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

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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.

Statistics

- 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)

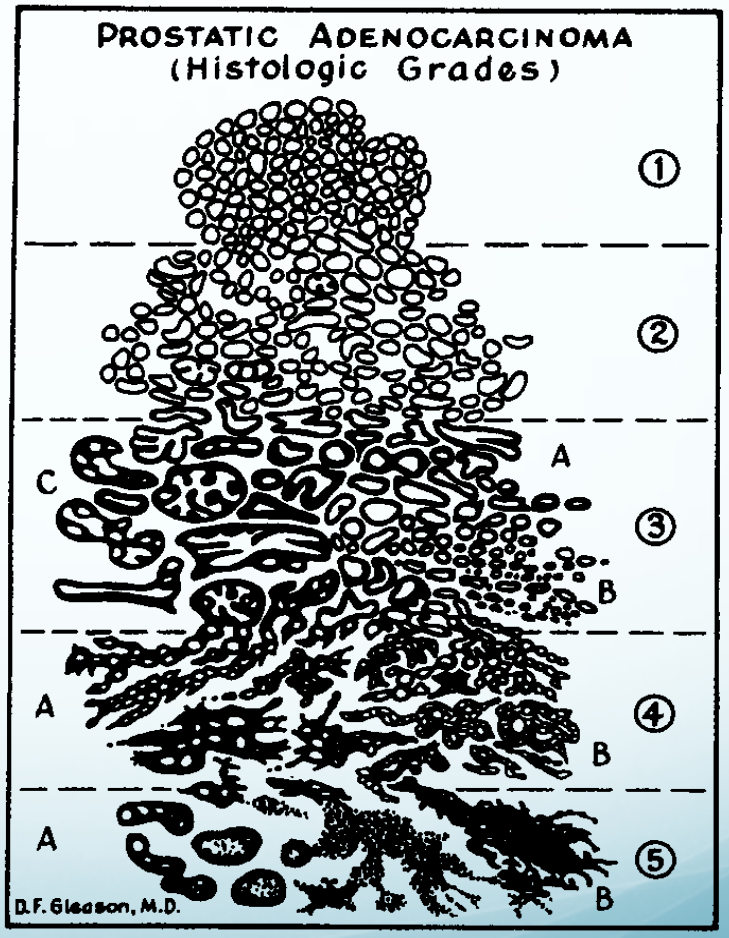
Prostate Cancer Overview

- 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)



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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

Normal lab value	< 4 nanograms/ mL
Factors that alter values	Age, prostatitis, benign hyperplasia, and sexual intercourse
PSA velocity	↑ PSA velocity are signs of aggressive PCa
PSA doubling time	↑ PSA doubling time are signs of PCa progression and aggressiveness.(4)

Digital Rectal Examination

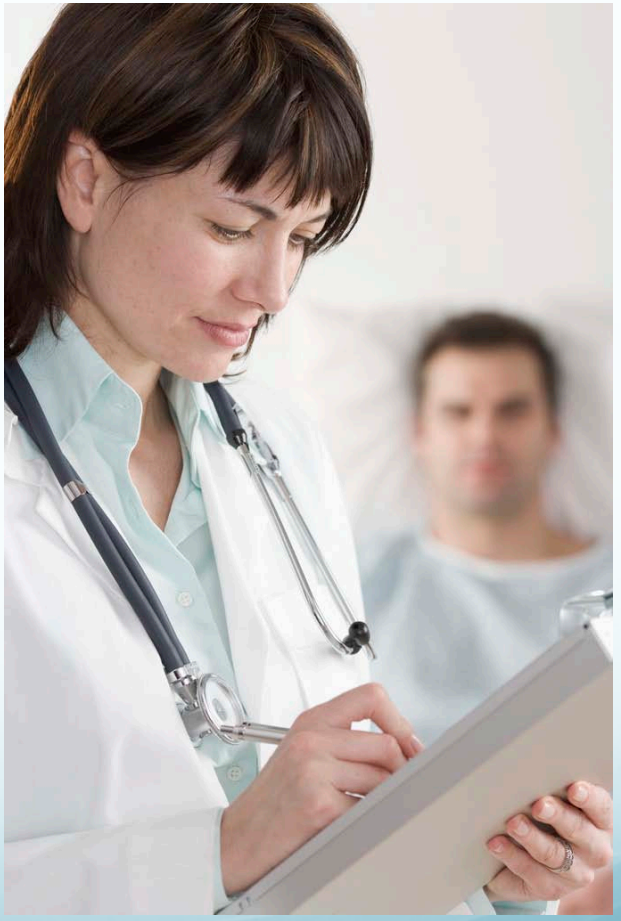
Physical examination of the prostate gland through the rectum looking for physical irregularities.	
Irregularities	Lumps, jagged areas, coarse spots, enlargement, and firm areas on the prostate tissue.
Limitations	Not reliable in early stage PCa, and not a measurable outcome for PCa treatment.(5)

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[3]

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

Historical Study

Study	Methods	Results	Correlation
Corder, et al. (1993) [7]	Case- Control Study 90 African American 91 White males Serum samples drawn between 1964-1971 for cases. Cases diagnosed with Prostate Cancer before Dec 32, 1987. 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).

Prostate Cancer Prevention

Study	Methods	Results	Correlation
Li, et al.(2007)[8]	Nested Case- Control study. Physicians Health Follow-Up Study. Cases: 1,066 men Control 1,618 men Blood samples drawn before Randomization.	↓ Vitamin D levels below 32ng/ml ↑ risk for aggressive PCa (OR 2.1; CI1.2-3.4)	Decreased levels of 25 vitamin D and 1,25 vitamin D is associated with increased risk of PCa.
Esther, et al. (2007)[9]	NHANES I Follow up Study. 5,811 men recontacted for interview on sun exposure and for prostate cancer diagnosis.	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.	Men with ↑ solar exposure during youth have ↓ risk for developing PCa. Increased risk for adult solar exposure.

Prostate Cancer Prevention

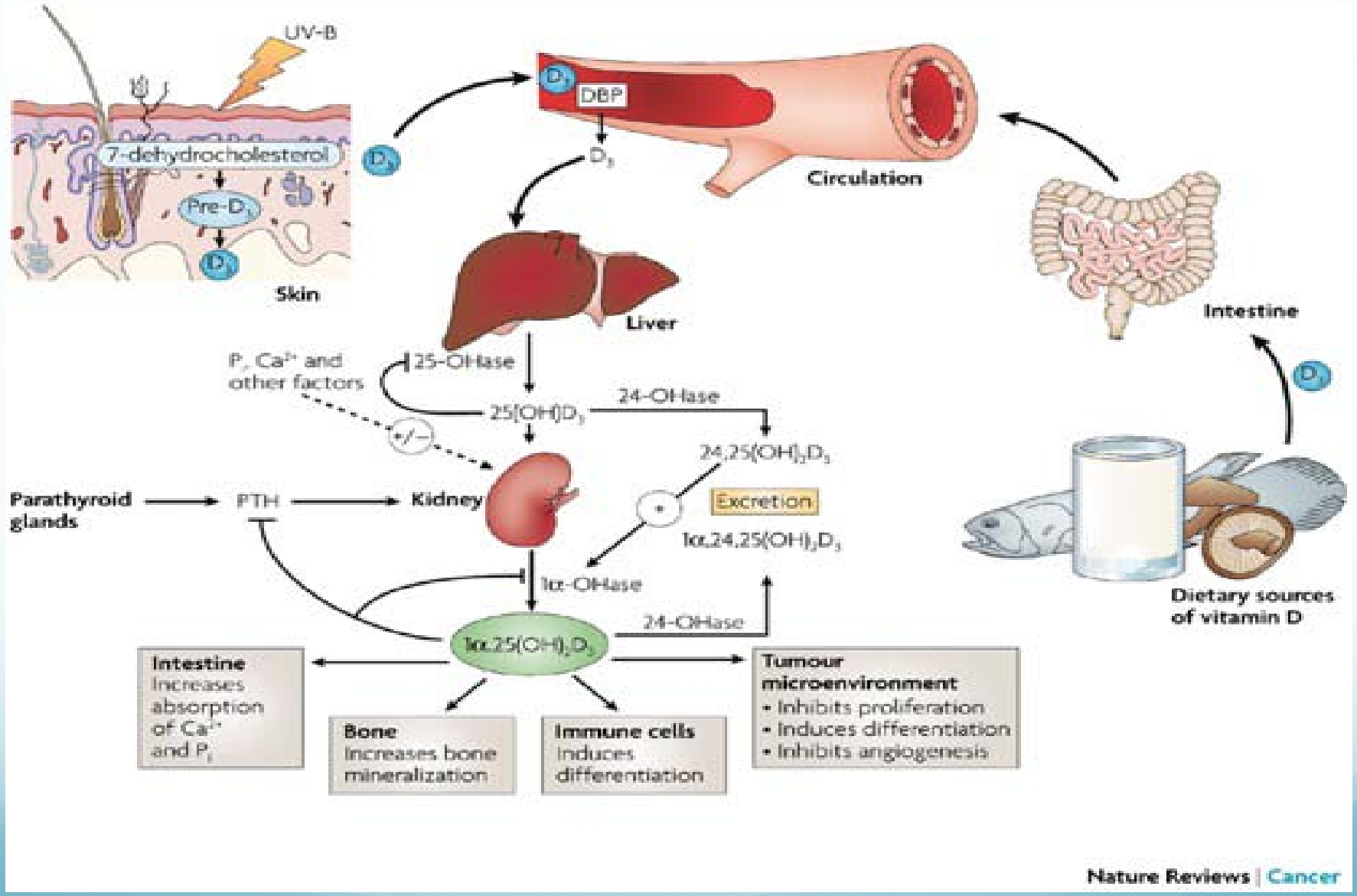
Study	Methods	Results	Correlation
Ahn, et al. (2008)[10]	Nested Case-Control Study 749 Cases 781 Controls Vitamin D levels are in quintiles.	Serum levels of 25-vitamin D greater than 42.5 nmol/ L resulted in increased risk of Aggressive PCa.	Vitamin D increases the risk for aggressive PCa.
Faupel- Badger, et al. (2007)[11]	Nested Case-Control Study. 296 Cases 296 Controls Drawing Baseline Serum levels	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	Null Results

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.[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



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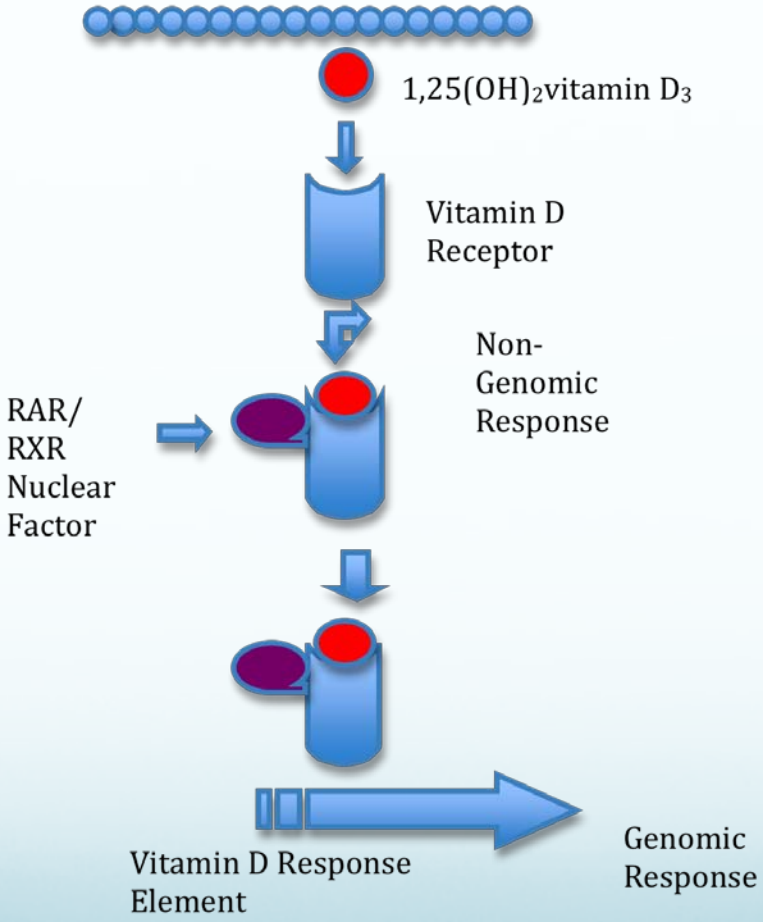
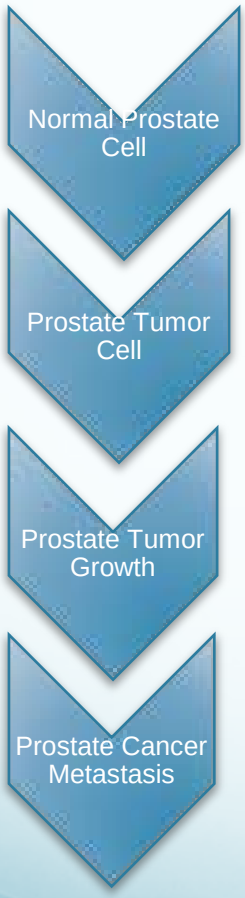
Vitamin D pathways



Vitamin D Pathways



- 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.

Factor	Effect
E- Cadherin (12)	↓ Tumorgenesis
Inhibited ERK/ MAPK pathway (11)	↓ proliferation and ↑ differentiation
P21(11)	Inhibits cellular proliferation and ↑ differentiation
Cytochrome C (13)	↑ Apoptosis
15-hydroxyprostaglandin dehydrogenase (14)	↑ Prostaglandin Degradation, ↓ inflammation
MKP5 (13)	↓ Cancer related inflammation

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

Study	Vitamin D Treatment	Type of PCa	Results	Findings
Chen, et al. (2000)[15]	Calcitriol, 25-Hydroxyvitamin D and 19-nor-1α,25-Dihydroxyvitamin D-2	LNCaP, androgen-dependent. PC-3 Androgen independent	No statistical differences in vitamin D type in inhibiting LNCaP cells at dosage of 10^{-7}moles. 2 analogs activate VDRE.	Both vitamin D treatments inhibit primary PCa cell growth. Both analogs can activate VDRE at 10^{-8} (M) and 25(OH) at 5 X10^{-8} (M)
Moreno, et al. (2005)[16]	Calcitriol	LNCaP and PC-3 cells. Androgen-dependent	COX-2 mRNA levels in both androgen-dependent LNCaP ~70% inhibition and androgen-independent ~45% inhibition.	Significantly decreased the activation of prostaglandin pathways decreasing cancer related inflammation.

Vitamin D In-vitro Studies

Study	Vitamin D Treatment	Type of PCa	Findings
Bao, et al. (2006)[17]	Calcitriol	PCa Cells, Androgen-Dependent	Suppressed Angiogenesis of PCa Cells via inhibiting IL-8 inflammations.
Hsu, et al. (2001)[18]	25- Hydroxyvitamin D-3 and Calcitriol	LNCaP, PC-3, DU-145 cell lines	Antiproliferative effects of vitamin D was dependent on the activity of 1α-hydroxylase. 25 vitamin D_3 group demonstrated minimal effect though 1, 25 Vitamin D_3 displayed the most inhibitory effects.

Hypervitaminosis D Symptoms

- Hypercalcemia Constipation, Nausea, kidney stones, bone aches, fractures, curing of the spine and 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

Study	Type of Vitamin D	Type of PCa	Findings
Gross, et al.(1998)[20]	Calcitriol	Recurrent PCa	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.
Schwartz, et al. (2005)[21]	Paricalcitol	Advanced, Androgen-independent PCa.	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.

Vitamin D Analogs in Randomized Control Clinical Trials

Study	Vitamin D Treatment	Type of Prostate Cancer	Findings
Liu, et al. (2003) [22]	1α- hydroxyvitamin D_2	Advanced Androgen-independent PCa	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.
Beer, et al. (2004) [23]	Calcitriol vs. Placebo	Primary Adenocarcinoma tumors.	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.

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 decrease 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 a alkylating agent often used for hormone refractory prostate cancer.[28]

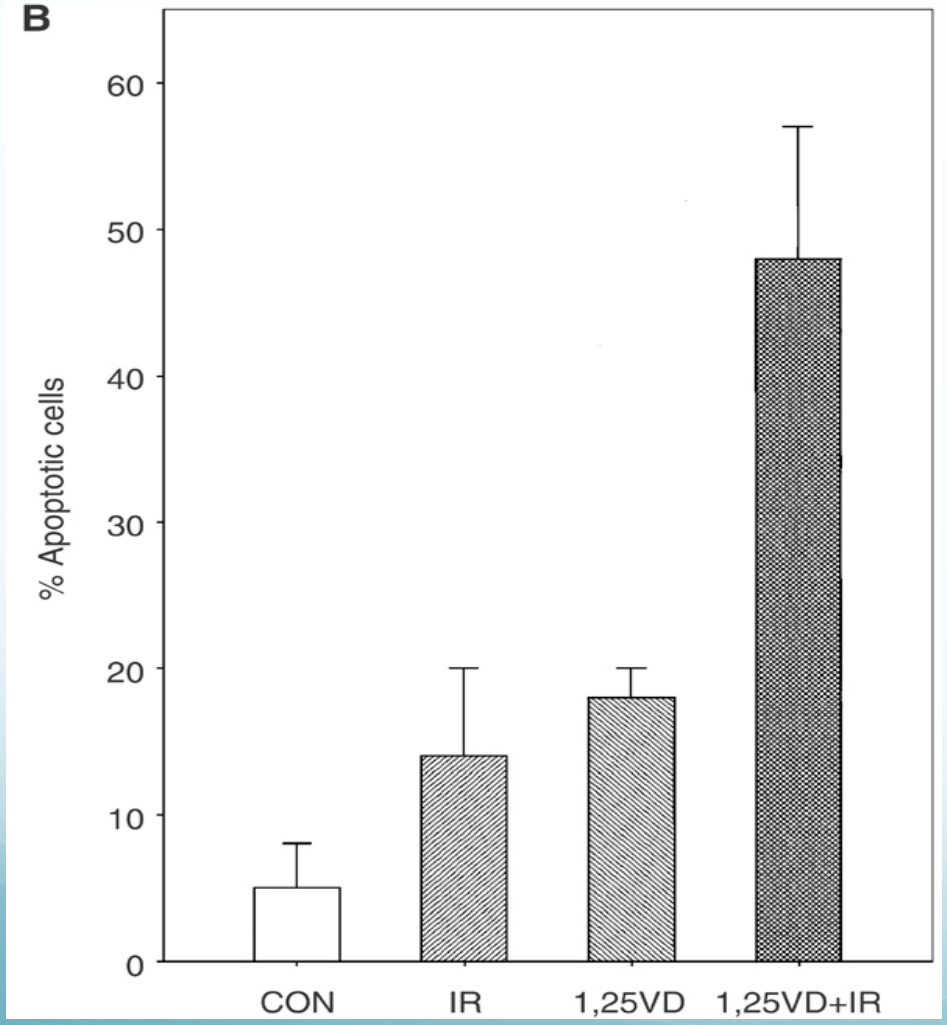
Vitamin D Analog Combination Therapies in In-Vitro

Vitamin D Analog Combination Therapies in In-vitro Studies

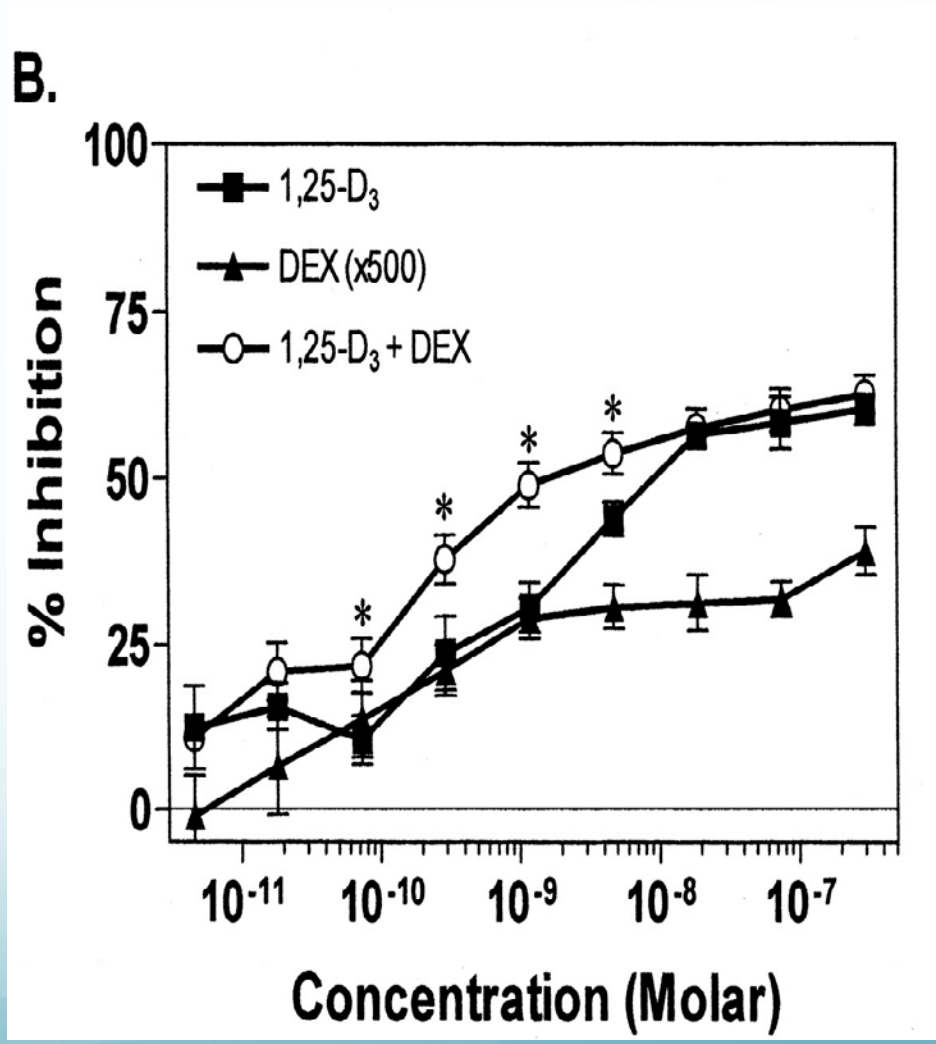
Study	Treatment	PCa Cell Line	Findings
Dunlap, et al. (2003)[29]	Calcitriol +19-nor-1α,25-Dihydroxyvitamin D-2 with radiation	LNCaP cell line	Pretreatment with vitamin D 24 hrs before irradiation resulted in 48% apoptosis of LNCaP compared to 17% apoptosis the same day.
Peehl, et al.(2002)[30]	Ketoconazole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

Vitamin D Combination Therapy Results

Dunlap, et al.(2003)[29]



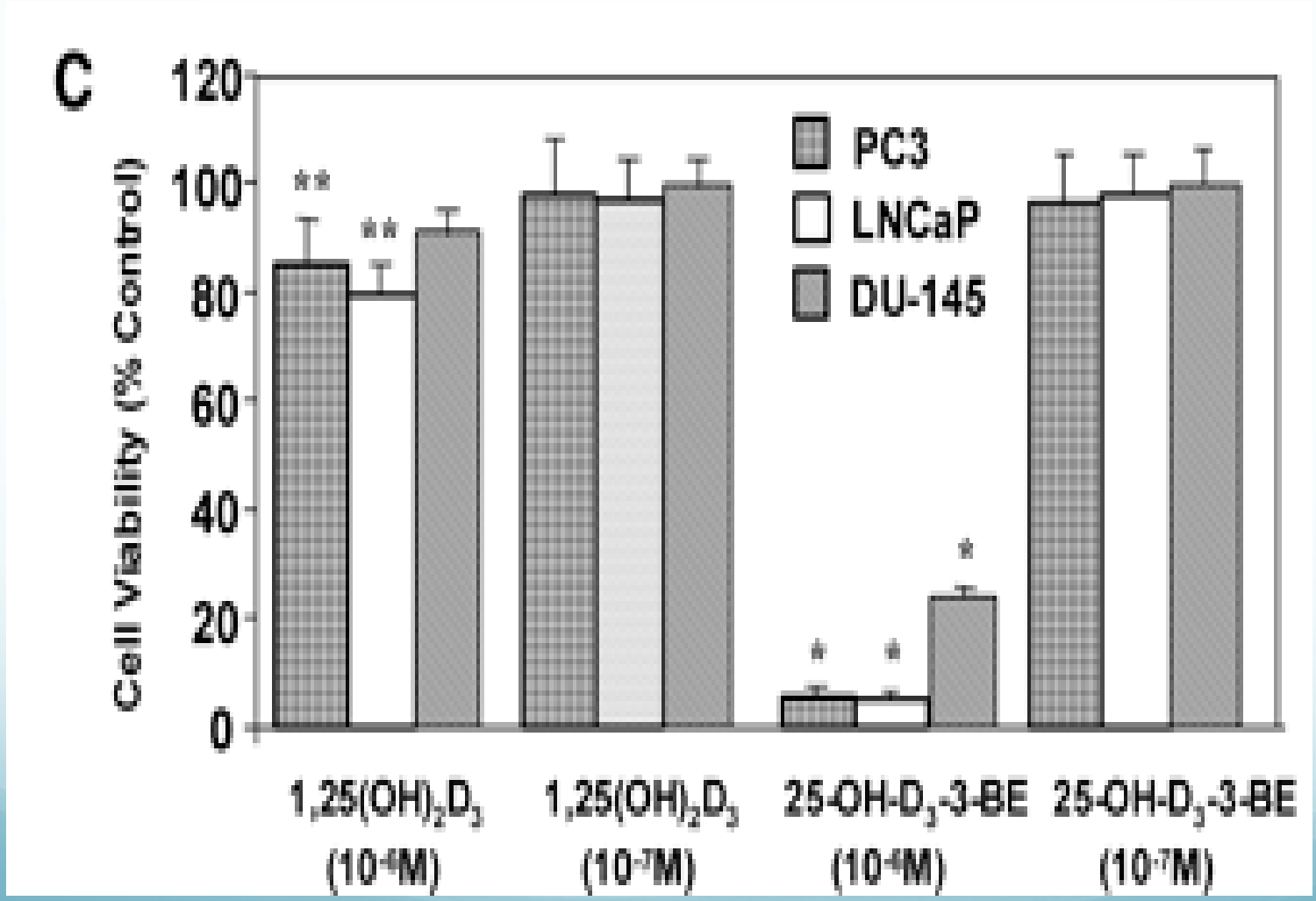
Bernardi, et al.(2002)[31]



Vitamin D Analog Combination Therapies in In-vitro Studies

Study	Treatment	PCa Cell Line	Findings
Ahmed, et al.(2002)[32]	Calcitriol and Mitoxantrone/ Dexamethasone	PC-3 cell line. Androgen Independent PCa	Increased tumor regression and enhanced antitumor activity. 50-85% inhibition of tumor proliferation
Swamy, et al. (2004)[33]	25-hydroxyvitamin D_3-BE and $1,25(OH)_2D_3$	PZ-HPV-7, PC-3, LNCaP, and DU-145	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

Swamy, et al. (2004)[33]



Vitamin D Analog Combination Therapies Clinical Trials

Randomized, Control Vitamin D Combination Therapy Clinical Trials

Study	Treatment	Type of PCa	Results
Beer, et al.(2003)[34]	Calcitriol and Docetaxel	Androgen- Independent Prostate Cancer	37 patient experienced PSA response overall and 22 had >75% PSA reduction, and treatment is well tolerated. Median survival time is 19.4 months and average is 1 year.
Flaig, et al.(2005)[35]	Dex, Calcitriol, and Carboplatin.	Androgen- Independent Prostate Cancer	13 of the 34 patients experienced PSA response >75% reduction.

Randomized, Control Vitamin D Combination Therapy Clinical Trials

Study	Methods	Type of Prostate Cancer	Results	Findings
Beer, et al. (2005)[36]	DN-101 (15mcg)	Advanced Solid Tumors. 38 patients in groups of 3-6. Each group given sequential doses of DN-101 15-165mcg.	No dose- limiting toxicities occurred. No statistical effects of DN-101 on serum calcium levels. Half-life 16.4 hours.	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.
Beer, et al. (2007)[37]	Calcitriol (DN-101) and Docetaxel.	Androgen-Independent Prostate Cancer	DN-101 PSA response 58% and estimate survival of 24.5 mo. Placebo PSA response 49% and survival 16.4 mo.	Increased survival and decreased toxicity with DN-101.

Randomized, Control Vitamin D Combination Therapy Clinical Trials

Study	Methods	Type of Prostate Cancer	Results	Findings
Attia, et al.(2008)[38]	Docetaxel and Doxercalciferol	Metastatic Androgen-Independent Prostate Cancer	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)	No benefit between the two arms of the study.

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.[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.[41]

Any Questions?
Thank You!