



• Innovative Science

• Breakthrough Therapies

• Clinical Advances

# Vitamin D and Cancer

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# Outline

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- **Background**
  - Metabolism, catabolism, and VDR polymorphisms
- **Recent Conflicting Studies**
- **NCI Funded Studies**
- **Future Studies/Needs**



# Vitamin D in the news

USA TODAY

Study backs Vitamin D in cancer fight

Vitamin D Deficiency Worsens Breast Cancer?

The Washington Post

No Dodging Prostate Cancer With Vitamin D

CNN.com

'Sunshine vitamin' may ward off breast cancer

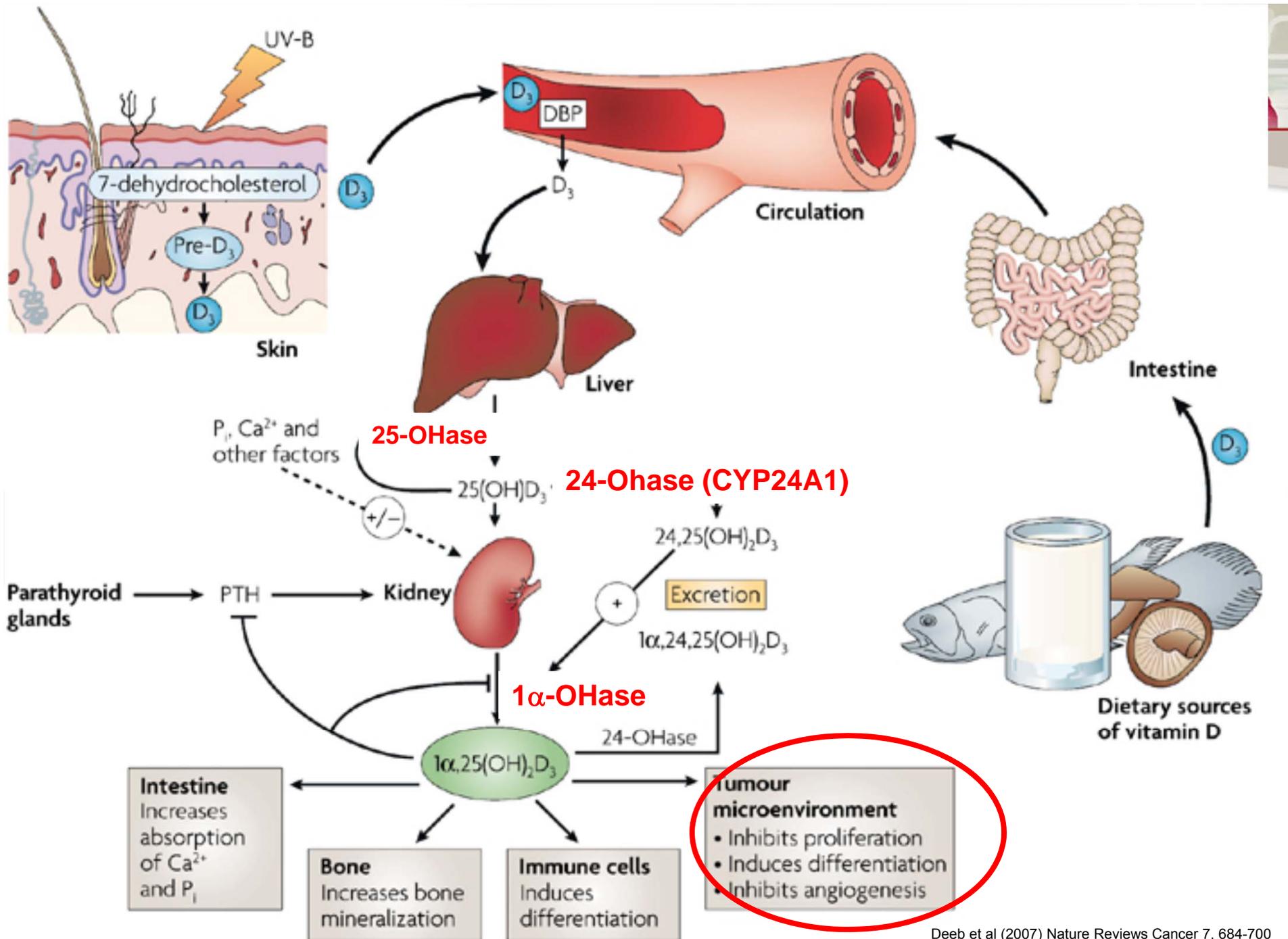
Vitamin D May Help Curb Breast Cancer, Study Finds

The New York Times



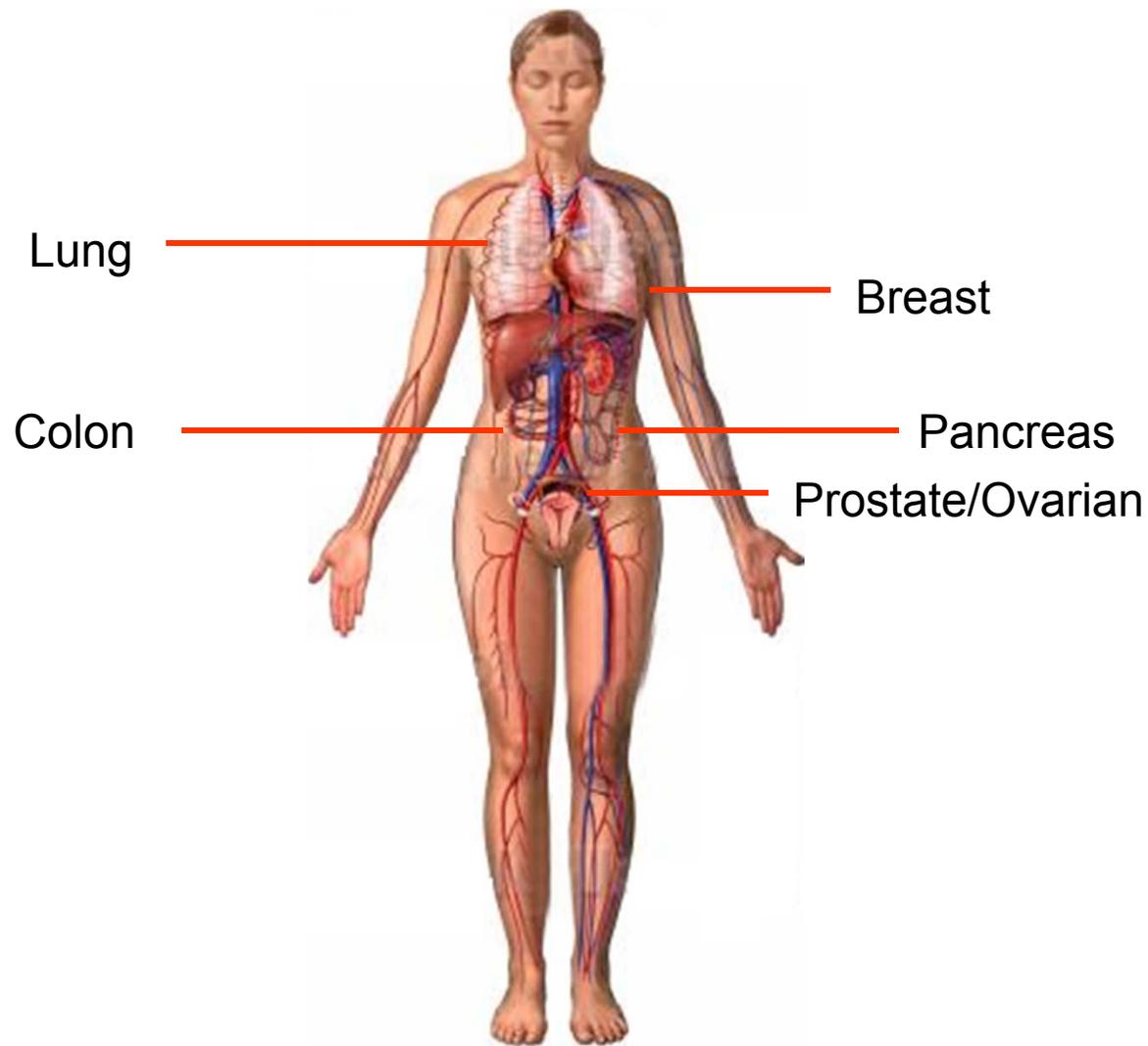
## Recent NIH Conferences

- 2003
  - Vitamin D and Health in the 21st Century: Bone and Beyond
- May 2007
  - Vitamin D and Cancer: Current Dilemmas/Future Needs
- Sept 2007
  - Vitamin D and Health in the 21st Century: An Update





# Vitamin D Implications in Cancer





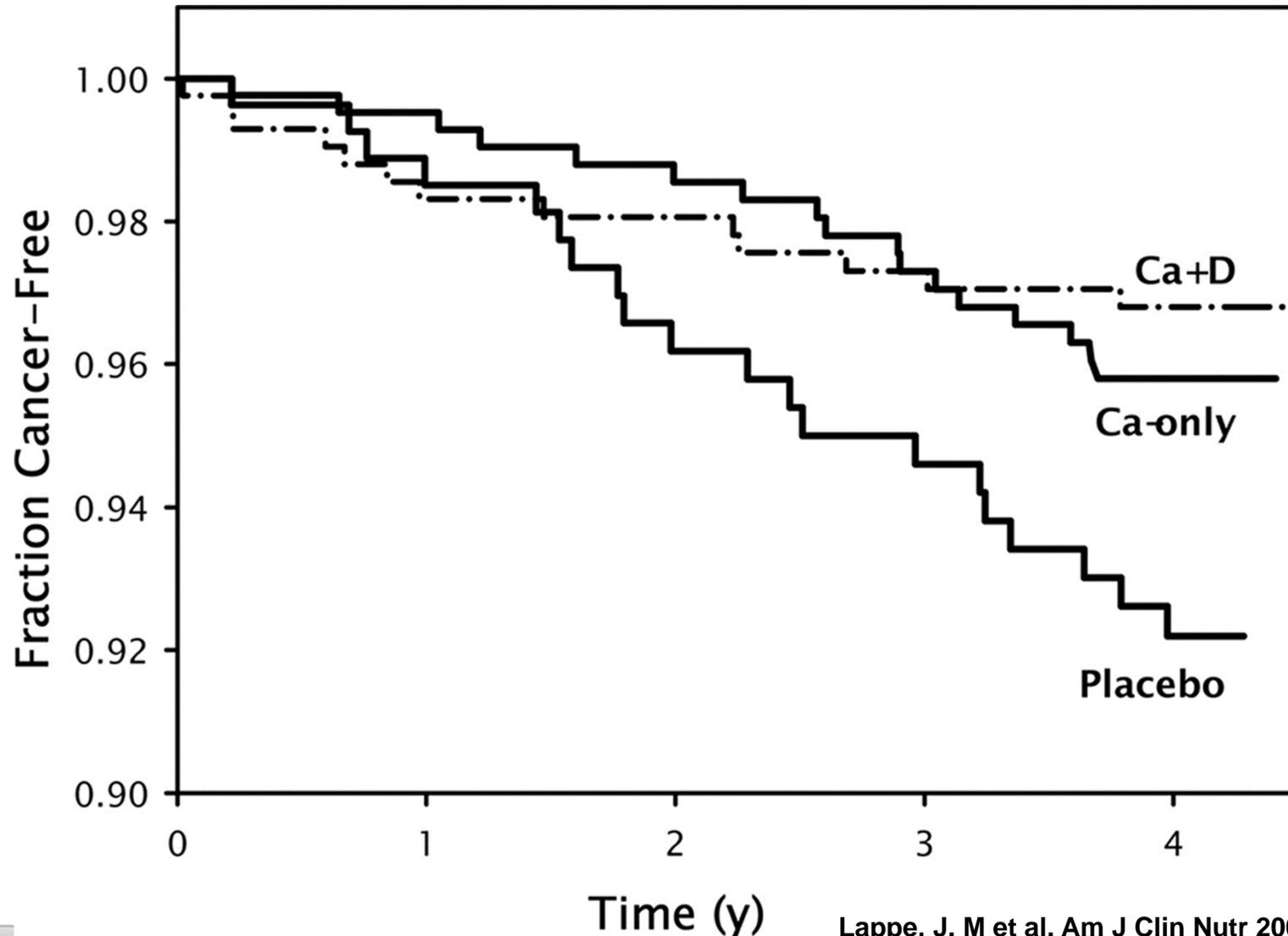
## Conflicting Evidence

- Vitamin D emerged as a protective factor in a prospective, cross-sectional study of 3,121 adults aged  $\geq 50$  years (96% men) who underwent a colonoscopy.
  - The study found that 10% had at least one advanced cancerous lesion. Those with the highest vitamin D intakes ( $>645$  IU/day) had a significantly lower risk of these lesions.
  
- Daily supplementation of calcium (1000 mg) with vitamin D (400 IU) for seven years had no effect on the incidence of colorectal cancer among postmenopausal women in the Women's Health Initiative *Wactawski-Wende et al (2006) NEJM, 354:7*
  
- More recently, a clinical trial focused on bone health in 1,179 postmenopausal women residing in rural Nebraska found that subjects supplemented daily with calcium (1,400-1,500 mg) and vitamin D3 (1,100 IU) had a significantly lower incidence of cancer over 4 years compared to women taking a placebo.



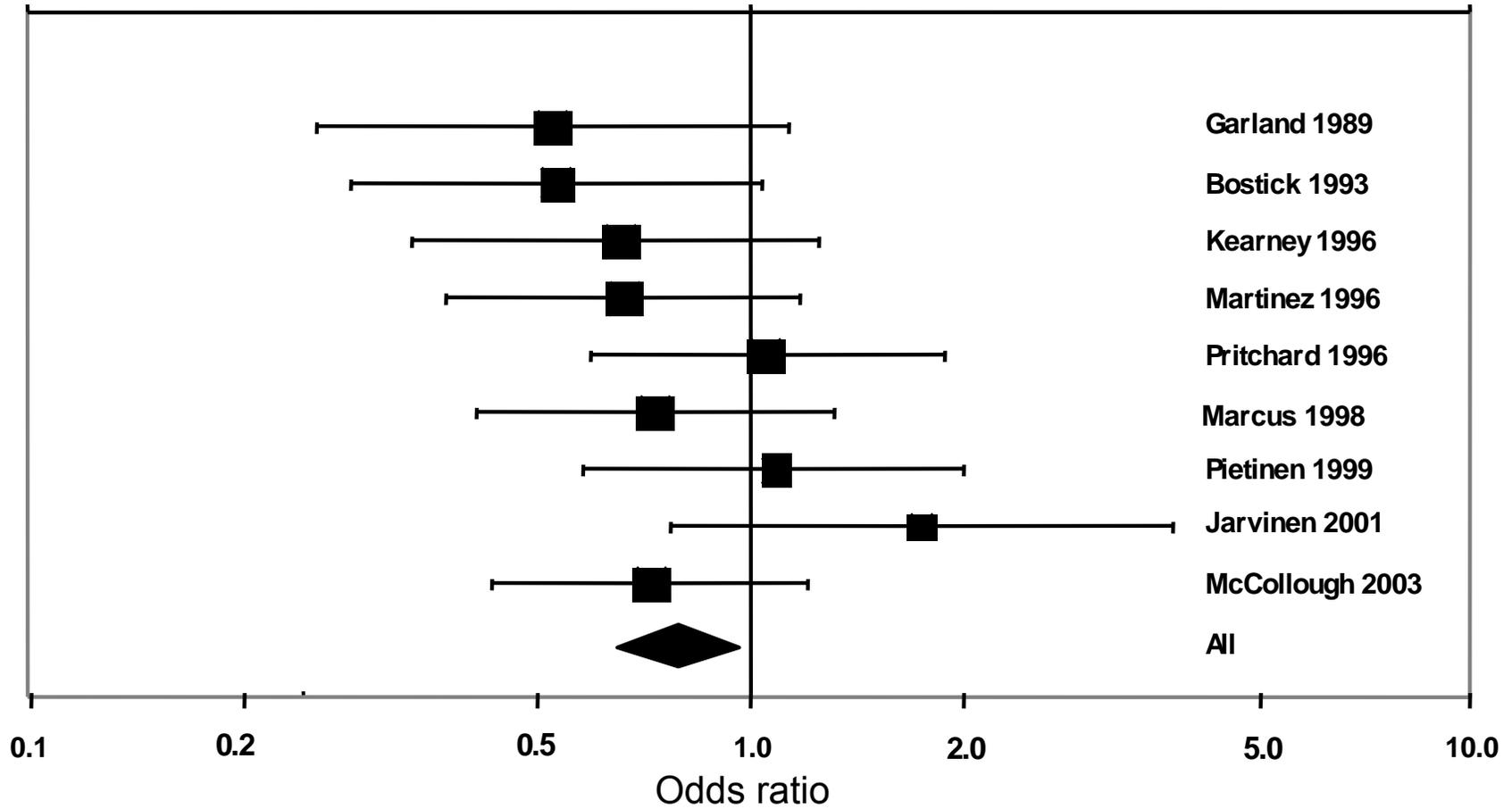
# Vitamin D and Cancer Incidence

Kaplan-Meier survival curves (ie, free of cancer) for 3 treatment groups randomly assigned in the entire cohort of 1179 women





# Dietary Vitamin D and Colorectal Cancer





## DCEG Vitamin D studies

- Examine the prospective relationship between the vitamin D status metabolite, 25-hydroxyvitamin D in serum and cancer mortality
- The study was conducted in more than 16,000 persons aged 17 and older who participated in the Third National Health and Nutrition Examination survey (NHANES III)
- Found total cancer mortality was unrelated to baseline vitamin D status in the entire population, men, women, non-Hispanic whites, non-Hispanic blacks, Mexican Americans in persons younger than 70 or 70 years or older
- Found no interaction between vitamin D and season or vitamin D and serum retinol
- Colorectal cancer mortality was inversely related to serum 25(OH)D level
  - levels  $>80$  nmol/L were associated with a 72% risk reduction than those  $<50$  nmol/L



## Clinical Trials

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- **571 trials on Vitamin D**
- **217 trials on Vitamin D and cancer**
- **77 trials on Vitamin D and cancer sponsored by NIH**

***ClinicalTrials.gov***  
A service of the U.S. National Institutes of Health



## NCI-sponsored trials

- Phase III Randomized Study of Zoledronate, Vitamin D, and Calcium With or Without Strontium Chloride Sr 89 or Samarium Sm 153 Lexidronam Pentasodium in Preventing or Delaying Skeletal-Related Events in Patients With Bone Metastases Secondary to Prostate, Lung, or Breast Cancer-Radiation Therapy Oncology Group--NCI
- Phase II Pilot Study of Vitamin D Deficiency and Myalgias and/or Arthralgias in Postmenopausal Women Receiving Adjuvant Letrozole for Stage I-III Breast Cancer-Fred Hutchinson Cancer Research Center
- Vitamin D and Soy Supplements in Treating Patients With Recurrent Prostate Cancer--Wake Forest University
- DNA Changes That Affect Vitamin D Metabolism in Patients With Colorectal Cancer Receiving Vitamin D Supplements--Roswell Park Cancer Institute
- Vitamin D in Treating Patients With Prostate Cancer-- Roswell Park Cancer Institute
- Vitamin D/Calcium Polyp Prevention Study--Dartmouth-Hitchcock Medical Center



## NCI funding

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- Search CRSIP FY08 funding of vitamin D by NCI
- 67 grants funded
  - 41 R01s
  - 9 R03s
  - Remaining 17 are: K07, K01, R41, F3, R21, P01, U54, P50, U10, K07, U01, P30



## DCEG- Ongoing Vitamin D Studies

- Examining the relationship between two vitamin D metabolites (25(OH)D and 1,25(OH)D) and breast cancer in Prostate, Lung, Colon, and Ovarian screening study cohort
  - Recently published no association found between vitamin D concentration in blood and risk of prostate cancer (Ahn et al, JNCI (2008) 100(11):796-804)
- We are also examining the relationship between pre-diagnostic 25(OH)D and lymphoid cancer risk in a case-control study nested in the Alpha-Tocopherol Beta Carotene Prevention Study cohort of Finnish smokers.
- Investigators in REB are also participating in a large pooled analysis of the association between 25(OH)D and several cancers, including pancreatic, upper GI, renal, endometrial, and ovarian cancer and NHL.
- The USRT project is also planning a study to assess the determinants of circulating vitamin D by examining self-reported host skin characteristics, sun exposure, and supplement and dietary behavior.
- Currently undertaking a small study to examine the methodological issues in blood samples measurement of 25(OH)D

# VDR genotype, Vit D levels and Cancer risk



Level of 25(OH)D <sup>a</sup>	Category	Total Prostate Cancer			Aggressive Prostate Cancer <sup>b</sup>		
		<i>n</i>	OR	95% CI	<i>n</i>	OR	95% CI
Low ( $\leq 24.4/32.0$ )	Low 1,25(OH) <sub>2</sub> D level	142/180	1.33	0.94–1.88	75/75	2.06	1.24–3.43
	High 1,25(OH) <sub>2</sub> D level	108/148	1.16	0.82–1.64	48/79	1.08	0.66–1.77
High ( $> 24.4/32.0$ )	Low 1,25(OH) <sub>2</sub> D level	119/152	1.20	0.85–1.70	57/81	1.24	0.75–2.04
	High 1,25(OH) <sub>2</sub> D level	123/184	Reference	—	56/97	Reference	—
<b>p-Value for interaction</b>		0.85			0.23		
Low ( $\leq 24.4/32.0$ ) <sup>c</sup>	FokI <i>ff</i> genotype	42/30	1.89	1.10–3.25	19/13	2.53	1.10–5.80
	FokI <i>FF/FF</i> genotype	194/244	0.96	0.72–1.28	99/118	1.17	0.77–1.77
High ( $> 24.4/32.0$ ) <sup>c</sup>	FokI <i>ff</i> genotype	30/47	0.70	0.42–1.15	18/27	0.76	0.38–1.51
	FokI <i>FF/FF</i> genotype	195/223	Reference	—	85/114	Reference	—
<b>p-Value for interaction</b>		0.01			0.05 <sup>d</sup>		

Li et al, PLoS Med. (2007) 4(3):562-71

OR and 95% CI; conditional logistic regression with patients and control participants matched on age and smoking status (never, past, and current) at baseline, adjusted for race (European descent, yes, or no) and exercise. Aggressive versus nonaggressive disease:  $p_{\text{heterogeneity}} = 0.01$  for the joint association of 25(OH)D with 1,25(OH)<sub>2</sub>D and  $p_{\text{heterogeneity}} = 0.18$  for the joint association of 25(OH)D with FokI genotype.

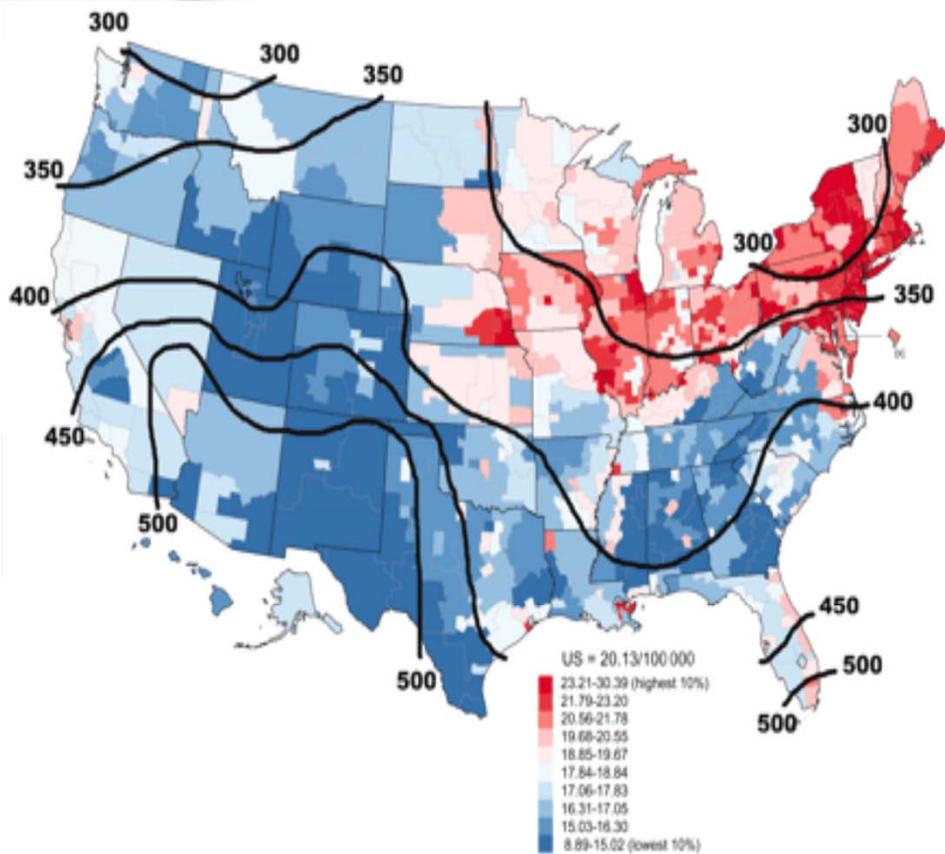
<sup>a</sup>Median cutoff points (average of two batches) for winter/spring- and summer/fall-collected control samples.

<sup>b</sup>Clinical stage for patients was determined based on the Whitmore-Jewett classification scheme: Aggressive disease, stage C, D, or Gleason score 7–10 tumor, patients who developed metastases or died during the follow-up.

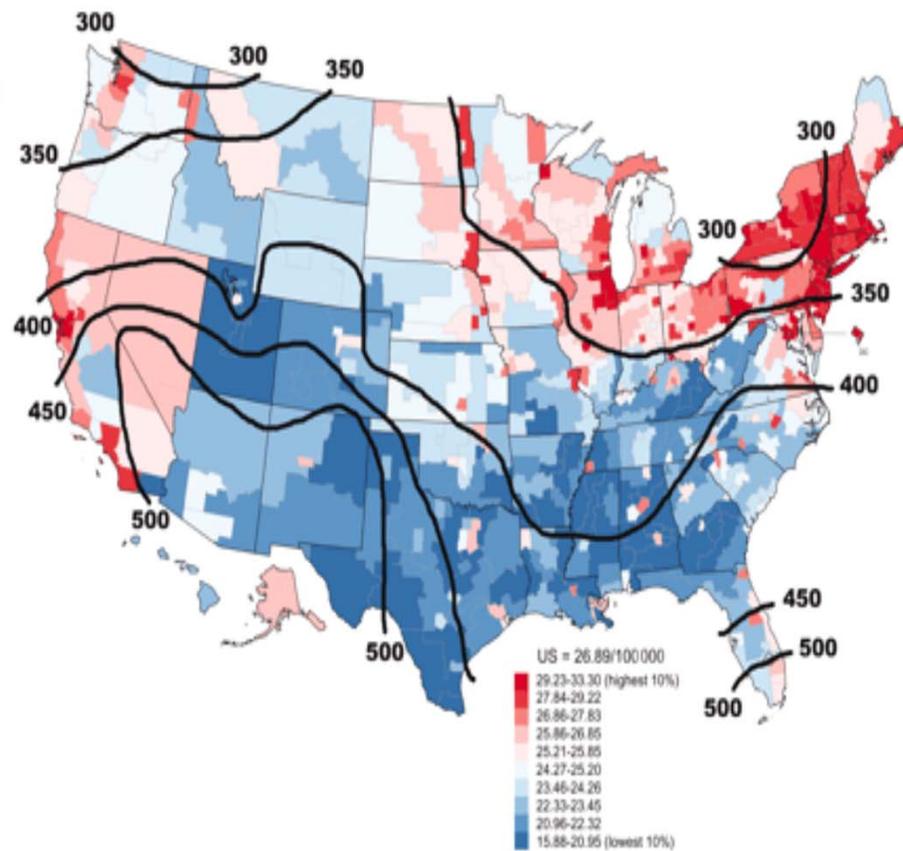
<sup>c</sup>Further adjusted for 1,25(OH)<sub>2</sub>D levels.



# Cancer Mortality by Annual Sun Exposure



**Colon Cancer**



**Breast Cancer**

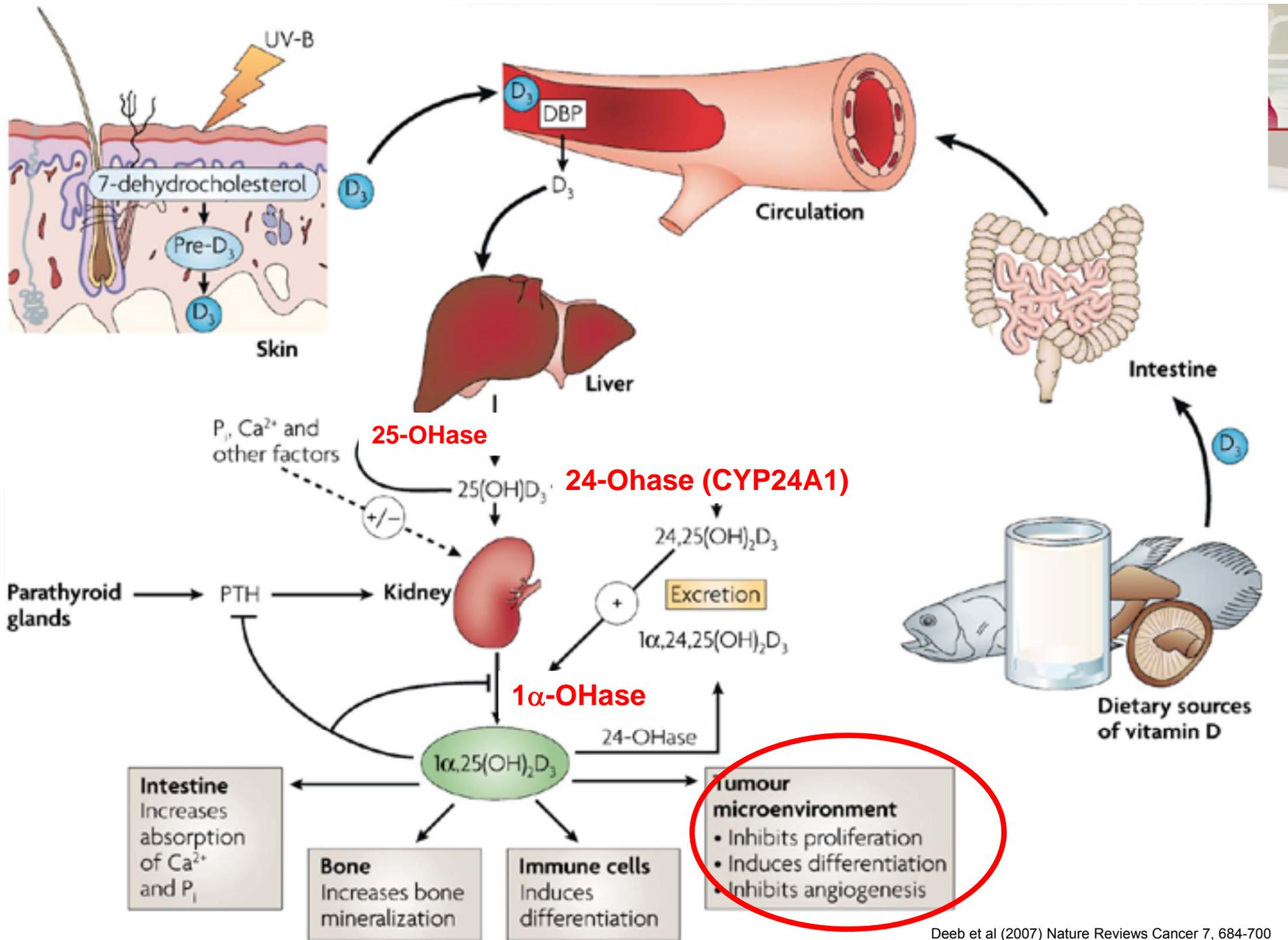


## HHS Report asks..

# **Is There a Level of Sunlight Exposure That Is Sufficient to Maintain Adequate Vitamin D Concentrations, But Does Not Increase the Risk of Skin Cancer?**

- “...did not retrieve any systematic reviews in our literature search that addressed this question
- This highlights an area for future research
- Suggested sun exposure times for vitamin D synthesis will vary with individual and environmental characteristics such as latitude and skin pigmentation (melanin)”

Evidence Report/Technology Assessment, Number 158  
Effectiveness and Safety of Vitamin D in Relation to Bone Health  
AHRQ Publication No. 07-E013, August 2007  
Prepared for: Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
By: University of Ottawa Evidence-based Practice Center





# Vitamin D Anticancer Properties

- Alterations in vitamin D receptor expression, and in the synthesis (25-hydroxylase and  $1\alpha$ -hydroxylase) and catabolism (24-hydroxylase) of vitamin D metabolites are involved in the growth regulation of tumors; thus, compromising  $1\alpha,25(\text{OH})_2\text{D}_3$  (also known as calcitriol; the active metabolite of vitamin D signalling) sensitivity and  $1\alpha,25(\text{OH})_2\text{D}_3$  signalling
- The antiproliferative effects of  $1\alpha,25(\text{OH})_2\text{D}_3$  have been demonstrated in various tumour types, as determined by preclinical trials
- The anti-tumor effects of  $1\alpha,25(\text{OH})_2\text{D}_3$  involve mechanisms that are associated with G0/G1 arrest, differentiation, induction of apoptosis and modulating different signalling pathways in tumor cells, as well as inhibiting tumor angiogenesis
- Glucocorticoids potentiate the anti-tumor effects of  $1\alpha,25(\text{OH})_2\text{D}_3$  and decrease  $1\alpha,25(\text{OH})_2\text{D}_3$ -induced hypercalcemia.  $1\alpha,25(\text{OH})_2\text{D}_3$  also potentiates the antitumor effects of many chemotherapeutic agents such as platinum analogues, taxanes and DNA-intercalating agents
- Given that the major vitamin D catabolizing enzyme, CYP24A1 (24-hydroxylase), is often amplified and overexpressed in tumor cells, agents that inhibit this enzyme can potentiate  $1\alpha,25(\text{OH})_2\text{D}_3$  anti-tumor effects
- Preclinical data indicate that maximal anti-tumor effects are seen with pharmacological doses of  $1\alpha,25(\text{OH})_2\text{D}_3$ , and can be safely achieved in animals using a high-dose, intermittent schedule of administration. Some clinical trial data indicates that  $1\alpha,25(\text{OH})_2\text{D}_3$  is well-tolerated in cancer patients within a proper dosing schedule
- Data support the hypothesis that vitamin D compounds may have an important role in cancer therapy and prevention, and merit further investigation



## Future Direction/needs

- Further research is needed to:
  - Determine whether vitamin D inadequacy increases cancer risk
  - Whether greater exposure to the nutrient is protective
  - Need to consider metabolism, catabolism, and VDR polymorphisms
  - Address methodology to measure serum vitamin D level --biomarkers
  - Need surrogate markers of Vit D activity
  - Determine molecular targets for vitamin D
  - Explore vitamin D/sun exposure dilemma