PCa, with some studies showing a beneficial link [10,61,62] and others reporting no significant association [62,88]. Jackson et al. reported a potential harmful effect of 25(OH)D

serum levels for Black Jamaican men with PCa. However, Jamaica is a low-latitude region where the population generally has sufficient vitamin D due to high solar UVB exposure, resulting in fewer vitamin D-deficient participants [53]. In several studies focusing on African American men, higher levels of 25(OH)D were linked to a reduced risk of high-grade PCa [61] and a lower risk of non-aggressive PCa [62]. Additionally, research shows that African American men with greater dietary vitamin D intake had a lower overall risk of PCa [10].

### 3.6. Mendelian randomization studies

Mendelian randomization (MR) studies are a powerful tool used to infer causal relationships between an exposure (e.g., vitamin D levels) and an outcome (e.g., PCa risk). By leveraging genetic variants as proxies for an exposure, MR studies help minimize confounding factors and reverse causation, common limitations of observational studies. In the context of vitamin D and PCa, results largely suggest that there is no causal relationship between genetically predicted vitamin D levels and PCa risk, including aggressive subtypes, as summarized in Table 2.

A large MR study with over 22,000 PCa cases from multiple cancer consortia found no significant association between genetically determined (25(OH)D) concentrations and PCa risk [55]. While the possibility of modest or clinically insignificant effects could not be entirely excluded, this study concluded that screening for and supplementing vitamin D at the population level is unlikely to reduce prostate cancer incidence [31]. Similarly, a UK Biobank study with over 46,000 cancer cases, including PCa, also reported no association between genetically predicted vitamin D levels and PCa risk or mortality [85]. Another study utilizing a larger set of vitamin D-associated genetic variants (74 SNPs) reinforced null findings, suggesting that lower vitamin D concentrations are unlikely to be a causal risk factor for PCa [84]. Additionally, the largest genome-wide association datasets to date found no evidence of a causal relationship between circulating 25(OH)D and PCa risk, even with increased statistical power [25]. Although these MR studies do not support a causal role for vitamin D in PCa risk, the potential for modest or non-linear effects in specific subpopulations with profound vitamin D deficiency cannot be ruled out. Future research should focus on these high-risk groups and further investigate the biological mechanisms involved.

### 3.7. Pilot/clinical trials

Pilot studies and clinical trials provide a unique opportunity to evaluate the potential effects of vitamin D intervention on PCa risk, progression, survival, and prostate specific antigen (PSA) levels. Randomized, placebo-controlled trials of vitamin D supplementation on PCa and overall survival in PCa patients have shown mixed results, as summarized in Table 3. Circulating levels of PSA is commonly used as a biomarker to monitor prostate cancer progression and recurrence. Some studies indicate a protective effect, with improved survival and reduced PSA levels as outcomes [121,14], while others report no significant findings [41,67,7]. Although, Scher et al. [96] found that high-dose calcitriol (1,25(OH)2D) supplementation was linked to reduced survival in PCa patients, this was a treatment study

that used calcitriol, the active form of vitamin D, which is not reflective of the normal circulating form that has been linked to reduced PCa risk.

Meta-analyses of these trials, excluding Manson et al. [67], suggest no substantial difference in PSA response or survival rates between vitamin D-supplemented patients and placebo groups [98]. Most of these randomized studies did not report patients' serum vitamin D levels, and the PCa treatments varied, leaving room for the possibility that vitamin D may still offer protective benefits.

Shahvazi et al. evaluated 16 single-arm clinical trials without placebo controls to examine vitamin D's impact on PSA levels or response rates. The results were nearly split: half suggested a protective association, with vitamin D supplementation linked to reduced PSA levels or a weak positive impact [11,20,35,81,92,110,115], while the other half showed no significant effect of vitamin D on reducing PSA levels [12,13, 19,64,78,87,97,105]. Despite the diversity in study populations, PCa stages, and prior therapies, the Shahvazi et al. meta-analysis demonstrated a statistically significant improvement of 19 % in PCa outcomes with vitamin D supplementation, regardless of chemotherapy use. Though the trials showed considerable variability in design, vitamin D forms, doses, and treatment protocols, the overall evidence points to a meaningful protective role of vitamin D in slowing disease progression in men with PCa.

### 3.8. Racial disparities in both vitamin D status and prostate cancer risk

Interpreting the impact of vitamin D supplementation on PCa in Black men remains difficult, as most clinical trials have primarily involved white participants. Skin pigmentation originally evolved as an adaptive mechanism to protect against the harmful effects of intense solar UVB radiation in lower latitude regions, helping to prevent severe sunburn, DNA damage, and the degradation of skin folate (Ames, Grant, and Willett 2021; P. Jones et al., 2018). However, as populations migrated to higher latitudes where UVB exposure is significantly diminished, skin pigmentation reduced cutaneous synthesis of vitamin D, resulting in vitamin D deficiency and potentially contributing to adverse health outcomes, which led to loss of pigmentation as populations evolved (Ames, Grant, and Willett 2021). Data from the National Health and Nutrition Examination Survey (2001–2010) showed that Blacks had the highest prevalence of deficiency at 71.9 %, compared to 42.8 % of Hispanics and only 18.6 % of non-Hispanic Whites (Xuefeng Liu, Baylin, and Levy 2018). These findings underscore the critical need for maintaining adequate vitamin D levels in the general population and highlight the importance of investigating how vitamin D deficiency affects the health of at-risk groups.

Black men face both vitamin D deficiency and disproportionately high rates of aggressive PCa. They have both a higher incidence and worse outcomes of PCa, as highlighted by data from 2017 to 2019 indicated that the lifetime risk of being diagnosed with PCa was 17.3 % for non-Hispanic Black men, compared to 12.6 % for non-Hispanic White men in the United States (Surveillance Research Program, NCI 2023). Furthermore, data from 2018 to 2020 showed that the lifetime risk of dying from PCa was 3.3 % for non-Hispanic Black men, while it was 2.1 % for non-Hispanic White men (Surveillance Research Program, NCI 2023). These marked disparities in the National Cancer Institute's

Surveillance Epidemiology and End Results (SEER) data underscore the need for ongoing research to unravel the complex array of factors contributing to these differences.

One study analyzed over 3000 pathology reports related to PCa and found that African American men had higher rates of cancer detection, more severe PCa (as indicated by Gleason scores), and were diagnosed at a younger age (Bigler, Pound, and Zhou 2011). However, it's important to note that this retrospective study relied on self-identified race/ethnicity rather than genetic ancestry testing. In 2020, a study involving a large and diverse cohort of 60,035 men diagnosed with PCa within the Veterans Affairs (VA) health care system aimed to examine how healthcare inequities contribute to racial disparities in PCa (Riviere et al., 2020). In this equal-access medical environment, researchers found that African American men did not present with more advanced disease stages or poorer outcomes compared to non-Hispanic White men (Riviere et al., 2020). Contrary to many national studies highlighting racial disparities in PCa, this study revealed that African American men were diagnosed at younger ages and had higher PSA levels; surprisingly, they were less likely to have high Gleason scores (8–10), advanced clinical T classifications (≥3, indicating tumor extension beyond the prostate), or distant metastatic disease (Riviere et al., 2020). In 2022, a similar investigation was conducted on an even larger group of 92,269 men diagnosed with PCa from the VA health care system, focusing on distant metastasis as a primary endpoint rather than long-term survival (Yamoah et al., 2022). Consistent with the previous study, they found that African American men were younger and had higher PSA levels at diagnosis. However, they also discovered that these men had double the incidence of developing both localized and metastatic PCa (Yamoah et al., 2022). Among those who received definitive treatment, African American men exhibited a higher residual metastatic burden after treatment compared to their non-Hispanic White counterparts, regardless of risk category (Yamoah et al., 2022). This study reinforced the existence of racial disparities in PCa, emphasizing the need to evaluate the effects of treatment and access to healthcare.

### 3.9. Vitamin D and prostate cancer in Black men

Few studies have exclusively focused on Black men, and the only randomized, placebo-controlled trial on vitamin D supplementation among healthy Black men without a PCa history found no significant effect on PSA levels [23]. Given the higher risk of both lethal PCa and vitamin D deficiency among Black men, these epidemiological findings highlight the need to include Black and other vitamin D-deficient populations in research to better understand the role of systemic vitamin D deficiency in PCa risk and progression, especially in those at increased risk.

Recognizing that Black men face higher rates of vitamin D deficiency as well as increased PCa incidence and mortality, numerous studies—including prospective, case-control, and clinical trials—have aimed to explore links between these disparities, as summarized in Table 4. In 1993, Corder et al. conducted a pre-diagnostic study using stored blood samples from 90 Black and 91 White men diagnosed with PCa, along with matched controls, to compare PCa risk in relation to vitamin D status between the two groups [26]. Although this small study did not find a significant link between vitamin D levels and PCa incidence in Black versus White men, it spurred further research on this disparity.

Subsequent larger-scale prospective studies have shown evidence supporting vitamin D's protective effect against PCa in African American men [106,79,80]. These studies have demonstrated that low levels of 25 (OH)D are linked to a higher overall risk of PCa among African American men [79] and are also significantly associated with more aggressive cancer and advanced tumor characteristics, such as higher Gleason scores and tumor stages [106,79,80]. A notable strength of these studies is their substantial representation of Black men and the higher prevalence of vitamin D deficiency (ranging from 40 % to 60 %) among participants, which has facilitated a more accurate evaluation of vitamin D deficiency's role in PCa.

## 4. Discussion

In sum, the epidemiological research on vitamin D's role in PCa is inconsistent, with several factors contributing to these discrepancies. This is primarily due to inherent challenges in study design and execution. Many studies do not account for factors such as sun exposure and dietary intake (Yeum, Song, and Joo 2016). Another major issue is the difficulty in controlling vitamin D intake, as participants often self-supplement with vitamin D, especially when they are aware they are part of a clinical trial. Furthermore, vitamin D levels can vary widely among individuals due to factors such as diet, sunlight exposure, and genetics, complicating the interpretation of results. Often, initial vitamin D status of the patients are not considered to ensure supplementation only in those who are deficient.

PCa itself is biologically complex, with multiple genetic, environmental, and hormonal influences, making it difficult to isolate the impact of vitamin D. Study designs often suffer from limitations, including small sample sizes, short durations, and inadequate control for confounding variables like age, lifestyle, and comorbidities. PCa is a slow growing tumor, and short term vitamin D interventions do not reverse decades, perhaps a lifetime of vitamin D deficiency. The timing and dosage of vitamin D supplementation may not always be optimal, which could influence the effectiveness of the intervention. Racial and genetic differences also play a significant role, as certain populations, particularly Black men, are more likely to have lower vitamin D levels and may respond differently to supplementation. The lack of diversity in study populations, often dominated by individuals of European ancestry, further limits the generalizability of findings.

For PCa, it essential to understand the endpoints analyzed in the study. Given the high incidence of indolent PCa, studies that evaluate overall PCa risk, are unlikely to be clinically informative. Whereas studies that assess aggressive and lethal PCa are highly relevant. For example, a large collaborative analysis combining data from 19 prospective cohort and nested case-control studies, including over 30,000 cases and controls, reported that higher 25(OH)D levels were linked to an increased overall incidence of PCa. However, this association was only observed for non-aggressive PCa, not for aggressive forms [112]. The authors propose that this positive link could be due to detection bias, as men who are health-conscious may maintain adequate vitamin D levels and are more likely to undergo PSA testing and seek medical care for early symptoms [112]. This undermines efforts to assess the true effect of vitamin D on PCa risk and progression.

Another significant trend is the U-shaped association observed between serum 25(OH)D levels and total PCa risk, indicating that both very high and very low vitamin D levels may elevate PCa risk [61,74, 117]. This U-shaped pattern also extends to advanced, high-grade disease [61] and PCa-specific mortality [74]. These findings highlight the importance of determining an optimal range for vitamin D levels to support prostate health, potentially reducing PCa incidence, disease aggressiveness, and PCa-specific mortality, as well as other health conditions.

In addition to observational studies, interventional research, including pilot studies and clinical trials, has explored vitamin D's role in PCa. Early pilot studies suggested a protective benefit of vitamin D for men with histologically confirmed PCa or clinical suspicion of the disease [46,124,37]. Prediagnostic studies, meaning before patients were diagnosed with PCa, found low serum 1,25(OH)D levels to be predictive of PCa risk [26]. Research on estimated dietary vitamin D intake has produced mixed results. Some studies found weak inverse associations between high dietary vitamin D intake and reduced PCa risk [10,116], while others found no significant relationship [45,90]. Similarly, studies assessing serum vitamin D levels and PCa incidence show contradictory findings. While some report a protective role of vitamin D [74], others observe harmful or null associations [123,9]. However, evidence points to a protective effect of vitamin D in aggressive or advanced PCa [44, 49]. When assessing PCa mortality, the role of vitamin D becomes clearer. Case-control studies consistently show that high serum 25(OH)D levels are associated with a decreased risk of lethal PCa [101,73]. Meta-analyses support this protective effect [104,27]. The discrepancies in these findings may be explained by variations in geographic location, sun exposure, and study design.

While the role of vitamin D in PCa remains an ongoing and debated topic, significant challenges persist in designing studies that can yield definitive results. Vitamin D is a complex metabolite, and it is impossible for any intervention to fully replicate the long-term effects of lifelong deficiency. The variability in vitamin D levels across individuals, compounded by racial disparities, underscores the need for more population-specific studies. While many studies in this review reported null findings, there remains strong evidence suggesting that vitamin D may play a critical role in PCa, particularly in populations at higher risk, such as Black men. This research has the potential to enhance diagnosis, prediction, prevention, treatment, and survival outcomes, while also shedding light on biological differences in disease progression across races. Ultimately, the question remains: Could maintaining sufficient vitamin D levels help prevent PCa or reduce its severity, especially in at-risk populations? These insights may not only address racial disparities but also inform broader strategies for PCa prevention and treatment in all populations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data availability

No data was used for the research described in the article.

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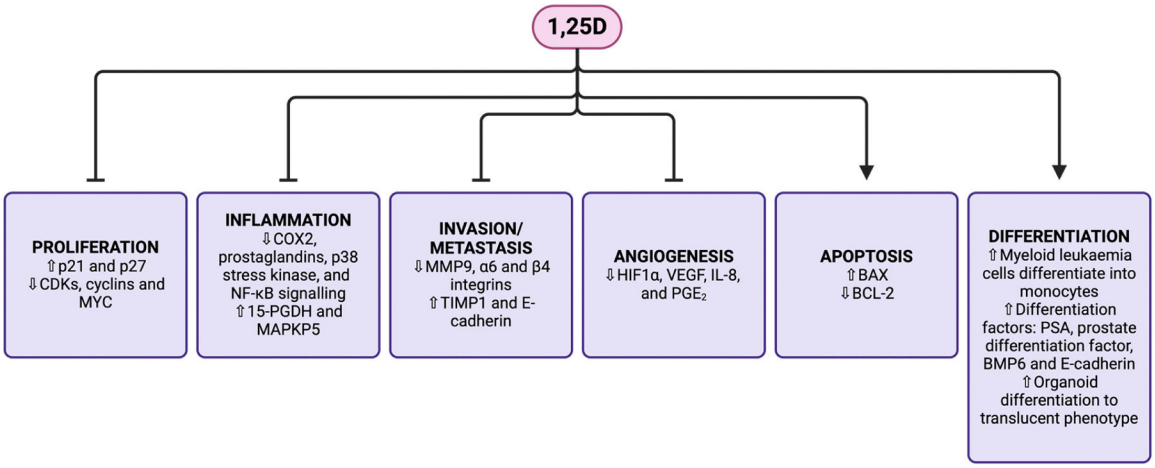


**Fig. 1.**

Vitamin D regulates cancer processes in prostate and inflammatory cells. The active form of vitamin D, 1,25(OH)2D, acts on cancer cells via various mechanisms including inhibiting proliferation, inflammation, invasion/metastasis, and angiogenesis as well as enhancing apoptosis and differentiation. Adapted from [34,71].

**Table 1**

Observational studies investigating the role of vitamin D on prostate cancer[a,b].

| Observational Studies | | | | | |
|---|---|---|---|---|---|
| **VitD Role** | **Author/ Year** | **Population** | **VitD Deficient Population (%)** | **Overall Findings** | **Study Type** |
| Protective | Tseng et al., [116][35] (Edward [44])[36] Tretli et al., [113][37] [74][38] Fang et al., [32][39] Pazdiora et al., [91][40] Der et al., [29][41] Murphy et al., [79][42] Brändstedt et al. [17][43] Mondul et al., [77][44] Nyame et al., [83][45] Nelson et al., [80][46] Deneo-Pellegrini et al., [28][47] Ahonen et al., [3][48] Tuohimaa et al., [117][49] Li et al., [63][50] Mikhak et al., [75][51] Tuohimaa et al., [118][52] Gilbert et al., [43][53] Kristal et al., [61][54] Atoum et al., [6][55] Deschasaux et al., [30][56] | (n = 3612) (88% white race)[35], (n = 1095 cohort used for model; n = 47800 model cohort)[36], (n = 1194)[38], (n = 262)[40] Potential PCa (n = 667)[42] White cigarette smokers with PCa (n = 1000 cases)[44] PCa (n = 160 cases)[37], (n = 1822 cases)[39] , (n = 16535 cases)[41], (n = 943)[43], (n = 190 cases)[45], (n = 155 cases)[46], (n = 175 cases/ n = 233 matched control)[47], (n = 149 cases/ n = 566 matched controls)[48], (n = 622 cases/ n = 1451 matched controls 1:4)[49], (n = 492 cases/ n = 664 matched control)[50], (n = 684 cases/ n = 692 matched control) (>90 % white)[51], (n = 132 cases/ n = 456 matched controls)[52], (n = 1447 cases/ n = 1449 matched control) (98.9 % self- identified white)[53], (n = | Not reported[35,36,40,43,47,49,57,59,60,61]<br>8 % of controls[53]<br>~11.5 % of cases[45]<br>~23 % of controls[48]<br>16 % of cohort (<26 nmol/L)[44]<br>12.7 % of controls (<37.5 nmol/L)[51]<br>~50 % of controls (<40 nmol/L)[52]<br>~25 % of cohort (<44 nmol/L)[39]<br>10 % of cohort (<46 nmol/L)[38]<br>~25 % of controls (<46.2 nmol/L)[58]<br>18.1 % of cohort (<50 nmol/L)[37]<br>19 % of controls (<50 nmol/L)[50]<br>> 25 % of cases and ~30 % of cohort (<50 nmol/L)[54]<br>~34 % of initial cohort (<50 nmol/L)[41]<br>~40 % of cohort (<50 nmol/L)[42]<br>54.5 % of controls (< 50 nmol/L)[56]<br>~60 % of cases (<50 nmol/L)[46]<br>83 % of controls (<50 nmol/L)[55] cohort studies (n = 10 studies; n = 10394 cases)[61] | PCa risk[35,40,42,47,48,49,51,52,53,54,55,56,57,59]<br>Advanced/aggressive/lethal PCa risk[36,45,46,48,50,51,53,54,57,58]<br>mPCa risk[39]<br>PCa mortality risk[37,38,43,60,61]<br>PCa incidence[38]<br>PCa survival[41,44]<br>Tumor stage[42]<br>Gleason Grade[42] | Prospective cohort study[35,36,37,38,39,40,42,43,58]<br>Cohort study[41,44,46]<br>Nested cohort study[45,48,49,50,51,52,53,54,56]<br>Case-control study[47,55,57,59]<br>Meta-analysis[60,61] |

**Observational Studies**

| VitD Role | Author/ Year | Population | VitD Deficient Population (%) | Overall Findings | Study Type |
|---|---|---|---|---|---|
| | ([10], 201)[57] Yuan et al., [128][58] Amiri et al., [5][59] Song et al., [104][60] ([27], 20)[61] | 1731 cases + n = 3203 cohort)[54], (n = 124 cases/ n = 100 matched control)[55], (n = 129 cases/ n = 167 matched control)[56], (n = 699 cases/ n = 958 controls)[57], (n = 111 cases/ n = 150 matched control)[59] Advanced PCa (n = 156 cases/ n = 156 matched control)[58] Prospective cohort studies (n = 7 studies)[60] Retrospective or prospective | | | |
| Null | (E. [45])[1] (J. M. [22])[2] Berndt et al., [15][3] [9][4] Holt et al., [50][5] Kristal et al., [59][6] Skaaby et al., [103][7] Gupta et al., [47][8] (J. M. [21])[9] Jacobs et al., [54][10] Faupel-Badger et al., [33][11] Holt et al., [51][12] Paller et al., [88][13] Shahvazi et al., [98][14] Freedman et al., [36][15] Park et al., | healthy (n = 47781)[1], (n = 454) (>85 % white)[3], (n=1294 cases)[5], (n = 9559)[6], (n = 5866 men)[7], (n = 7493)[15], (n = 4124)[17], (n = 672)[4] Male cigarette smokers (n = 27062)[2] White male cigarette smokers with PCa and matched controls (n = 296 cases/ n = 297 matched control)[11] PCa (n = 4404)[16] stage IV PCa (n = 125 cases)[8] PCa and matched controls (n = 526 cases/n = 536 matched control pairs)[9], (n = 83 | Not reported[1,2,3,14,16,5,6,7,9,12,20,21,22,23,24,25,29,30,31,32,33,34] ~15 % of controls[17] ~25 % of controls (<37 nmol/L)[11] ~35 % of cohort (<50 nmol/L)[15] 25.6 % of cohort (<50 nmol/L)[8] ~15 % of controls (<50 nmol/L)[10] > 25 % of controls (<50 nmol/L)[18] ~50 % of cohort (<50 nmol/L)[19] ~38 % of controls (<50 nmol/L)[26] 31 % of controls (<50 nmol/L)[27] 25 % of controls (<50 nmol/L)[28] ~68 % of controls (<75 nmol/L)[13] | PCa risk[1,2,3,5,6,7,9,10,11,12,13,16,17,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34] Lethal PCa[18] Progression[14] PCa mortality[15] PCa survival[8] | Prospective cohort study[1,2,3,6,7,15,16,17,18,19,30] Cohort study[5,8] Case-control study[20,21,22,9,24,25,12,27,29,13] Nested case-control study[23, 10,11,26,28] Retrospective[29] Meta-analysis[31,32,33,14,34] |

**Observational Studies**

| VitD Role | Author/ Year | Population | VitD Deficient Population (%) | Overall Findings | Study Type |
|---|---|---|---|---|---|
| | [90][16] Ordóñez-Mena et al., [86][17] Shui et al., [100][18] Stephan et al., [107][19] Braun et al., [18][20] Key et al., [56][21] Vlajinac et al., [120][22] Ma et al., [66][23] Kristal et al., [60][24] Tavani et al., [109][25] Travis et al., [111][26] Trump et al., [114][27] Barnett et al., [8][28] Yaturu et al., [126][29] Heath et al., [48][30] Huncharek et al., [52][31] Yin et al., [127][32] Gandini et al., [38][33] Gilbert et al., [42][34] | cases/n = 166 matched controls 1:2)[10], (n = 827 cases/n = 787 matched control pairs)[12], (n = 90 cases/n = 62 matched control pairs)[13], (n = 61 cases/n = 122 controls)[20], (n = 328 cases/ n = 328 controls)[21], (n = 101 cases/ n = 202 controls)[22], (n = 231 cases/ n = 410 controls)[23], (n = 605 cases/ n = 592 controls)[24], (n = 1294 cases/ n = 1451 controls)[25], (n = 652 cases/ n = 752 control)[26], (n = 170 cases/ n = 100 controls)[27], (n = 297 cases + n = 1433 cohort) (>90 % white race)[28] , (n = 479 cases/ n = 479 control)[29] , (n = 833 cases/ n = 1664 controls)[30] Lethal PCa and controls (n = 518 cases/n = 2986 controls)[18] Single arm studies and randomized controlled trials (n = 22 studies)[14] Initial and repeat biopsies (n = 480)[19] Observational studies (n = 6 studies)[31] Prospective cohort studies | | | |

**Observational Studies**

| VitD Role | Author/ Year | Population | VitD Deficient Population (%) | Overall Findings | Study Type |
|---|---|---|---|---|---|
| | | and nested case-control studies (n = 11 studies)[32], (n = 11 studies; n = 3956 cases)[33], (n = 25 studies)[34] | | | |
| Harmful | Wong et al., [123][62], Albanes et al., [4][63], Brändstedt et al., [16][64], Meyer et al., [72][65], [122][66], Jackson et al., [53][67], Xu et al., [125][68], [40][69] | (n = 4208) (>95 % Caucasian)[62] Cigarette smokers with PCa (n = 1000 cases/ n = 1000 matched control)[63], (n = 950 cases/ n = 964 matched control)[66] PCa with matched controls (n = 943 case/n = 838 matched control)[64], (n = 2106 cases/ n = 2106 matched control pairs)[65], (n = 146 cases/n = 191 controls) (predominantly black)[67] Prospective cohort studies and nested case-control studies (n = 21 studies; n=11941 cases)[68], (n = 19 studies; n=12786 cases)[69] | Not reported[64,68,69]<br>< 5 % of controls[65]<br>~33 % of controls (<25 nmol/L)[63,66]<br>~20 % of cohort (<50 nmol/L)[62]<br>~13 % of controls (<50 nmol/L)[67] | PCa risk[62,63,64,65,66,67,68,69]<br>Aggressive PCa risk[63] | Prospective cohort study[62]<br>Nested case-control study[63,64,65,66]<br>Case-control study[67]<br>Meta-analysis[68,69] |
| Null/ Protective | Holt et al., [49][70], Cheney et al., [24][71], Corder et al., [26][72], Gann et al., [39][73], Nomura et al., [82][74], Shui et al., | PCa (n = 1476 cases) (~90 % white race)[70], (n = 90 black and n = 91 white cases/n = 90 black and n = 91 white matched control)[72], (n = 232 cases/ n = 414 matched controls)[73], (n = | Not reported[74,75,76]<br>8.4 % of cohort[70]<br>~13 % of controls (<25 nmol/L)[77]<br>81.1 % of controls (< 50 nmol/L)[78]<br>6.5 % of controls (<37.5 nmol/L)[73]<br>13.3 % of controls (< 37.5 nmol/L)[72]<br>~75 % of cohort (<50 nmol/L)[71] | PCa risk[71,72,73,74,75,76,77,78]<br>Progression/recurrence/mortality[70]<br>Aggressive PCa risk[70]<br>Lethal PCa[75]<br>Gleason Score[76] | Prospective cohort study[70,71,72]<br>Nested case-control study[73,74,75,76,77,78] |

**Observational Studies**

| VitD Role | Author/ Year | Population | VitD Deficient Population (%) | Overall Findings | Study Type |
|---|---|---|---|---|---|
| | [101][75], Schenk et al., [95][76], Layne et al., [62][77], Acikgoz et al., [1][78] | 136 cases/ n = 136 matched controls)[74], (n = 1260 cases/ n = 1331 matched control pairs) (>95 % white)[75], (n = 1695 cases/ n = 1682 matched control)[76], (n = 226 cases/ n = 452 matched controls)[77], (n = 52 cases/ n = 211 matched controls)[78] (n = 2003)[71] | | | |
| Protective/ Harmful | Meyer et al., [73][79] Miles et al., [76][80] Steck et al., [106][81] Travis et al., [112][82] | PCa (n = 2259 cases/n = 2120 matched control)[79], (n = 1695 cases/ n = 1682 matched control)[80], (n=1200 cases)[81] Prospective cohort studies and nested case-control studies (n = 19 studies; n = 13462 cases/ n = 20261 controls)[82] | Not reported[80] 4 % of controls[79] ~7 % of controls[82] ~47 % of cohort (<50 nmol/L)[81] | PCa risk[79,80,82] PCa aggressiveness[81,82] Mortality[79] | Prospective case-control study[79] Prospective cohort study[81] Nested case-control study[80] Collaborative analysis[82] |
| Null/ Harmful | Platz et al., [93][83] Ahn et al., [2][84] Park et al., [89][85] Sawada et al., [94][86] | PCa (n = 460 cases/n = 460 matched control) (>90 % white)[83], (n = 749 cases/ n = 781 matched control)[84], (n = 201 cases/ n = 402 matched controls)[86] invasive PCa (n = 329 cases/ n = 656 matched controls)[85] | Not reported[86] 11.3 % of controls (<37.5 nmol/L)[83] ~20 % of controls (<42.5 nmol/L)[84] ~16 % of controls (<50 nmol/L)[85] | PCa risk[83,84,85,86] Aggressive PCa risk[84] Advanced PCa[86] | Nested case-control study[83,84,85,86] |

[a] Studies ordered in subsections by study result: Null, Protective, Harmful, Mixed.

[b] For consistency, the percentage of study population with vitamin D deficiency is based on controls only with <30 nmol/L as standard deficiency definition (unless otherwise noted). Serum concentrations of 25(OH)D given in ng/mL were converted to nmol/ L, using the conversion factor (1ng/mL =2.5 nmol/L).

**Table 2**

Mendelian randomization studies investigating the role of vitamin D on prostate cancer[a,b].

| Mendelian Randomization Studies | | | | | |
|---|---|---|---|---|---|
| **VitD Role** | **Author/Year** | **Population** | **VitD Deficient Population (%)** | **Endpoint** | **Study Type** |
| Null | Ong et al., [85][1]<br>Jiang et al., [55][2]<br>Cheng et al., [25][3]<br>Ong et al., [84][4] | UKB[1,3] and PRACTICAL[1] (n = 86726 cases/n = 194384 controls)<br>PRACTICAL[2,4] consortium (n = 79148 cases/n = 61106 controls) | Not reported | PCa risk | Mendelian randomization study |
| Null/Protective | Dimitrakopoulou et al., [31] | GAME=ON, GECCO, and PRACTICAL consortiums; (n = 22898 cases/n = 23054 controls) | Not reported | Total or aggressive PCa risk | Mendelian randomization study |

[a]Studies ordered in subsections by study result: Null, Mixed.

[b]For consistency, the percentage of study population with vitamin D deficiency is based on controls only with < 30 nmol/L as standard deficiency definition (unless otherwise noted). Serum concentrations of 25(OH)D given in ng/mL were converted to nmol/ L, using the conversion factor (1 ng/mL = 2.5 nmol/L).

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## Table 3

Pilot and clinical studies investigating the role of vitamin D on prostate cancer[a].[b].

| Pilot Studies and Clinical Trials | | | | | |
|---|---|---|---|---|---|
| **VitD Role** | **Author/Year** | **Population** | **VitD Deficient Population (%)** | **Endpoint** | **Study Type** |
| Protective | Gross et al., [46][13]<br>Beer et al., [11][14]<br>Tiffany et al., [110][15]<br>Woo et al., [124][16]<br>Flaig et al., [35][17]<br>Trump et al., [115][18]<br>Petrioli et al., [92][19]<br>(J. S. [20])[20]<br>Newsom-Davis et al., [81][21]<br>Marshall et al., [68][22]<br>Shamseddine et al., [99][23]<br>Wagner et al., [121][24]<br>Galunska et al., [37][25] | Suspicion for PCa (n = 53)[25]<br>PCa (n = 7 cases)[13], (n = 15)[16], (n = 44 cases)[22], (n = 63) (>80 % white race)[24]<br>mPCa (n = 26 cases)[21]<br>mCRPC (n = 37 cases)[14], (n = 26 cases)[19], (n = 19 cases)[20]<br>CRPC (n = 24 cases)[15], (n = 34 cases)[17], (n = 43 cases)[18], (n = 23 cases)[23] | Not reported[13,14,15,16,18,19,20,21,23]<br>25 % of cases (<20 nmol/L)[22]<br>~9 % of cohort (<37.5 nmol/L)[17]<br>~20 % of cases (<50 nmol/L)[24] | PSA[13,15,16,17,18,19,20,21,23,24]<br>PCa risk[25]<br>Progression[14,15,17,18,22]<br>Survival[14] | Clinical trial[21]<br>Phase I/II clinical trial[15]<br>Phase II[14,16,18.19,20,22,24]<br>Pilot study[25]<br>Non-randomized pilot trial<br>Prospective[16,22]<br>Randomized[24]<br>Double-blind[24]<br>Open label[13,22] |
| Null | Osborn et al., [87][1]<br>Beer et al., [13][2]<br>Liu et al., [64][3]<br>Beer et al., [12][4]<br>Morris et al., [78][5]<br>Schwartz et al., [97][6]<br>Attia et al., [7][7]<br>Srinivas, Feldman. [105][8]<br>Chadha et al., [19][9]<br>Gee et al., [41][10]<br>Chandler et al., [23][11]<br>Manson et al., [67][12] | PCa (n = 14 cases)[1], (n = 22 cases)[2]<br>CRPC (n = 20 cases)[3], (n = 18 cases)[6], (n = 70 cases) (>90 % white race)[7], (n = 18 cases)[9]<br>mPCa (n = 17 cases)[4]<br>progressive PCa (n = 31 cases)[5]<br>recurrent PCa (n = 21 cases)[8]<br>HGPIN or PCa (n = 31 cases) (>95 % white race)[10]<br>healthy black men (n = 105)[11]<br>healthy men (n = 12786 men)[12] | Not reported[1,2,3,4,7,8,9,10,11]<br>12 % of cohort[6]<br>~12 % of cohort (<50 nmol/L)12 | PSA[1,2,4,6,7,8,9,11]<br>PCa progression[3,5,10]<br>Survival[7]<br>PCa risk[12] | Phase I clinical trial[2,4,5,6]<br>Phase II clinical trial[1,3,6,7,8,9,10]<br>Randomized[7,10,11,12]<br>Double-blind[7,11,12]<br>Single arm[8]<br>Open label[8,10]<br>Prospective[11]<br>Placebo-controlled[11,12] |
| Harmful | Scher et al., [96] | mCRPC (n = 953 cases) | Not reported | Survival | Phase III, open-label, randomized clinical trial |
| Null/ Protective | Beer et al., [14] | mPCa (n = 250 cases) | Not reported | PSA<br>Survival | Phase II, double-blinded, randomized clinical trial |

[a]Studies ordered in subsections by study result: Protective, Null, Harmful, Mixed.

[b]For consistency, the percentage of study population with vitamin D deficiency is based on controls only with < 30 nmol/L as standard deficiency definition (unless otherwise noted). Serum concentrations of 25(OH)D given in ng/mL were converted to nmol/ L, using the conversion factor (1 ng/mL = 2.5 nmol/L).

**Table 4**

Research studies investigating the role of vitamin D on prostate cancer in African American men[a].[b]. This table consists of research studies selected from SUPPLEMENTAL TABLE I that specifically demonstrate the relationship between vitamin D and prostate cancer in African American or Black men. Each article was thoroughly reviewed, and relevant data were extracted and documented in the table, including population demographics, the percentage of vitamin D deficient participants (if reported), the key findings, study type classification, as well as the proposed role of vitamin D in prostate cancer. Each study was classified by study type and sorted into subsections: Prospective Cohort and Cohort, Prospective Case-Control, Nested Case-Control, and Case-Control Studies; Pilot Studies and Clinical Trials. Within each subsection, studies are organized chronologically by publication year and subsequently alphabetized by the authors' names.

| Author/Year | Population | VitD Deficient Population | Overall Findings | Study Type | VitD Role |
|---|---|---|---|---|---|
| **Prospective Cohort and Cohort Studies** | | | | | |
| Murphy et al., [79] | Men 40–79 in Chicago, Illinois US undergoing first prostate biopsy for elevated PSA or abnormal DRE (n = 667) | ~40 % of cohort (<50 nmol/L) | Low 25(OH)D levels associated with higher Gleason grade and tumor stage in European men. Low 25(OH)D levels associated with increased PCa risk and high Gleason grade and tumor stage in African American men (measured 25(OH)D levels only). | Prospective cohort study | Protective |
| Steck et al., [106] | Men 40–79 in North Carolina and Louisiana, US with initial diagnosis of histologically confirmed PCa (n = 1200 cases) | ~47 % of cohort (<50 nmol/L) | High 25(OH)D levels associated in African American men with increased PCa aggressiveness with low calcium intake and decreased PCa aggressiveness with high calcium intake (measured 25(OH)D levels only). | Prospective cohort study | Harmful/ Protective |
| Nelson et al., [80] | African American (self-described) men 40–85 in Washington, DC, US diagnosed with incident PCa (n = 155 cases) | ~60 % of cases (<50 nmol/L) | Low 25(OH)D levels associated with increased risk of aggressive PCa (measured 25(OH)D levels only). | Cohort study | Protective |
| **Prospective Case-Control, Nested Case-Control, and Case-Control Studies** | | | | | |
| Corder et al., [26] | Black and White men in California, US diagnosed with PCa along with matched controls (n = 90 black and n = 91 white cases/ n = 90 black and n = 91 white matched control pairs) | 13.3 % of controls (<37.5 nmol/L) | No significant associations between 25(OH)D levels and PCa risk. High 1,25(OH)2D levels associated with decreased PCa risk, especially in older men (>57) or those with low 25(OH)D (measured both 25(OH)D and 1,25(OH)2D levels). | Prospective case-control study | Null/ Protective |
| Kristal et al., [61] | Men ≥ 50 (for African American) or ≥ 55 (other) in US, Canada, and Puerto Rico diagnosed with primary PCa for cases or blood samples available for cohort (n = 1731 cases + n = 3203 cohort) | > 25 % of cases and ~30 % of cohort (<50 nmol/L) | U-shaped association of 25(OH)D levels and total PCa risk, especially in high-grade disease. In African American men, high 25(OH)D levels associated with decreased risk of high-grade PCa only (measured 25(OH)D levels only). | Nested case-cohort study | Protective |
| Jackson et al., [53] | Men 40–80 in Jamaica recently diagnosed with histologically confirmed PCa along with controls (n = 146 cases/n = 191 controls) (predominantly black) | ~13 % of controls (<50 nmol/L) | High 25(OH)D levels associated with increased PCa risk (measured 25(OH)D levels only). | Case-control study | Harmful |
| Paller et al., [88] | Black men ≥ 40 in Washington, D.C., US diagnosed with PCa along with matched controls (n = 90 cases/n = 62 matched control pairs) | ~68 % of controls (<75 nmol/L) | No significant associations between 25(OH)D levels or dietary intake/supplementation and PCa risk (measured 25(OH)D levels and dietary intake). | Case-control study | Null |

| Author/Year | Population | VitD Deficient Population | Overall Findings | Study Type | VitD Role |
|---|---|---|---|---|---|
| **Prospective Cohort and Cohort Studies** | | | | | |
| ([10], 201) | Men 40–79 in Chicago, Illinois and Washington, D.C., US diagnosed with histologically confirmed PCa along with controls (n = 699 cases/n = 958 controls) | Not reported. | High vitD dietary intake associated with decreased risk of aggressive PCa. High vitD dietary intake associated with decreased total PCa risk in African Americans (measured dietary intake only). | Case-control study | Protective |
| Layne et al., [62] | Black men 55–74 in US diagnosed with PCa along with matched controls (n = 226 cases/ n = 452 matched controls 1:2) | ~13 % of controls (<25 nmol/L) | No significant associations between 25(OH)D levels and PCa risk. High 25(OH)D levels associated with decreased risk of nonaggressive disease (measured 25(OH)D levels only). | Nested case-control study | Null/ Protective |
| **Pilot Studies and Clinical Trials** | | | | | |
| Chandler et al., [23] | Black men supplemented with 1000, 2000, or 4000 IU vitD or placebo (n = 105) | Not reported. | No significant effect of vitD supplementation and PSA levels (measured 25(OH)D levels only). | Prospective, randomized, double-blind, placebo-controlled clinical trial | Null |

[a]Studies ordered in subsections by study type classification: Prospective Cohort and Cohort Studies; Prospective Case-Control, Nested Case-Control, and Case-Control Studies; Pilot Studies and Clinical Trials. Within each subsection, studies ordered chronologically by publication date and subsequently alphabetically by authors' last name.

[b]For consistency, the percentage of study population with vitamin D deficiency is based on controls only with <30 nmol/L as standard deficiency definition (unless otherwise noted). Serum concentrations of 25(OH)D given in ng/mL were converted to nmol/ L, using the conversion factor (1ng/mL =2.5 nmol/L).