The Current Status of Vitamin D in the Prevention and Treatment of Prostate Cancer

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- Prostate cancer background
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- Review of clinical studies of vitamin D analogs
- Review of clinical studies of combination therapies with vitamin D analogs
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Why I Chose this Topic

- Prostate Cancer is a familiar subject to me after attending many of my father’s lectures on Prostate Cancer treatment. After listening to his lectures I was inspired to look at the nutritional indices that affect Prostate Cancer where I came across vitamin D.
Currently 1 in 6 men will be diagnosed with prostate cancer within their life time.

Based on rates between 2002-2006 age-adjusted death rate for prostate cancer is 25.6 per 100,000 men per year.

In 2005 185,895 men developed prostate cancer.

In 2005 28,905 men died from prostate cancer.  

(1)
Prostate Cancer Overview

- Prostate Cancer is the malignant growth of cells of the prostate gland most often originating in the glandular tissue resulting in an adenocarcinoma.

- Prostate Cancer classifications include:
  1. Organ confined, also known as localized.
  2. Metastatic Prostate Cancer, also known as aggressive or advanced Prostate Cancer.
  3. Androgen- dependent
  4. Androgen- independent, also known as Hormone Refractory Prostate Cancer.
  5. Recurrent Prostate. (2)
Gleason Scores

- The Gleason system is based on how effectively the cells of any particular cancer are able to structure themselves into glands resembling the normal gland.

- The Gleason score is determined by a physician assigning the cancerous tissue two sets of number that can range from 1 (least aggressive) to 5 (most aggressive).

- The first number of the Gleason score is the primary predominant type of cancer in the sample and the second number is the second most common tumor type seen in the sample. (3)

http://aztec.asu.edu/azustoo/Gleason%20Grading_files/Gleason.gif
Risk Factors for Prostate Cancer

- Age
- Race/ethnicity
- Nationality
- Family history
- Genes
- Diet
- Obesity
- Inflammation of the prostate(3)
# Current Screening Methods

## Prostate Specific Antigen (PSA) Assay

<table>
<thead>
<tr>
<th>Normal lab value</th>
<th>&lt; 4 nanograms/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors that alter values</td>
<td>Age, prostatitis, benign hyperplasia, and sexual intercourse</td>
</tr>
<tr>
<td>PSA velocity</td>
<td>↑ PSA velocity are signs of aggressive PCa</td>
</tr>
<tr>
<td>PSA doubling time</td>
<td>↑ PSA doubling time are signs of PCa progression and aggressiveness (4)</td>
</tr>
</tbody>
</table>

## Digital Rectal Examination

Physical examination of the prostate gland through the rectum looking for physical irregularities.

<table>
<thead>
<tr>
<th>Irregularities</th>
<th>Lumps, jagged areas, coarse spots, enlargement, and firm areas on the prostate tissue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>Not reliable in early stage PCa, and not a measurable outcome for PCa treatment (5)</td>
</tr>
</tbody>
</table>
Prostate Cancer Symptoms

- Frequent need to urinate, especially at night
- Difficulty starting urination or holding back urine
- Weak or interrupted flow of urine
- Discomfort during urination
- Difficulty in having an erection
- Blood in urine or semen
Current Recommendations for Prostate Cancer Screening

- Men over the age of 50 should be screened annually.

- African-American men and men with a strong family history of prostate cancer should begin screening at the age of 40 or the age if family member developed prostate cancer at younger ages.

- Men who are experiencing symptoms suggestive of Prostate Cancer should see their physician ask whether testing is needed.\(^{(3,4)}\)
Research Question

- What is the current status in literature of vitamin D in the prevention and treatment of Prostate Cancer?
Prostate Cancer Prevention
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
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</tr>
</thead>
</table>
| Corder, et al. (1993)  | Case- Control Study  
90 African American  
91 White males  
Serum samples drawn between 1964-1971 for cases.  
1,25 vitamin D serum levels divided into quartiles.  
(5-26) (27-32) (33-39) (40-81) pg/ml. | Mean serum 1,25 D was 1.81 pg/ml lower in cases than in matched controls (P= 0.002).  
Lowest risk for PCa was found in the highest quartile for serum 1,25 vitamin D for both blacks and white 0.15 (95% CI 0.03-0.85) | Lowest risk for PCa was found in men with increased serum 1,25 vitamin D levels between 40-81 pg/ml and the lowest quartile for 25(OH) vitamin D 3-18ng/ml with an Odds ratio of 0.15 (95% CI. 0.03-0.85). |

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# Prostate Cancer Prevention

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<tbody>
<tr>
<td>Li, et al. (2007)⁸</td>
<td>Nested Case-Control study. Physicians Health Follow-Up Study. Cases: 1,066 men Control 1,618 men Blood samples drawn before Randomization.</td>
<td>↓ Vitamin D levels below 32ng/ml ↑ risk for aggressive PCa (OR 2.1; CI1.2-3.4)</td>
<td>Decreased levels of 25 vitamin D and 1,25 vitamin D is associated with increased risk of PCa.</td>
</tr>
<tr>
<td>Esther, et al. (2007)⁹</td>
<td>NHANES I Follow up Study. 5,811 men recontacted for interview on sun exposure and for prostate cancer diagnosis.</td>
<td>Men born in a state of high solar radiation (RR,0.52; 95% CI, 0.33-0.81) 53% risk ↓ for fatal PCa with frequent solar exposure.</td>
<td>Men with ↑ solar exposure during youth have ↓ risk for developing PCa. Increased risk for adult solar exposure.</td>
</tr>
</tbody>
</table>
# Prostate Cancer Prevention

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<tr>
<td>Ahn, et al. (2008)(^{10})</td>
<td>Nested Case-Control Study 749 Cases 781 Controls Vitamin D levels are in quintiles.</td>
<td>Serum levels of 25-vitamin D greater than 42.5 nmol/ L resulted in increased risk of Aggressive PCa.</td>
<td>Vitamin D increases the risk for aggressive PCa.</td>
</tr>
<tr>
<td>Faupel-Badger, et al. (2007)(^{11})</td>
<td>Nested Case-Control Study. 296 Cases 296 Controls Drawing Baseline Serum levels</td>
<td>No differences in risk for developing PCa. Average Case serum 25(OH) level is 18.54ng/ml and Control 18.73ng/ml; (P=0.80)</td>
<td>Null Results</td>
</tr>
</tbody>
</table>
Prostate Cancer Prevention
Summary

- Literature reviews and meta-analyses state they have found an association with low total vitamin D levels and an increase in risk for the development of Prostate Cancer.\textsuperscript{39}

- The results of the studies I reviewed have provided mixed results and are not conclusive in showing a strong association between serum vitamin D levels and risk for developing Prostate Cancer.
Vitamin D Metabolic Pathways
Vitamin D pathway

[Diagram showing the vitamin D pathway from skin to circulation to intestine, with labels for UV-B, 7-dehydrocholesterol, Pre-D3, D3, DBP, Liver, Parathyroid glands, Kidney, Intestine, Dietary sources of vitamin D, and effects on Intestine, Bone, and Immune cells.]

http://www.nature.com/nrc/journal/v7/n9/images/nrc2196-f1.jpg
Vitamin D pathways

1,25(OH)₂vitamin D₃

Vitamin D Receptor

Non-Genomic Response

RAR/RXR Nuclear Factor

Vitamin D Response Element

Genomic Response
Vitamin D Pathways

Normal Prostate Cell
- Initiation Phase
  - Transformation into a tumor
  - Activation of transcription factors, and decrease in tumor suppression genes.
- Proliferation Phase
  - Over expression of growth factors
- Invasion
  - Increased mediated anchorage independent growth, angiogenic factors, and COX-2 synthase.
- Metastasis to the bones and other organs.

Prostate Tumor Cell

Prostate Tumor Growth

Prostate Cancer Metastasis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>E- Cadherin (12)</td>
<td>↓ Tumorigenesis</td>
</tr>
<tr>
<td>Inhibited ERK/ MAPK pathway (11)</td>
<td>↓ proliferation and ↑ differentiation</td>
</tr>
<tr>
<td>P21(11)</td>
<td>Inhibits cellular proliferation and ↑ differentiation</td>
</tr>
<tr>
<td>Cytochrome C (13)</td>
<td>↑ Apoptosis</td>
</tr>
<tr>
<td>15-hydroxyprostaglandin dehydrogenase (14)</td>
<td>↑ Prostaglandin Degradation, ↓ inflammation</td>
</tr>
<tr>
<td>MKP5 (13)</td>
<td>↓ Cancer related inflammation</td>
</tr>
</tbody>
</table>
Vitamin D Metabolism Summary

- 1,25- dihydroxyvitamin D$_3$ can activate numerous pathways via the VDRE or non-genomic pathways such as P21, E-Cadherin, and many other cellular pathways that can prevent the formation of a tumor or promote differentiation of the cells.

- Once cancer cells form vitamin D pathways that halt the progression or causes programmed cell death like Cytochrome C that can cause apoptosis.

- Additionally vitamin D can decrease inflammation via prostaglandin degradation that inhibits cancer cell anchorage, and angiogenesis into surrounding tissues.
Review of In Vitro Studies involving Vitamin D Analogs
### Vitamin D In-Vitro Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Treatment</th>
<th>Type of PCa</th>
<th>Results</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, et al. (2000)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Calcitriol, 25-Hydroxyvitamin D and 19-nor-1(\alpha),25-Dihydroxyvitamin D-2</td>
<td>LNCaP, androgen-dependent. PC-3 Androgen independent</td>
<td>No statistical differences in vitamin D type in inhibiting LNCaP cells at dosage of (10^{-7}) moles. 2 analogs activate VDRE.</td>
<td>Both vitamin D treatments inhibit primary PCa cell growth. Both analogs can activate VDRE at (10^{-8}) (M) and 25(OH) at (5 \times 10^{-8}) (M)</td>
</tr>
<tr>
<td>Moreno, et al. (2005)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Calcitriol</td>
<td>LNCaP and PC-3 cells. Androgen-dependent</td>
<td>COX-2 mRNA levels in both androgen-dependent LNCaP ~70% inhibition and androgen-independent ~45% inhibition.</td>
<td>Significantly decreased the activation of prostaglandin pathways decreasing cancer related inflammation.</td>
</tr>
</tbody>
</table>
## Vitamin D In-vitro Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Treatment</th>
<th>Type of PCa</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bao, et al. (2006)¹⁷</td>
<td>Calcitriol</td>
<td>PCa Cells, Androgen-Dependent</td>
<td>Suppressed Angiogenesis of PCa Cells via inhibiting IL-8 inflammations.</td>
</tr>
<tr>
<td>Hsu, et al. (2001)¹⁸</td>
<td>25- Hydroxyvitamin D-3 and Calcitriol</td>
<td>LNCaP, PC-3, DU-145 cell lines</td>
<td>Antiproliferative effects of vitamin D was dependent on the activity of 1α-hydroxylase. 25 vitamin D₃ group demonstrated minimal effect though 1, 25 Vitamin D₃ displayed the most inhibitory effects.</td>
</tr>
</tbody>
</table>
Hypervitaminosis D

Symptoms

- Hypercalcemia
- Constipation
- Nausea
- Kidney stones
- Bone aches
- Fractures
- Curing of the spine
- Loss of height

- Polyuria

- Renal Failure

- Proteinuria

- Azotemia

- Metastatic Calcifications
Vitamin D Analogs in Randomized Control Clinical Studies
# Vitamin D Analogs in Randomized, Control Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Vitamin D</th>
<th>Type of PCa</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross, et al.(1998)$^{20}$</td>
<td>Calcitriol</td>
<td>Recurrent PCa</td>
<td>Overall decreased rate of PSA rise was statistically significant ($p=.02$). Optimal dose of 2.5 milligrams was not met due to early signs of hypercalcemia.</td>
</tr>
<tr>
<td>Schwartz, et al. (2005)$^{21}$</td>
<td>Paricalcitol</td>
<td>Advanced, Androgen-independent PCa.</td>
<td>Of the 18 patient none sustained a 50% drop in PSA the Primary end point. Well tolerated at the highest dose of 25 mg with 1 patient developing hypercalcemia.</td>
</tr>
</tbody>
</table>
### Vitamin D Analogs in Randomized Control Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Treatment</th>
<th>Type of Prostate Cancer</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, et al. (2003) 22</td>
<td>1α- hydroxyvitamin D₂</td>
<td>Advanced Androgen-independent PCa</td>
<td>20 of the 26 patients enrolled completed therapy. The participants did not meet the primary endpoints of the study. Finding of the study were not significant.</td>
</tr>
<tr>
<td>Beer, et al. (2004) 23</td>
<td>Calcitriol vs. Placebo</td>
<td>Primary Adenocarcinoma tumors</td>
<td>37 of 39 tumors from patients were evaluable. VDR expression was reduce in 75.3% Calcitriol group and 98.6% Placebo Group. The effect of down regulation of the VDR is unknown on the PCa.</td>
</tr>
</tbody>
</table>
Common Prostate Cancer Medications

- Ketoconazole is an anti-fungal medication that in high doses between 800-1200mg is used for androgen deprivation therapy. Side effect of the medication is that it inhibits 1 alpha-hydroxylase needed to activate vitamin D hormone.\(^{24}\)

- Dexamethasone is a steroid that decreases inflammation and can bind to nuclear receptors and cause apoptosis.\(^ {25}\)

- Mitoxantrone is a chemotherapy used for hormone refractory prostate cancer that is used in combination with steroids.\(^ {26}\)

- Docetaxel is a chemotherapy for hormone refractory Prostate cancer.\(^ {27}\)

- Carboplatin is a chemotherapy agent that has an alkylating agent often used for hormone refractory prostate cancer.\(^ {28}\)
Vitamin D Analog Combination Therapies in In-Vitro
## Vitamin D Analog Combination Therapies in In-vitro Studies

<table>
<thead>
<tr>
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<th>Treatment</th>
<th>PCa Cell Line</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunlap, et al. (2003)²⁹</td>
<td>Calcitriol + 19-nor-1α,25-Dihydroxyvitamin D-2 with radiation</td>
<td>LNCaP cell line</td>
<td>Pretreatment with vitamin D 24 hrs before irradiation resulted in 48% apoptosis of LNCaP compared to 17% apoptosis the same day.</td>
</tr>
<tr>
<td>Peehl, et al. (2002)³⁰</td>
<td>Ketoconazole with either calcitriol or EB 1089</td>
<td>E-CA-77, E-CA-85, AND E-CA-96</td>
<td>Both vitamin D treatments with Ketoconazole resulted in growth inhibition. The EB1089 inhibited 2x more growth than calcitriol and ketoconazole.</td>
</tr>
<tr>
<td>Bernardi, et al. (2002)³¹</td>
<td>Calcitriol and Dexamethasone (Dex)</td>
<td>Tumor-Derived Endothelial Cells.</td>
<td>Calcitriol and Dex inhibited the proliferation of Tumor-Derived Endothelial Cells and modulates angiogenesis and cell cycle. At similar concentrations needed for antitumor effects.</td>
</tr>
</tbody>
</table>
Vitamin D Combination Therapy

Results

Dunlap, et al. (2003)\textsuperscript{29}  
Bernardi, et al. (2002)\textsuperscript{31}
## Vitamin D Analog Combination Therapies in In-vitro Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>PCa Cell Line</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed, et al. (2002)³²</td>
<td>Calcitriol and Mitoxantrone/ Dexamethasone</td>
<td>PC-3 cell line. Androgen Independent PCa</td>
<td>Increased tumor regression and enhanced antitumor activity. 50-85% inhibition of tumor proliferation</td>
</tr>
<tr>
<td>Swamy, et al. (2004)³³</td>
<td>25-hydroxyvitamin D₃-BE and 1,25(OH)₂D₃</td>
<td>PZ-HPV-7, PC-3, LNCaP, and DU-145</td>
<td>Analog with the alkylatying analog substantially reduced the viability of DU-145 compared to Calcitriol alone. In addition inhibited all of the other cell lines</td>
</tr>
</tbody>
</table>
Vitamin D Analog Combination Therapies Clinical Trials
### Randomized, Control Vitamin D Combination Therapy Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Type of PCa</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer, et al. (2003)</td>
<td>Calcitriol and Docetaxel</td>
<td>Androgen- Independent Prostate Cancer</td>
<td>37 patient experienced PSA response overall and 22 had &gt;75% PSA reduction, and treatment is well tolerated. Median survival time is 19.4 months and average is 1 year.</td>
</tr>
</tbody>
</table>
### Randomized, Control Vitamin D Combination Therapy Clinical Trials

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Beer, et al. (2005)&lt;sup&gt;36&lt;/sup&gt;</td>
<td>DN-101 (15mcg)</td>
<td>Advanced Solid Tumors. 38 patients in groups of 3-6. Each group given sequential doses of DN-101 15-165mcg.</td>
<td>No dose-limiting toxicities occurred. No statistical effects of DN-101 on serum calcium levels. Half-life 16.4 hours.</td>
<td>DN-101 has been found to have less toxic side effects and has a 5 to 8 fold higher systemic exposure achieved than that of commercial formulations of calcitriol.</td>
</tr>
</tbody>
</table>
## Randomized, Control Vitamin D Combination Therapy Clinical Trials

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Attia, et al.(2008)</td>
<td>Docetaxel and Doxercalciferol</td>
<td>Metastatic Androgen-Independent Prostate Cancer</td>
<td>PSA Response with vitamin D 46.7%(95%CI) and Placebo 39.4%(95%CI). Survival Rate with vitamin D 17.8 mo(95%CI) And Placebo 16.4 mo(95%CI)</td>
<td>No benefit between the two arms of the study.</td>
</tr>
</tbody>
</table>
Vitamin D Clinical Limitations

- Instrumental limitations are a factor in the clinical trials due to the reliability of the PSA Assay. PSA Assay is the gold standard for measuring the effectiveness of Prostate Cancer Interventions, though easily skewed by any sexual activity or stress to the prostate.

- Hypercalcemia is a common side effect of high dose Calcitriol or vitamin D analog interventions causing patients who are suffering from the side effects to drop out of the study, or preventing the study from reaching optimum antitumor dosages or meeting the time intervals of the treatment.
Synthesis of Studies

- Epidemiological studies found a correlation with prostate cancer and vitamin D. Individuals with lower serum vitamin D levels were at increased risk for developing Prostate Cancer.

- Vitamin D Analogue treatments alone and in combination with other Prostate Cancer treatments were successful in the in vitro studies.

- Vitamin D in combination with other Prostate Cancer treatments clinical studies resulted in decreases in PSA and increase survival time.

- Note that all of the clinical combination therapy studies were conducted on Androgen- Independent Prostate Cancer and not on any Androgen- Dependent Prostate Cancer patients.
Application to Clinical Practice

- Currently there is not enough evidence for Dietitians to recommend the supplementation of vitamin D for Prostate Cancer patients for treatment.

- The American Cancer Society Supplement Guidelines for patients during cancer treatment discourages the usage of vitamin D supplements beyond that of the RDA. 40

- Important for dietitians to be aware of these studies and watch for future Randomized Control Studies that provide strong evidence for the use of vitamin D supplementation beyond that of the RDA.
Future research needs

- Majority of vitamin D and prostate cancer has been completed on Calcitriol and hormone refractory PCa. Future research is needed on the use of vitamin D analogs on androgen-dependent PCa in order to determine whether vitamin D can prevent the progression to Hormone Refractory PCa.\textsuperscript{39}

- Some research has found that there is a dose dependency reaction with vitamin D and prostate cancer, requiring additional research on effective dosages of vitamin D.\textsuperscript{41}
Any Questions?
Thank You!