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Does Vitamin D Deficiency Increase Prostate Cancer Risk? A Systematic Review of the Literature

Nancy Espelin
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Does Vitamin D Deficiency Increase Prostate Cancer Risk? A Systematic Review of the Literature

Abstract

Background: The concept that cancer incidence and mortality are related to latitude was first suggested in 1930. Since then, there have been a plethora of studies addressing that connection. Studies of vitamin D have demonstrated its anti-proliferative, anti-angiogenesis and differentiating properties which are all anti-neoplastic. The relationship between prostate cancer and latitude has long been suspected. Prostate cells have vitamin D receptors and enzymes for hydroxylation of vitamin D metabolites and enabling anti-carcinogenetic effects. As a result of these findings, many ongoing studies are evaluating whether vitamin D deficiency impacts prostate cancer risk. This review summarizes the last two years of published studies on this topic.

Methods: The search used Ovid/Medline, PubMed, CINAHL and Web of Science databases limited to include clinical studies, English language, major journals and including articles from 2007 to the present. Review of the abstracts produced the relevant studies, and the bibliographies of these articles led to other sources not found in the search. Keywords: prostate cancer, risk, vitamin D and vitamin D deficiency.

Results: Five studies reviewed from the end of 2007 to the present were germane to the research topic. One study was an observational study, one a prospective study and the remainder were case control studies from much larger randomized controlled trials. Only one case reviewed the relationship between solar radiation and prostate cancer risk and all the relationships were positive for low solar radiation and higher prostate cancer risk. Three studies reviewed the relationship of serum levels of vitamin D and prostate cancer risk relative to polymorphisms of the VDR and two found that low levels of serum vitamin D increase prostate cancer risk, especially aggressive prostate cancer risk. One large study examining serum concentrations of only one vitamin D metabolite found no association with PCa.

Conclusions: Vitamin D deficiency is a widespread health issue. There is an increased risk of prostate cancer with low vitamin D levels.The risk is greater with more aggressive disease. Conflicting results regarding PCa risk and VDR polymorphisms in light of low vitamin D levels, and it may be a one-time serum sample which causes these discrepancies. There is an association between solar radiation and PCa risk, need to follow the serum levels or solar exposure of patients much younger. Both metabolites need to be measured to understand the impact on prostate cancer risk, especially since the data shows an increased risk with aggressive disease with the one typically not measured. One serum sample does not provide information needed for understanding the relationship between vitamin D and PCa. More prospective studies beginning at an earlier age with more serum samples and solar radiation studies are needed in order to better understand the relationship between prostate cancer and vitamin D.

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Degree Name
Master of Science in Physician Assistant Studies

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Keywords
prostate cancer, risk, vitamin D, vitamin D deficiency

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NOTICE TO READERS

Does Vitamin D Deficiency Increase Prostate Cancer Risk? A Systematic Review of the Literature.

Nancy Espelin

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Judy Ortiz, MPAS, PA-C
Clinical Graduate Project Coordinators:
Rob Rosenow PharmD, OD
&
Annjanette Sommers MS, PAC

Biography

       Born and raised in Montana, Nancy attended Montana State University Bozeman for her bachelor in Political Science and her master's degree in Public Administration. She took an active role in the campus community by editing her university newspaper, directing the campus media including literary magazine, yearbook and public radio station and directing the university transit system. She also worked at the Bozeman Chronicle, the local paper.

       Following graduate school, she worked for the states of Montana, Arizona and Iowa in performance and program improvement and in research for legislative and executive branch agencies. Following a move to the Kansas City area, she consulted in marketing and finance. Missing family and the West, she moved with her family to and purchased a small business in Spokane, Washington. After selling her business to complete her master's thesis and taking a small break with her family, she tackled customer service and sales for a concrete tie manufacturer and, later, a major aluminum manufacturer. Always interested in process improvement, she learned and led lean manufacturing through shop floor and office kaizens at the aluminum manufacturer and later at a Spokane steel foundry.

       Nancy lived in Spokane for over 18 years with her two children Kellie, 21 and Bryan, 24, before selling her house and moving to the Methow Valley in late. Her companion Alex Kerr and she moved there where they live on the family's Methow River farm, four miles west of the small community of Methow. Her daughter Kellie is working as an emergency room technician at Sacred Heart, in Spokane, while attending EWU, but plans to return to WSU Pullman August 2009 to complete her biology degree before applying to PA school. Bryan is a 2008 WSU alumnus, currently living with the love of his life Teresa Gjendom, and working as an electrical engineer in Bothel, Washington.

       Nancy volunteers extensively in the community by providing emergency medical care in the outdoor environment for activities including skiing, mountain and road bike races and foot races. Additional training provided her the skills she needed, to not only train people within her local area, but also to travel throughout the region training students and new instructors in pre-hospital scene management and medical skills. She also taught CPR when there was a shortage of instructors.

       Nancy helped design and implement an educational program to help identify young children with developmental delays within Spokane County and then worked with a group that provided them into services to help them reach their maximum potential before they entered the school based programs.

       Her volunteering led her to the realization that she could make a difference in people's lives, while challenging herself to continuously improve her medical knowledge and skills. She now is completing her Masters in Physician Assistant Studies degree at Pacific University so that she can fulfill that desire in her vocation as well as her volunteering. Nancy is excited to be attending Pacific as it was her late father's alma mater where he completed his degree in optometry.

Abstract

Background
        The concept that cancer incidence and mortality are related to latitude was first suggested in 1930. Since then, there have been a plethora of studies addressing that connection.
        Studies of vitamin D have demonstrated its anti-proliferative, anti-angiogenesis and differentiating properties which are all anti-neoplastic. The relationship between prostate cancer and latitude has long been suspected. Prostate cells have vitamin D receptors and enzymes for hydroxylation of vitamin D metabolites and enabling anti-carcinogenetic effects. As a result of these findings, many ongoing studies are evaluating whether vitamin D deficiency impacts prostate cancer risk. This review summarizes the last two years of published studies on this topic.

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Results
        Five studies reviewed from the end of 2007 to the present were germane to the research topic. One study was an observational study, one a prospective study and the remainder were case control studies from much larger randomized controlled trials. Only one case reviewed the relationship between solar radiation and prostate cancer risk and all the relationships were positive for low solar radiation and higher prostate cancer risk. Three studies reviewed the relationship of serum levels of vitamin D and prostate cancer risk relative to polymorphisms of the VDR and two found that low levels of serum vitamin D increase prostate cancer risk, especially aggressive prostate cancer risk. One large study examining serum concentrations of only one vitamin D metabolite found no association with PCa.

Conclusions
        Vitamin D deficiency is a widespread health issue. There is an increased risk of prostate cancer with low vitamin D levels.The risk is greater with more aggressive disease. Conflicting results regarding PCa risk and VDR polymorphisms in light of low vitamin D levels, and it may be a one-time serum sample which causes these discrepancies. There is an association between solar radiation and PCa risk, need to follow the serum levels or solar exposure of patients much younger. Both metabolites need to be measured to understand the impact on prostate cancer risk, especially since the data shows an increased risk with aggressive disease with the one typically not measured. One serum sample does not provide information needed for understanding the relationship between vitamin D and PCa. More prospective studies beginning at an earlier age with more serum samples and solar radiation studies are needed in order to better understand the relationship between prostate cancer and vitamin D.

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Thanks go to my children Bryan and Kellie Brennan who have not disowned me for selling their home and running off to Oregon to attend PA school. Instead, they have endured and thrived, and in all of this adversity, supported my dreams while they worked on their own. I knew we could do it. Remember, education is a journey, not a destination. May yours be long and rewarding.

Very special thanks go to my companion of many years Alex Kerr, who, through his kind and gentle manner, supported my decision to go to PA school, was there when the children or I needed him, and who handled all the small details of life that escaped me during the past two and-a half years.

Thanks to the Kerr family who supported me and my family in kindness and bricks and mortar from time to time, throughout this quest. Bill and Angus for hospitality, Sheila for grub and support and Neil for connectivity and humor. It takes a village to put a PA student through school, and with your help, the task is near complete.

Thanks also to my small circle of 'us girls' here at school Emily, Andrea, Nicole and Amy, who kept the insanity in check with wine not whine, with turns on the mountain not of the mountain of pages, and with assurance that we were all losing our minds.

And it would be remiss of me not to acknowledge my small cadre of girlfriends from high school, especially Jayme Wendland, DeAnn Miller and Deb Harris, who have been the voice of reason and comfort. I especially thank Jayme and her lovely family, who listened to all my stories of the past couple years with laughter and a good glass of the vintage. With my family being so far away, it was most excellent that Alex and Paige allowed me to be their 'ant' fulfilling that gap..

The most underpaid people in this process, are the scores of volunteer preceptors who take extra time out of their lives to pay back the time others gave to them, by taking on a student and helping them learn, not only the science, but also the great art of medicine. These folks went out of their way to impart, not just their knowledge, but also their skills and insights. I wish to thank: Robert Shelley, M.D., Mark Vance, MD**,** Jared Papa, PA-C, and Donna Dabney, PA-C of Quincy Community Health Center; Ken Wiscomb, PA-C, North Bend Medical Center, North Bend, WA; Karen LeJomb, ARNP, Snowqualmie, WA; Judah Gold-Merkel, PA-C, Marcos Barnatan, M.D, and Mathew Foley, M.D, Legacy Columbia Vascular and Endovascular Specialists, Portland, OR; Jose' Diaz, PA-C and Chris Casey, PA-C, OkanoganDouglas County Hospital District, Brewster, WA; Mark Pico, M.D., Hillsboro, OR; Wendy Tong, M.D., John Oakland, M.D., Britta Fischer, PA-C, Danhua Wallace, ARNP, Julio Gonzolez, M.D., Whidbey General Hospital, Coupeville, WA; and Bruce Bowman, M.D., Bellingham, WA. These preceptors are exemplary physicians, excellent instructors and phenomenal people, and it was a privilege for me to be allowed to be a part of their practices and to take part in treating their patients. I hope to someday repay my debt to their investment by also taking on students.

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List of Abbreviations

1,25(OH)$_2$D…………………………………………...……………………. ………calcitriol

25(OH)D…………………………………………………...……25-hydroxyvitamin D

CGEMS……………………….National Cancer Institute Cancer Genetic Markers of Susceptibility

D$_3$ …………………………………………………………………….. cholecalciferol

DRE…………………………………………..…………………..……………direct rectal exam

EPIC……………………………..…European Prospective Investigation into Cancer and Nutrition

HPFS…………………………………..………………….Health Professionals Follow-up Study

mL …………………………………………..……………………………………...milliliter

NHANES………...…………………………..National Health and Nutrition Examination Survey

NHEFS……………………...………Nutrition Examination Survey I Epidemiologic Follow-up Study

NIH…………………………...……………………………..…National Institutes of Health

ng…………………………...………………..……………………………...…..nanogram

nmol…………………………………………...…………………….....nanomoles per liter

PCa…………………………………………..…………………...…………...… prostate cancer

PHS……………………………………………………………………Physicians Health Study

PICO………………………………….Prostate, Liver, Colorectal and Ovarian Cancer Screening Trial

PSA…………………………………..…………………….…...prostate specific antigen

SNP………………………………………….……………single nucleotide polymorphism

UVB……………………………………………..…………………….....ultraviolet B

VDR…………………………………………………..….….Vitamin D receptor

UTR…………………………………………………………………….untranslated region

Does Vitamin D Deficiency Increase Prostate Cancer Risk? A Systematic Review of the Literature.

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in the country. It is the second leading cancer affecting males in the U.S.. There are approximately 220,000 new incidences and about 20,000 deaths each year.[1] The five-year survival rate for localized or regional prostate cancer (PCa) is 100%, but if the cancer is metastasized at diagnosis, the rate drops to as low as 32%.[2] About 80% of PCa is diagnosed at the localized stage, and two-percent is diagnosed after spread just beyond the primary site or lymph nodes. [3]

Prostate cancer will effect one in every six men in the U.S..[3] This cancer primarily affects elderly men, with the median age at diagnosis, at 68 years (see Figure I).[3] The risk of PCa increases with age, beginning at around 40. For the most part, the disease remains subclinical until around the age of 45, when the rate of diagnosis significantly increases (see Figure I). Fifty-seven percent of PCa diagnoses are in men 65 years and older, and roughly one third of those diagnosed are between the ages of 55-64.[4, 5] In one study, autopsy prostate tissue samples revealed that there is an age-dependent increase in PCa.[6] In this study, about 35% of deceased men from ages 60-69 had PCa and 46% of men from the ages 70-81 had PCa, demonstrating the significant increase in the disease as men age, and the pervasiveness of the disease at the older ages.

Prostate cancer incidence rate varies significantly depending on race and ethnic background (see Figure II). Asian and Pacific Islanders have relatively low incidence rates and this is partially attributable to their fish diet.[3] African American men are impacted at a substantially higher rate than white men, and their mortality rate is nearly double that of white men. (See Figure II).[2, 3]

Prostate cancer impacts the lives of a great number of people each year with medical costs, worry regarding possible disease progression, medication side-effects, multiple medical office visits and frequent testing. Medical costs of PCa each year per patient amount to roughly $13,000.[2, 3] As of 2006, there were approximately 2.2 million people living with a prostate cancer history, and, as the U.S. population ages, this number is expected to rise significantly in spite of recent trends downward (see Table II). [2, 3]

BACKGROUND

Prostate cancer is generally thought of as an insidious disease, developing many years subclinically. It typically is diagnosed at the point men are old enough for prostate exam screening, normally at age 50 unless if there is a family history or clinical signs. Sometimes it is never diagnosed and it becomes something men die with, rather than of, only being discovered during autopsy. Screening may be changing that scenario as it identifies up more and more disease. Screening consists of annual digital rectal exams (DRE) and prostate specific antigen (PSA) blood tests. Following initiation of the screening process, once the DRE notes asymmetric indurations or nodules or the PSA rises above 4ng, further investigation usually occurs with patients being referred to an urologist for a prostate biopsy. Some prostate cancer develops rapidly and signs appear clinically in a shorter time period.[2]

Prostate cancer, confined to the gland, is potentially curable, typically with resection of the gland. But within ten years of radiation therapy or radical prostactectomy, approximately 20-40% of PCa recurs, heralded by increasing PSA. Of these recurrent cases, a third will progress to clinical disease within eight years and treatment, at this point, is not well defined.[4]

Extraprostatic cancers are treated with hormone or radiation therapy. Prostate growth and prostate cancer growth is androgen dependent and the treatment for advanced prostate cancer is androgen deprivation that results in prostate cell death. This treatment lasts a brief 14-20 months when the natural course of progression of prostate cancer leads to androgen independence. At that point, mean survival decreases to 19 months utilizing doxetaxel-based therapies.[4] Side effects of prostate cancer treatment can include urinary incontinence, erectile dysfunction, sterility, proctitis, rectal bleeding, diarrhea, bleeding.[7] This area of androgen-independent PCa is one of great resource expenditure with a large number of studies directed at treatment of aggressive or advanced prostate cancer.

The etiology of prostate cancer is not fully understood, but several risk factors have been identified, including obesity and dietary fat which some studies show it is a risk factor while others do not.[2, 8, 9] Some studies indicate red meat increases prostate cancer risk.[10] Research investigating the relationship between diet and prostate cancer risk is ongoing.[10]

VITAMIN D & PROSTATE CANCER

Vitamin D has been investigated for years as having a potential impact on cancer in general.[4] Schwartz et al noted in 1990, that the major risk factors for prostate cancer include: older age, black race and residence at northern latitudes.[11] All of these risk factors have in common the reduced ability to synthesize vitamin D. In 1992, they printed a cartographic analysis which showed that the U.S. country-wide mortality rates for prostate cancer among white men, were correlated inversely with ultraviolet radiation, the major source of vitamin D (also see Figure III).[11] Schwartz also found that although levels of 25(OH)D were lower at higher latitudes, the levels of the active form of vitamin D, $1\alpha,25(OH)_2D$, remained the same. Schwartz and his group proposed

that the reason for this was that the prostate produced its own active form of vitamin D in spite of levels of 25(OH)D .[4]

Prostate cells and PCa cells have vitamin D receptors (VDR) in the nucleus that have a high affinity for the $1,25(OH)_2D$ form of vitamin D. These receptors initiate "pleotropic anticancer effects" on normal and PCa cells inhibiting cell proliferation, invasion, migration and metastasis.[4] They also inhibit cells that promote cell differentiation and angiogenesis.[10] With the recognition that vitamin D has protective qualities, the possibility of using vitamin D for preventing prostate cancer was introduced. Since then, several studies have addressed the etiology of prostate cancer and the vitamin D hypothesis.[11]

VITAMIN D METABOLITE SYNTHESIS

Vitamin D is a fat-soluble prohormone that plays an active role in bone health, neuromuscular modulation, immune modulation and anti-inflammatory activity. Vitamin D is essential for calcium absorption in the intestine and for maintaining serum and phosphate concentrations for normal cell functioning and the maintenance of bone health. Not only is it important for bone mineralization, but also it serves roles in modulating neuromuscular and immune functions and in regulating inflammation.[12] A key component in our immune system, T-cells have a vitamin D receptor which, when filled, modulates T-cell activity.[13]

Approximately 90% of vitamin D is produced endogenously from the absorption of UVB in the skin, and the remaining 10% is absorbed from the intestine.[14] Vitamin D is available in fatty fish, eggs and fortified dairy products. Vitamin D levels also can be supplemented with vitamin D or multivitamin pills.[14]

Vitamin D must go through two hydroxylations in the body before it is transformed to its active form.[14] Synthesis of vitamin D metabolites begins in the skin with the production of D_3 (cholecalciferol) after the 7-dehydrocholesterol in the skin is exposed to ultraviolet radiation.[4, 14] Cholecalciferol is then hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D) or calcidiol. The second hydroxylation occurs principally in the kidney resulting in bioactive vitamin D, 1α,25-dihydroxyvitamin D (1,25(OH)$_2$D or calcitriol). Organs other than the liver and the kidneys that also hydroxylize vitamin D into 1,25(OH)$_2$D include the colon, breasts and the prostate.[12]

Influences that can decrease the absorption of UVB in the skin include age, skin pigmentation, sunscreen usage, latitude of residence, season and time of day.[12] The enzyme that is necessary for the hydroxylization of vitamin D in the skin, is diminished in elderly people due to the age-related reduced production of the enzyme responsible for hydroxylation. This effectively decreases the amount of vitamin D hydroxylized. A 70 year-old person makes about 25% of the cholecalciferol made by a 20-year old.[12] Skin color also impacts the amount of vitamin D produced. People with darker skin have more melanin which protects the skin from UV absorption, so they need extended exposure in order to gain the same benefit from absorption that lighter skinned people obtain. The latitude, season and time of day also impact the absorption of UVB into the skin as these conditions all cause an oblique angle for the sun's rays, thereby increasing the distance that it travels through the ozone before being absorbed.[12] Hence, latitudes further from the equator decrease the body's ability to synthesize vitamin D. UVB absorption in winter months can be reduced as much as 80%-100%, again depending on the latitude and hours of the day due to the oblique angle of the suns rays.[12]

Vitamin D absorption into the serum is also affected by gastrointestinal, parathyroid, hepatic and renal diseases. These diseases impact the absorption of vitamin D and the conversion

of vitamin D into its active form. Additionally, since vitamin D is a fat soluble vitamin, it is stored in the fat of obese people and not maintained in the serum which can lead to a vitamin D deficiency in this population.[14]

Vitamin D deficiency is widespread in the United States. Data from the National Health and Nutrition Examination Survey (NHANES) demonstrated that a large proportion of men had a suboptimal vitamin D level.[15] The study found that this especially was prevalent during winter and spring months with a 33% deficiency and with a 66% insufficiency. [15]

Currently considered the best indicator of vitamin D levels in the body, is the serum concentration of 25(OH)D, which reflects both cutaneous production and dietary absorption.[14] One reason why 25(OH)D is considered a good indicator of serum vitamin D, is because of its relatively long half-life of 15 days versus $1\text{-}\alpha,25(OH)_2D$ at only four hours.[12] Serum concentrations are tightly controlled by parathyroid hormone, calcium and phosphate. Calcitriol is also produced locally to maintain levels in the body when a 25(OH)D deficiency exists, which means that calcitriol levels only fluctuate in the presence of a severe 25(OH)D deficiency. Serum 25(OH)D is limited in its value as a measure of total body stores however, since it can only indicate serum levels and not the levels stored in other body tissues (see Figure IV).

Recommendations for daily intake of vitamin D are listed on the NIH Office of Dietary Supplement's website, but, in spite of these recommendations, vitamin D deficiency is widespread in the U.S., especially in white and Black males. NHANES I found serum 25(OH)D at these levels:[15]

- 1-9%   <11 ng/mL (<27.5 nmol/L)
- 8-36% <20 ng/mL (<50 nmol/L)
- 50-78% <30 ng/mL (<75 nmol/L).[14]

Generally < 30 ng/mL is considered by health experts to be inadequate.[14] Roughly 50-78% of the NHANES I participants were vitamin D deficient. See Table III for details regarding recommendations for healthy levels of vitamin D.

VITAMIN D AND PROSTATE CANCER

Prostate cells and prostate cancer cells have receptors with a high affinity for the hormonal vitamin D form, $1\text{-}\alpha,25(OH)_2D$. These receptors are referred to as vitamin D receptors (VDR). The the vitamin D metabolite $1\text{-}\alpha,25(OH)_2D$ is the one that has pleiotrophic anticancer effects on normal and cancerous prostate cells which have been demonstrated in numerous studies.[4] The metabolite interaction with the VDR facilitates apoptosis and inhibition of cell proliferation, invasion, migration, metastasis and tumor angiogenesis. Vitamin D maintains the normal phenotype of prostatic cells through the differentiation of those cells.

Throughout the years, there have been a myriad of studies surrounding this topic. Some examined at the relationship between vitamin D serum levels and prostate cancer risk. Others tried to associate it with solar exposure, a vitamin D surrogate, with PCa risk, and still other researchers looked at vitamin D intake and PCa risk.[10] A systematic review on the topic estimated that 42% of PCa risk may be genetic.[10] The review summarized that the relationship between the genetic factors and the environment are complicated and more, larger interdisciplinary epidemiological studies are needed.[10]

Indications are that the vitamin D receptor (VDR) has a significant impact in the course of the disease, and it is for this reason tests are ongoing which use vitamin D in the treatment regimen for advanced cancer.[4] This topic continues to interest the research community as they question if vitamin D deficiency increases prostate cancer risk. In the last year-and-a-half, one hundred

articles have been published on the topic of prostate cancer and vitamin D (MEDLINE search). If vitamin D deficiency can be managed through either UVB exposure or vitamin D supplementation to reduce prostate cancer incidence, then this public health issue could make a turnaround in terms of quality of life and cost of health care. To date, studies continue to show conflicting results with regard to the vitamin D association, but in spite of this, a systematic review of the epidemiological literature through much of 2008, concluded that the association between vitamin D and PCa risk is conclusive whether that association is through UVB or endogenous deficiency.[4, 10] Since this topic gives rise to conflicting conclusions within the research world, this paper evaluates the results and the quality of the studies in the past two years to determine if there could be definitive conclusions regarding the question of whether vitamin D deficiency increases prostate cancer risk.

METHODS

The thorough literature review used medical databases including Ovid/Medline, PubMed, CINAHL and Web of Science. The criteria limited articles to clinical studies, English language, major journals articles published from 2007 to the present. The review process included reading all the abstracts for relevancy and then reading the bibliographies from these articles to determine if there were any missing studies. The included articles in this study are listed in Table I. Keywords: prostate cancer, prostate cancer risk, risk, vitamin D and vitamin D deficiency.

RESULTS

Table I summarizes all the studies and their findings. Only one case reviewed the relationship between solar radiation and prostate cancer risk and all the relationships were positive for low solar radiation and higher prostate cancer risk. [20] Three studies reviewed the relationship of serum levels of vitamin D and prostate cancer risk relative to polymorphisms of the VDR and two found that low levels of serum vitamin D increase prostate cancer risk, especially aggressive prostate cancer risk.[15, 16, 18] One large study examining serum concentrations of only one vitamin D metabolite found no association with PCa.[17] Descriptions of these studies and their findings are found in this section, and a discussion of the merits of these cases and their findings are found in the following section.

The John et al study published in 2007 study was a nested case study from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHEFS). [20] This study cohort included 14,407 people 25-74 years of age in the (National Health and Nutrition Examination Survey) NHANES I in 1971-75. Of this group, there were 5,811 male participants from 55- 77 years of age of whom 306 were lost to follow-up (5.3%). In the follow-up study, researchers examined prostate cancer risk with early-life adult residential sun exposure and adult sun exposures that were assessed through self-report and a physician report and a dermatologic exam. Of the 5,811 total male participants, there were 249 who were diagnosed or deceased from PCa during the follow-up period which lasted from 1982-1992. Of these 249, there were 161 white cases selected. In NHEFS, there were 3,367 non-Hispanic men without prostate cancer for whom sun exposure information was available to researchers. [20]

In John et al solar radiation in the state of birth was used as a measure of early-life sun exposure. Interviews with patients allowed them to determine solar exposure relative to the

residence length, to workplace exposure or to recreational exposure. They used Cox proportional regression modeling to estimate the relative risk of prostate cancer with 95% confidence intervals, which they age-adjusted. Only age needed to be adjusted because previous experience with the NHANES I study demonstrated no confounding relative to PCa by family history, fat or calcium intake. [20]

Researchers looked at whether the vitamin D was more influential on early-state disease versus advanced by analyzing the combined PCa cases of those that were nonfatal verses fatal. They also stratified results for non-fatal and fatal cases to see the relationship with each type of PCa. They concluded that there was a significant reduction in PCa risk of fatal prostate cancer with both early-life and adult residence in an area with high solar radiation. [20]

John et al found significant inverse associations between PCa incidence and men born in areas of high solar radiation with a 48% lower risk of PCa (RR 0.52); 95% CI, 0.32-0.8. They postulated a possible reason for this early-life association may lie in the development of the neonatal prostate because it expresses VDR receptors. Early life-exposure of rats with high 1-α,25(OH)$_2$D results in changes of the cellular composition of the prostate, from highly epithelial, to more stromal.[19] Since epithelial cells are the targets for oncogenesis, researchers proposed that this may be a possible way in which early-life exposure to vitamin D can reduce prostate cancer risk. [21]

John also concluded that people who live in an area of high residential solar radiation associates with reduced PCa risk (RR 0.59) 95% CI, 0.39- 0.88. With the data bifurcated, the study revealed that the state of high solar radiation and frequent solar exposures as an adult, produces a significant reduction for total PCa (RR 0.66) 95% CI, 0.47-0.93. The relationship between adult exposure and reduced risk especially holds true for fatal PCa (RR 0.34) 95% CI, 0.18-0.66. [20]

Study researchers concluded that their results were consistent with other studies that showed 1-α,25(OH)$_2$D inhibits PCa cell invasion and metastasis. They commented that these findings illustrate the need for additional studies to distinguish effects of early-sun exposure and the impact on advanced/fatal prostate cancer.[20]

The Li study et al was a nested case-control study of the Physician's Health Study (PHS) which was a randomized, double-blinded and placebo controlled trial of aspirin and β-carotene with 22,071 healthy male physicians in the U.S.. The study began in1982 with follow-up complete through the year 2000; the aspirin arm was terminated in 1987 due to the positive effects on cardiovascular health. Blood samples of 14, 916 men were drawn before randomization between the months of September and November, and it was from this baseline blood draw that study participants were selected. There were 1,066 men who developed PCa between the study initiation in 1982, and the end of the follow-up period in 2000. Due to financial constraints, only baseline plasma concentrations of 25(OH)D and 1-α,25(OH)$_2$D of 492 patients and 664 controls were measured along with DNA extraction. Cases were matched with three to four controls by age and smoking status. The final count evaluated 461 cases, matched to 471 controls, to discover the association between plasma vitamin D metabolites and VDR polymorphisms relative to PCa risk. They also checked to determine whether the interaction of the aspirin and the β-carotene modified the interaction of vitamin D and VDR polymorphisms and what their impact was on PCa risk.[15]

Li et al confirmed that vitamin D is a significant health issue, demonstrating that one-third of the study participants had a vitamin D deficiency, and that in the winter and spring, over half of the study participants were deficient. Over two-thirds had insufficiency in this crucial vitamin.[15]

The study results suggested that both vitamin D metabolites (25(OH)D and 1α,25(OH)$_2$D) may play a role in PCa progression. They indicated that men with low levels of both of the vitamin

D metabolites, had an increased risk of aggressive PCa (advanced stage or high-grade), but not of non-aggressive prostate cancer. The authors reason that there has been inconsistency in other studies because those studies did not separate aggressive prostate cancer out from total PCa generally. Since the etiology of advanced PCa is different than the less aggressive form, these studies miss important data.[15]

The study examined the VDR polymorphisms that may be influenced by the vitamin D metabolite. Li et al found that vitamin D interacts with the VDR FokI polymorphism and modifies PCa risk. Also, men with the less functional FokI *ff* genotype were more susceptible to PCa in presence of low 25(OH)D levels, and this susceptibility translates into a two-fold increased PCa risk. Conversely, men with the FokI *ff* genotype and high levels of 25(OH)D had a reduced risk for total and aggressive PCa. In this study, the authors indicated that two other studies reported the opposite finding: an increased risk with this genotype in the presence of high sun exposure. In past studies the BsmI polymorphism had been indicated as having interactions with vitamin D metabolites, however, this was not supported in the Li study with the winter and spring timeframe.[15]

This study also refuted other studies conclusions that age differences related to either metabolite, were insignificant. They found that low plasma $1\text{-}\alpha,25(OH)_2D$ levels and the risk of aggressive PCa was prevalent among older men or men with insufficient 25(OH)D levels. Their research also suggested that the depletion of $1\text{-}\alpha$-hydroxylase, which converts vitamin D to its active form, has a role in the development and progression of PCa. As mentioned earlier in this paper, it is known that the levels of this enzyme decreases with advancing age. It was determined that low 25(OH)D did not impact $1,25(OH)_2D$ status with increased $1\text{-}\alpha$-hydroxylase activity, and this finding was attributed to the possibility that there may not be a correlation between the two

metabolites in samples collected in the winter and spring timeframe. With a lower 1-α-hydroxylase activity and low 25(OH)D status, this predisposes older men to a higher risk of PCa. The study suggested that low levels of both metabolites may be more indicative of vitamin D insufficiency than the current serum measurement of only 25(OH)D. Typically, the prostate produces its own $1,25(OH)_2D$ with a 25(OH)D deficiency, and it does so unless those levels are so low, it can no longer maintain $1,25(OH)_2D$ levels due to the lack of substrates. Since it is this active form of the metabolite that has the anticancer activity, they propose that a profound deficiency has the most impact on PCa risk.[15]

The Travis et al study, published in April 2009, found no significant association between concentrations of 25(OH)D and overall risk for PCa. This multicountry (7) nested-case control study was selected from the European Prospective Investigation into Cancer and Nutrition (EPIC). Blood samples from 139,209 men (91% of the 153,457 EPIC total) were provided before randomization. Travis et al used the identified 652 prostate cancer patients from the larger study and matched them with 752 controls, with a mean follow-up period of 4.1 years. Matching criteria for cases and controls included study center, age at enrollment (+/- 6 months), time of day of blood collection (+/-1 hour) and time of blood draw and last consumption of food or drink (<3, 3-6, >6 hours).[18]

Travis examined the relationship between pre-diagnostic serum concentrations of 25(OH)D and risk of PCa from EPIC prostate cancer cases and matched controls. They also evaluated the associations by stage and grade of the disease. Serum concentrations of 25(OH)D were assayed in the same batch, for both the cases and controls, with specimens blinded to the lab personnel.[18]

Statistical analysis, with a weighted version of the paired-sample t test, evaluated differences between cases and controls in age, height, weight, body mass index and serum concentration of vitamin D. Data were then compared using conditional logistic regression models to calculate the odds ratios. The month of serum sample draw was evaluated to determine the influence on vitamin D concentrations. This was done using a mathematical model. Likelihood ratio-chi squared tests compared local and advanced prostate cancer with the trends in PCa risk and the logs of 25(OH)D concentration. They evaluated the risks relative to concentrations of vitamin D and calcium intake.[18]

Travis et al found no significant association between 25(OH)D and risk of prostate cancer (highest vs. lowest quintile: odds ratio 1.28, 95% confidence interval: 0.88, 1.88). They did acknowledge a significant variation in concentrations, which varied by month of collection and by country of recruitment. A subgroup analysis did not show a significant difference with regard to cancer stage or grade, age at diagnosis, body mass index, time from blood collection to diagnosis or calcium intake.[18]

After they standardized for month of collection, they found that men from ages 50-54 had vitamin D concentrations that were 12.5 nmol/L higher (P=.0.001) than men older than 70 years of age. This affirmed other studies' findings indicating that vitamin D levels decrease with increasing age. Additionally they showed borderline significant association for men diagnosed before age 60 (P for trend = 0.046). There was no difference noted between serum 25(OH)D and risk of PCa between men with an early (<4 years) versus a later (≥ 4 years) diagnosis.[18]

Travis also concluded that there was no association between 25(OH)D and PCa risk and calcium intake. It did not find an association between vitamin D deficiency and risk for men with a high (≥ 1,200 mg/day) or low (< 1,200 mg/day) intake of calcium. They found that high levels

calcium may increase risk of PCa, which was possibly attributable to reducing the amount of 1,25(OH)$_2$D synthesized from the suppression of parathyroid hormone by the calcium level.[18]

The study focus of Mikhak et al was on VDR gene polymorphisms and haplotypes and their interaction with vitamin D metabolites and PCa risk. The study was a nested-case control study in the Health Professionals Follow-up Study. That study started in 1986 with 51,529 healthy U.S. male health professionals. Three separate blood sample draws taken at three different times between 1986 and 2000, revealed a total of 704 PCa cases. Researchers drew one blood sample from each patient, which was measured for levels of both vitamin D metabolites (25(OH)D and 1,2(OH)$_2$D) and for VDR genotyping.[16]

Mikhak concluded that VDR polymorphisms in BsmI and FokI are unlikely to be major determinants of PCa risk. They also did not find *ff* genotype to be associated with increased risk of aggressive PCa. Unlike previous studies, they did not observe an association between Cdx2 and the GATA3 SNP, which is a G to A substitution. Only with aggressive PCa, did not find an association between haplotypes, globally or with the individual Cdx2, Fok1 and Bsm1 common haplotypes and a risk of all PCa subtypes. They found a lower susceptibility to PCa with haplotypes A-f-b and A-F-B. They found that carriers of the variant Cdx2 A allele, who were low in plasma 25(OH)D, had lower risk of total, aggressive and poorly differentiated PCa. Also, those carriers of the Cdx2 A allele with 1,25(OH)$_2$D deficiency had risks of aggressive and poorly differentiated prostate cancer more than non-carriers. They did note that the FokI SNP might lead to a reduction in both aggressive and poorly differentiated PCa risks in individuals with only one copy of the of the FokI *f* allele, who were deficient in 1,25(OH)$_2$D. Carriers with the *FF* genotype who were deficient in 1,25(OH)$_2$D had an increased risk of total, aggressive and poorly differentiated cancers.[16]

The authors found a suggested inverse linear relationship between 25(OH)D and advanced PCa risk. Men with plasma 25(OH)D deficiency were at a lower risk for total and poorly differentiated PCa. They were surprised to find that men with low 25(OH)D had a decreased PCa risk. They conjectured that this could be incidental or more likely due to a hormonal response of the parathyroid gland, stimulating additional enzymes to maintain plasma 1,25(OH)$_2$D at normal levels.[16]

The Ahn et al 2009 study looked at the association of 48 SNPs in four vitamin D metabolizing genes, using 749 PCa cases and 781 controls from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). This randomized-controlled multicenter trial, of approximately 150,000 U.S. men and women, was designed to evaluate screening mechanisms for the early detection of the enumerated cancers. Enrollment started in 1993 and ended in 2001. Male study participants were enrolled in the National Cancer Institute Cancer Genetic Markers of Susceptibility (CGEMS) investigation of SNPS and prostate cancer risk. In this screening arm, there were 38,350 randomized men. Non-hispanic men with no prior history of prostate cancer were selected for cases and controls. Before October 1, 2003, study participants filled out a questionnaire and gave blood for the Prostate Specific Antigen test (PSA) and vitamin D serum levels. From this group, prostate cancer cases were detected, the tumors staged and clinical state determined. After eliminating the cases diagnosed within the first year due to the potential impact of the subclinical cancer on serum vitamin D, the initial 1,172 cases were whittled to 749 cases and 781controls.[17]

CGEMS also examined the significant effects of SNPs associated with prostate cancer in PLCO and in four other replication studies totaling 4,020 cases and 4,028 controls (American Cancer Society Cancer Prevention Study II, 1790/1797; the Health Professionals Follow-Up Study,

619/620; the CeRePP French Prostate Case-Control Study, 671/671; and the Alpha-Toceopherol, Beta-Carotene Cancer Prevention Study, 940/940). They genotyped data in 212 tag SNPS in 12 genes in PLCO prostate cancer cases and controls and the CGEMS cases and controls; this was a genome-wide association study. Blinded lab personal completed a vitamin D assay from non-fasting cases and controls. Ahn et al claim this was the first large scale evaluation of both serum vitamin D status and candidate genes in the vitamin D pathway in relation to prostate cancer.[17]

The study found genetic variation in genes related to vitamin D metabolism and serum concentrations. After multivariate modeling, only two SNPs with associations to serum 25(OH)D concentrations remained: rs2282679 and rs1155563. No other tag SNPs were associated with serum concentrations. None of previous tag SNPs, including two previously implicated VDR SNPs (BsmI and FokI), were strongly associated with prostate cancer risk. None of the 61 SNPs in the VDR were associated with prostate cancer risk (Cdx2,TaqI,ApaI). The association of serum vitamin D and the results were null for disease aggressiveness, age at diagnosis and family history of prostate cancer.[17]

Genetic variation in the vitamin D pathway and PCa risk were stratified by serum vitamin D concentrations. They found a significant association between VDR genetic variation and PCa risk in men in the lowest tertiles of serum concentrations. Individual SNP analysis showed significant associations in men in the lowest tertiles of vitamin D concentration with three tag SNPS in or near the 3' untranslated region (UTR) of the VDR. And contrary to other studies, greater serum vitamin D concentration was related to increased risk of prostate cancer in A allele carriers.[17]

Haplotype analysis was consistent with the SNP-based analysis, and it indicated the greatest risk was in the carriers of the GGG haplotype (of the three VDR SNPs). The sliding

window haplotype analysis was based on 89 geneotyped SNPS in VDR in men with low vitamin D status, and the authors suggested that additional unmeasured risk variants around these SNPs may exist which may influence prostate cancer risk (rs11574143, rs757343, rs1544410). This study claims that other genetic studies were limited to selected VDR RFLP SNPs and show inconsistent results.[17]

There was only a modest differential in season-standardized vitamin D concentrations by variants in GC, which is the major protein carrier of vitamin D in serum. SNPs in GC were related to serum vitamin D, however, these SNPs were not associated with total or aggressive prostate cancer risk. Ahn et al conclude, that men in the lowest tertile of serum 25(OH)D, have an increased risk with tag SNPS in the 3' UTR of the VDR [17]

DISCUSSION

John et al was the only study that attempted to evaluate subjects' vitamin D exposure at a point both early in life and then later. In assembling the data, the researchers used physician impression, patient comments and patient occupational or recreational exposure to derive a value. Physicians simply rated their impression of sun exposure as unimpressive, moderate or considerable. Nowhere in the printed account is there an indication that the physicians were trained to make anything other than a subjective analysis. The dermatological exam suffers the same fate. In order for a study to be somewhat valid, the use of terminology has to be standardized from one evaluator to the next, and that is not the case here.

Additionally, all the years of exposure are derived from estimated exposure hours in the state of birth, the state of residence, occupation and recreational exposure. They accumulated these hours in person years in order to gain more statistical power in their data analysis. Since the solar

exposure is already based on estimates, these person years are built on those estimates, and hence, their conclusions are based on those estimates. The actual case numbers used to draw these conclusions in this study are actually fairly small compared to the person years. This is particularly evident with the conclusion the authors make relative to fatal prostate cancer risk reduced by 66% for people who were both born in a state with high solar radiation and who lived the longest in a state with high solar radiation. This conclusion is made with a case size of 12 men, however, this represents 22,162 person years.[20] Table IV and Table V of this paper shows the results of this study indicating sun exposure in adulthood and the risk of fatal and nonfatal prostate cancer. Note the sample sizes for the 'significant' findings are small: 25, 33, 55 and 12 and the confidence intervals wide. Having noted the issues with this study, though, it still is evident that there is an inverse association with solar exposure at many points in life. Since the study is based on these broad assumptions relative to the exposures, the purpose of this study remains as associative and more comprehensive and better designed prospective studies are needed to ascertain at which points in life, solar exposure has the biggest impact on PCa development.

Generally, the Li et al study was a well designed nested case control study from a much larger randomized controlled study, the Physicians Health Study (PHS). There was an 18 year follow-up of patients which was 99% complete for which they obtained vital status on 100% of the participants.[15] They had 1,618 cases from a population of 14,916 from which they also carefully drew their controls matching the cases as closely as possible. They Table I in the Li et al indicates the cases and controls were fairly similar except for differences in their vitamin D levels.[15]

The Li study found significant associations between serum vitamin D metabolites and aggressive prostate cancer risk in patients of the *second* lowest quartile of $1\text{-}\alpha,25(OH)_2D$ levels. This result is puzzling, and the study authors do not try to explain this anomaly.[15]

Li et al, like several other studies on this topic, only take one serum sample, which, in this case, was the baseline serum draw.[15] This issue is addressed further in this section.

Additionally, seventy-five percent of the samples were drawn in the summer and fall time frame, which is the time of year serum levels of vitamin D are the highest. Li handles this issue by creating cutoffs for the season based on vitamin D levels in the controls. It is questionable whether this methodology can account for the huge number of samples taken on the season with the highest levels of the specific component being tested. [15]

Interesting to note, Li et al conclude that the physicians in this study have higher overall vitamin D levels than participants in other studies on the topic. They attribute this possibly to their general overall better understanding of health issues.[15] This may also be why there are few significant findings in this group; their vitamin D status is actually higher, so if there were a connection between vitamin D deficiency and PCa, it would be less pronounced in this select population. If the Li et al statement is true, one would expect their prostate cancer rate to be less than the general male population, but they do not address this anywhere in the study.

A major asset to Travis et al was that it was a very large prospective study with large case and matched control populations. Table 1 in the published account showed the only difference between the groups is that the control group was more physically active than the case group.[18] Interesting to note, is that mean concentration of 25(OH)D does not vary between the case and the control groups. The authors looked at the data from every angle imaginable, so they were able to evaluate many relationships. Since it was such a large study, this provided the study the statistical power for their analysis.[18]

In the Travis study, P values were only significant with men less than 60 years of age in the lower third of 25(OH)D concentrations, but confidence intervals are wide and crossed one, making their only finding insignificant.[18]

Another issue in this study, was that the authors did not match controls to cases relative to the month of blood collection. They tried to diffuse this issue by standardizing the vitamin D levels before they analyzed the data. Standardizing the month of blood draw removes one of the main attributes confirmed by a litany of studies; vitamin D levels vary by season, and hence, by month.

Additionally, the follow-up period for this study was a mere 4.1 years median. Taking 10-15 years to develop, PCa onset typically is insidious, and with only a 4.1 year window of time, this may not have been captured in this study. With such a short follow-up period, one cannot be certain whether subclinical prostate cancer was developing and consequently affecting the vitamin D levels in the body.[18]

They acknowledged that they did not look at $1,2(OH)_2D$ specifically, which could be a potential limitation of the study since it is at this level, where vitamin D exerts its actions. This study also relied on a one serum draw for 25(OH)D levels. [18] This is discussed further in this section.

Mikhak et al also is a well designed study. This was a nested case-control study from the much larger prospective Health Professions Follow-up Study with 51,529 US male health professionals. The study included men diagnosed with PCa between 1993-2000 and the follow-up period ranged from 17-21 years, and this follow-up is key in understanding the risk of prostate cancer.[16]

Mikhak argued that both metabolites need to be measured in order to fully understand the body vitamin D levels, and this is apparent from other studies in which both metabolites were

measured and where the bioactive metabolite conferred a higher risk for PCa. The one major issue, that Mikhak et al relies on one blood draw for serum levels; this point is discussed further in this section.[16]

The major issue with the Ahn study is that they also only took one serum sample; this is discussed later in this section. They also tried to adjust for seasonal variation in vitamin D collection between cases and controls by calculating a season-standardized vitamin D levels.[17] Again, since the serum levels fluctuate with the seasons, one would consider that season would be an important factor not to adjust.

The sample size in this study limited Ahn's findings. With such small sample sizes, they were not able to make statistically supported conclusions relative to the any relationship with vitamin D. The authors concluded on only one finding: two SNPs were impacted by serum vitamin D.[17]

Ahn et al only measured 25(OH)D.[17] Mikhak et al postulated that both metabolites may need to be measured to provide a more definitive indication of vitamin D status since there is such an inter-relationship when levels of calcidiol drop severely.[16] Giovannucci argued that there may be a dose response relationship that may only be operative at lower limits of vitamin D.[21] Mikhak speculated that there also is an increase in PCa risk with low $1\text{-}\alpha,25(OH)_2D$ (with the Cdx2 A) and no association with 25(OH)D since there would not be enough substrate or enough $1\text{-}\alpha\text{-}$hydroxylase to convert the latter. [16] Ahn et al did note that there was an inverse linear relationship between 25(OH)D and advanced PCa risk. [17]

Many authors have hinted at the possibility that the effect of vitamin D may be more relevant for prostate cancer progression or the subgroup of aggressive prostate cancer. Most of the studies thus far have evaluated the relationships with total PCa and not specifically with the two

subgroups of indolent disease or aggressive disease. The possibility of aggressive disease having different risk factors was supported in part with the studies in this review. Li et al point out that 1-α-hydroxylase plays a role in progressive PCa, especially since as men age, the amount of this enzyme used in the hydroxylation of 25(OH)D to 1-α,25(OH)$_2$D decreases, and the protective effect no longer keeps the cancer contained.[15] This is true with aggressive disease. Mikhak et al also supported this concept in their findings that, if one is a carrier of a Cdx2 A allele, and if both levels are low, there is an increase in the risk of aggressive disease. [16]

Other concerns regarding these studies center around the taking of the serum draw and the analysis of it. Serum measurements of vitamin D were drawn in each of the studies in this review except the John et al study. Mikhak, Li and the Travis studies all had only one serum measurement upon which to run their data comparisons. [15, 16,18] Although the article does not stipulate, Ahn et al appears to only have done an initial vitamin D assay upon PCa diagnosis for both the cases and the controls.[17] With only one serum draw, each of these studies only captured a snapshot in time of serum levels for the metabolite they measured. Such a limited draw ignores the fact that these levels fluctuate. This small snapshot in time does not adequately explain the impact of vitamin D serum levels on the evolution of the disease. Yet, all of these studies (except John et al) in this review and other studies utilizing serum draws, draw conclusions on associations between PCa and vitamin D using one serum sample.

The risk for prostate cancer may begin earlier in life and that these adult studies may not represent a relevant time period. Giovannucci notes that prostate cancer likely begins in a person's 30's, because of the presence of microscopic neoplastic lesions present in the prostate by that time.[21] The activity of 1-α-hydroxylase decreases with prostate cancer, and this would have a direct impact on vitamin D levels. This means that the most useful period of time to evaluate

vitamin D levels would be early in the process. All of the studies reviewed here sampled serum in men older than 50 years. Serum levels of vitamin D need to be measured earlier in life to determine at what point vitamin D has the greatest impact on prostate cancer risk.

Another issue relative to serum measurement of vitamin D, is that in Travis, Mikhak and Ahn, controls were not matched to month of blood collection.[16,17,18] They tried to diffuse this issue with standardization of the serum vitamin D levels by month of blood draw before they analyzed the data. Because of the significance of the monthly fluctuation in vitamin D levels, they may have not been able to assess the impact they had on PCa risk because of the standardization they performed in their analysis.

Mikhak et al postulated that both metabolites may need to be measured to provide a more definitive indication of vitamin D status.[16] In a 2007 review, Giovannucci argued that there may be a dose response relationship that may only be operative at lower limits of vitamin D.[21] Mikhak et al brought this up in their study noting that there was an inverse linear relationship between 25(OH)D and advanced prostate cancer risk. [16]

CONCLUSION

All the studies in this review acknowledge, with good evidence, the presence of vitamin D deficiencies in the study participants demonstrating that this is a widespread health issue.

Four of the five studies conclude that there is an increased risk of prostate cancer with low serum vitamin D levels, and most indicate that this is more prevalent with the more aggressive disease. The only study not confirming the association has an extremely short follow-up period which may impact the findings they made as there may not have been enough time for PCa to develop in the population they studied.

Evolving from this general discussion is the identification of the genetic components influenced by vitamin D levels. Studies continue to show conflicting results regarding PCa risk with the presence of VDR polymorphisms in light of low vitamin D levels. Mikhak et al demonstrated this issue with their finding that it was unlikely that BSMI and FOKI were unlikely determinants of PCa risk when previous studies, conducted by others, found that these polymorphisms *were* contributory to the increased risk.[16] The fact that these studies conflict with previous studies, may demonstrate something is influencing the results: possibly variability of the timing in which the serum levels are being checked. It still is not known at what point vitamin D serum levels influence prostate cancer neogenesis. With the one-time serum draws concluding on vitamin D status, perhaps it is the variability itself that is possibly influencing the conflicting conclusions from study to study.

The associations drawn in the John et al study indicate that more information is needed regarding solar exposure and the PCa connection.[20] The attempt to estimate solar exposure early in life is novel in this study, but this is only a beginning in an area of study that is really needed: prospective studies starting with ages much younger than 50 years. Giovannuci and John et al postulated that prostate cancer genesis is probably in the third decade of life.[20,21] With such an early genesis, it would be beneficial to follow the serum levels or solar exposure of patients much younger than these studies typically follow.

Li et al discuss the need for measurement of both metabolites since it is in the presence of a deficiency of $1\text{-}\alpha,25(OH)_2D$, that the risk of aggressive prostate cancer is increased.[15] It appears that measurements of both metabolites provide a more comprehensive picture of the true severity of the deficiency because the status of $25(OH)D$ does not provide any information on the other

metabolite, $1\text{-}\alpha,25(OH)_2D$. It may be crucial to measure both metabolites to gain understanding the complex nature of the impact on prostate cancer risk.

Finally, one serum sample does not seem to provide the information needed for determining the relationship between vitamin D and PCa. It does not seem reasonable that this one-time serum sample would have an impact on a disease that develops subclinically for so many years. Since this snapshot draw can happen anytime along the disease course, this one time draw cannot provide enough information to determine the impact of the deficiency on the disease course. With potentially a multitude of points in which serum vitamin D levels could relate to PCa's course, each of the studies may be finding different points that may or may not influence PCa risk depending on when they draw that sample. The one measurement and the measurement of only one metabolite of serum vitamin D may be why study results continue to be in conflict.

More prospective studies beginning at an earlier age with more serum samples and solar radiation studies are needed in order to better understand the relationship between prostate cancer and vitamin D. One conclusion is clear in these studies reviewed: low vitamin D levels have an impact on prostate cancer risk.

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Tables

Table I: Vitamin D and Prostate Cancer Risk Cases Reviewed 2007-Present

Table II: Trend in Incidence Rates for Prostate Cancer for all Races

Table III: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health

Table IV: Sun Exposure in Adulthood and Risk of Fatal and Nonfatal Prostate
                Cancer

Table V: Residential Sun Exposure Early Life and Adulthood Relative to Risk of
                Fatal and Nonfatal Prostate Cancer

Table I. Does Vitamin D Deficiency Increase Prostate Cancer Risk? A Systematic Review of the Literature

Source	Study Type	Population	Ages	Intervention	Sample Size	Years Follow-up	Validity	Findings
John et al[20]	Nested case	NHEFSAdults ages 25-74 including 5,811; part of the NHANES Follow-up Study	25-74	Blood samples serum 25(OH)D	161 cases 3,367 non-hispanic noncases (w/sun exp info)	10	Lab work blinded.	PCa risk reduced for men born in, lived in or frequently exposed to solar radiation. Frequent adult exposure PCa risk reduction especially with fatal PCa.
Li et al1[15]	Nested-case control	Physicians Health Study 14,916 men initially free dx ca	40-84	Predx levels both vit D metabolites; DNA	1,066 PCa cases 1,618 ctls.	18	NCC. RCT; Lab blinded. Well designed with excellent follow-up. PCa pts matched with controls were similar. All testing randomized.	Vitamin D is major health issue. Low levels both metabolites had increased PCa risk for aggressive PCa. FokI *ff* genotype increases susceptibility for PCa in presence of low vitamin D. High 25(OH)D decreases PCa risk for total & aggressive disease. Low 1,25 vitamin D increased aggressive PCa risk with older men OR men with low 25(OH)D. Greatest risk of PCa risk with low levels both metabolites.
Travis et al[18]	Nested-case control	Part of the EPIC with EPIC Multicountry (10) to investigate relationships between diet, nutritional status, lifestyle &environmental factors & incidence of cancer & other chronic diseases. 153,457 men of 520,000 recruits; blood samples from 139,209	35-73	Blood samples serum 25(OH)D	652 PCa cases; 752 ctls.	4.1	NCC; from larger Prospective study; Lab blinded. Blood samples from 139,209 men drawn pre-randomization	No significant association with 25(OH)D and PCa risk. Men 50-54 concentration levels 12.5nmol > men > 70 yrs. No PCa risk with calcium intake, but high Ca+ increases PCa risk.
Mikhak et al[16]	Nested - case control	Health Professions Follow-up Study with 51,529 US male health professionals. Study included men dx with PCa between v1993-2000.	45-70	Blood samples to investigate the role of VDR Cdx2, Fok1 and Bsm1 gene polymorphisms and assoociated haplotypes & interaction with plasma vitamin D metabolites in relation to Pca risk	684 PCa cases 684 ctls.	17-21	NCC from larger prospective study; lab blinded	Cdx2 A allele carriers have lower risk aggressive & poorly differentiated PCa with low metabolites. Men with low 25(OH)D at risk for total & poorly differentiated PCa. Suggestion of inverse relationship between 25(OH)D and advanced PCa risk.
Ahn et al[16, 16-18]	Nested-case control	PLCO Cancer Screening Trial of 155,000 men and women; (also part of CGEMS investigation of SNPs & PCa risk). 38,350 men randomized to the screening arm	≥ 50	Blood samples for serum; questionaire	749 PCa cases 781 ctls	10	NCC; from RCT; lab blinded	Men with lowest 25(OH)D have an increased PCa risk with tag SNPs in or near 3' UTR if VDR.

Table II. Trend in incidence rates for Prostate Cancer for all Races[16]				
Trend Period	1975-1987	1987-1991	1991-1994	1994-2006
Average percentage trend %	+ 0.9	+ 3.0	-0.6	-4.1

Table III: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health[21]		
ng/mL**	nmol/L**	Health status
< 11	< 27.5	Vitamin D deficiency and rickets in infants and young children .
< 10-15	< 25-37.5	Considered inadequate for bone and overall health in healthy individuals.
≥ 30	≥ 75	Proposed by some as desirable for overall health and disease prevention, although a recent government-sponsored expert panel concluded that insufficient data are available to support these higher levels.
Consistently > 200	Consistently > 500	Considered potentially toxic, leading to hypercalcemia and hyperphosphatemia, although human data are limited. In an animal model, concentrations ≤400 ng/mL (≤1,000 nmol/L) demonstrated no toxicity.

Table IV. Sun exposure in adulthood and risk of fatal and nonfatal prostate cancer[20]

			Nonfatal & Fatal				Nonfatal cases			Fatal cases	
			n	Person-yrs	RR (95% CI)		n	RR (95% CI)		n	RR (95% CI)
Physician-assessed	Sun exposure	Unimpressive	44	14,798	1.0		27	1.0		17	1.0
		Moderate	63	21,610	0.85 (0.58-1.25)		39	0.87 (0.54-1.43)		24	0.81- (0.44-1.51)
		Considerable	52	15,598	0.78 (0.52-1.17)		35	0.89 (0.53-1.47)		18	0.62 (0.32-1.20)
	Solar skin damage	None	35	22,461	1.0		25	1.0		10	1..0
		Minimal	48	13,625	1.18 (0.76-1.84)		28	1.07 (0.62-1.86)		20	1.42 (0.66-3.04)
		Moderate to severe	78	16,387	1.13 (0.75-1.71)		49	1.16 (0.70-1.94)		29	1.13 (0.55-2.34)
Self-reported	Recreational sun exposure	Never or rare	18	4,453	1.0		8	1.0		10	1.0
		Occasional	32	15,453	0.79 (0.44-1.4)		23	1.19 (0.53-2.66)		9	0.45 (0.18-1.12)
		Frequent	102	40,027	0.92 (0.55-1.52)		77	1.46 (0.70-3.02)		**25**	**0.47 (0.23-0.99)**
	Occupational sun exposure	Never or rare	42	18,803	1.0		29	1.0		13	1.0
		Occasional	25	12,377	0.93 (0.57-1.53)		18	0.95 (.053-1.71)		7	0.88 (0.35-2.21)
		Frequent	86	28,750	1.05 (0.73-1.52)		62	1.11 (0.72-1.73)		24	0.89 (0.45-1.74)
	Occupational or recreational sun exposure	Both, never, rare or occasional	35	14,246	1.0		21	1.0		14	1.0
		One frequent	47	22,574	0.80 (0.52-1.24)		36	1.02 (0.60-1.75)		11	0.46 (0.21-1.02)
		Both frequent	70	23,058	1.05 (0.70-1.58)		51	1.28 (0.77-2.13)		19	0.70 0.35-1.40)

Confidence interval adjusted for age (continuous)

Table V. Residential Sun Exposure Early Life and Adulthood Relative to Risk of Fatal and Nonfatal Prostate Cancer[20]

		Nonfatal & Fatal					Nonfatal cases			Fatal cases	
		n	Person-yrs	RR (95% CI)	RR (95% CI)		n	RR (95% CI)		n	RR (95% CI)
Solar radiation in state of birth	Low	78	20,098	1.0	1.0*		44	1.0*		34	1.0*
	Medium	47	15,817	0.75 (0.52-1.07)	0.73 (0.48-1.09)		33	0.85 (0.52-1.40)		14	0.57 (0.28-1.14)
	High	25	12,773	0.52 (0.33-0.81)	**0.49 (0.27-0.90)**		20	0.59 (0.29-1.21)		5	0.31 (0.09-1.03)
Solar radiation in state of longest residence	Low	86	21,887	1.0	1.0*		43	1.0*		34	1.0*
	Medium	41	14,835	0.72 (0.50-1.05)	0.90 (0.58-1.38)		29	1.07 (0.63-1.81)		12	0.70 (0.32-1.50)
	High	33	14,591	**0.59 (0.39-0.88)**	**0.80 (0.44-1.49)**		25	1.02(0.49-2.13)		7	0.49 (0.15-1.59)
Solar radiation in state of birth vs. state of longest residence	Low vs low	82	22,210	1.0			47	1.0		35	1.0
	Low vs high	8	2,055	0.87 (042-1.79)			4	0.78 (0.28-2.17)		4	1.00 (0.36-2.82)
	High vs low	5	1,920	0.54 (0.22-1.33)			3	0.60 (0.19-1.93)		2	0.46 (0.11-1.93)
	High vs high	55	22,162	**0.66 (0.47-0.93)**			43	0.89 (0.59-1.34)		12	**0.34 0.18-0.66**

* Adjusted for age and solar radiation in state of longest residence or in state of birth (continuous)

Figures

FIGURE I. Prostate Cancer Age at Diagnosis[3]

Prostate Cancer Age at Diagnosis 2002-2006

■ < 35   ■ 35 – 44   ■ 45-54   ■ 55-64   ■ 65-74   ■ 75-84   ■ >85

0%   1%
5%   9%
21%
29%
35%
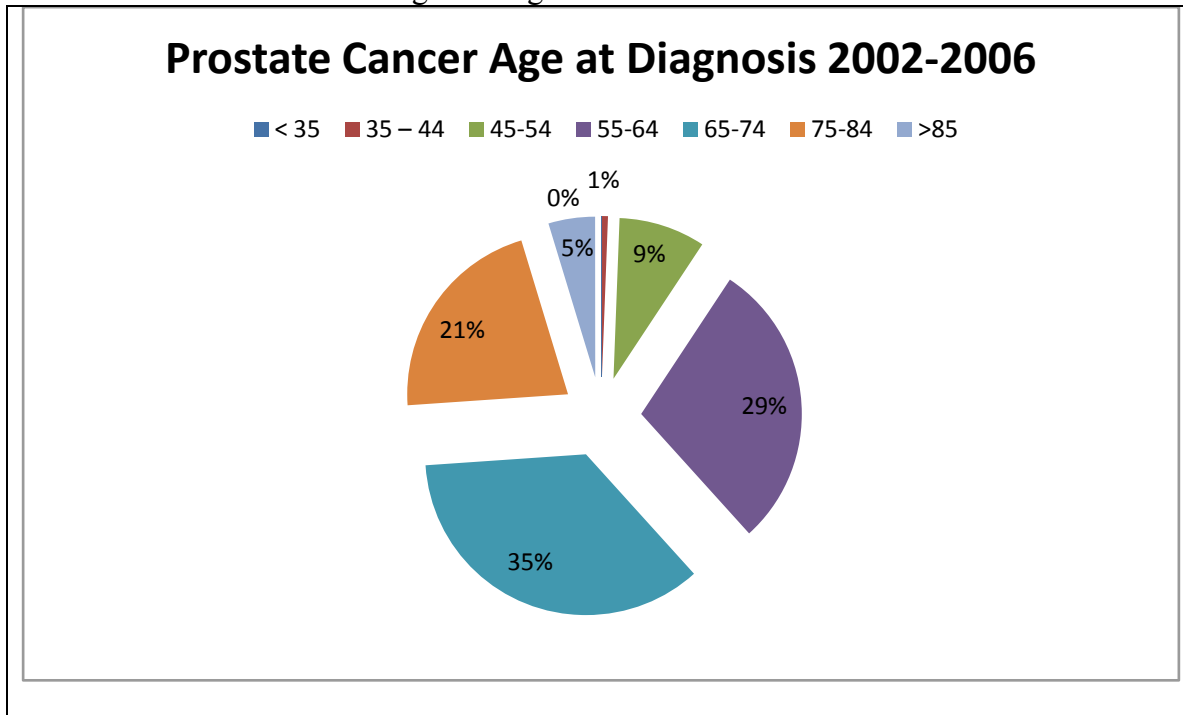
FIGURE II. Incidence and Death Rates of Prostate Cancer by Race per 100,000[3]

Incidence and Death Rates of Prostate Cancer by Race per 100,000

Race	Death Rate	Incidence
Hispanic	19.6	133.4
American Indian/Alaska Native	20	76.1
Asian/Pacific Islander	10.6	91.1
Black	56.3	239.8
White	23.6	153
All Races	25.6	159.3

0   50   100   150   200   250   300
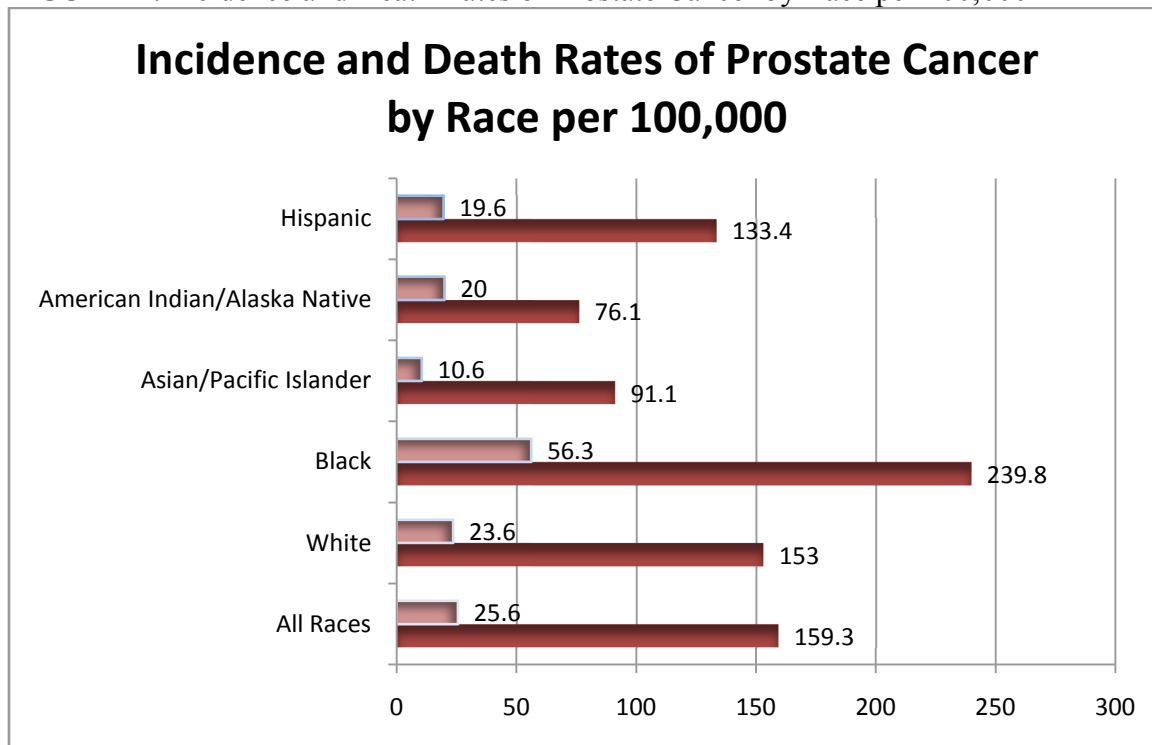
FIGURE III. Prostate Cancer Mortality by State[22]

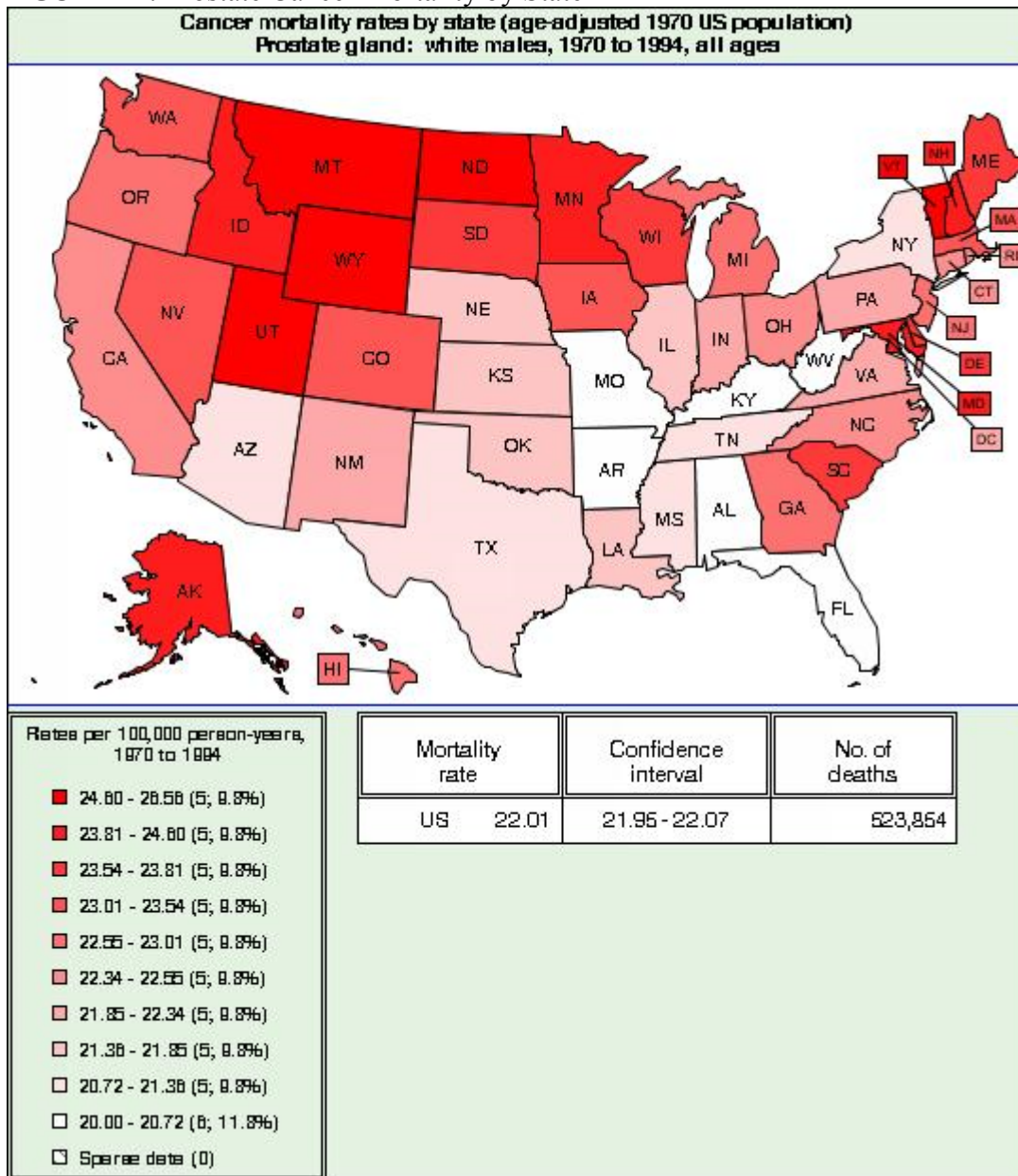Cancer mortality rates by state (age-adjusted 1970 US population)
Prostate gland: white males, 1970 to 1994, all ages

Figure IV: Vitamin D in Homeostasis[19]

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