National Cancer Institute

Vitamin D and Cancer: Current Dilemmas/Future Needs

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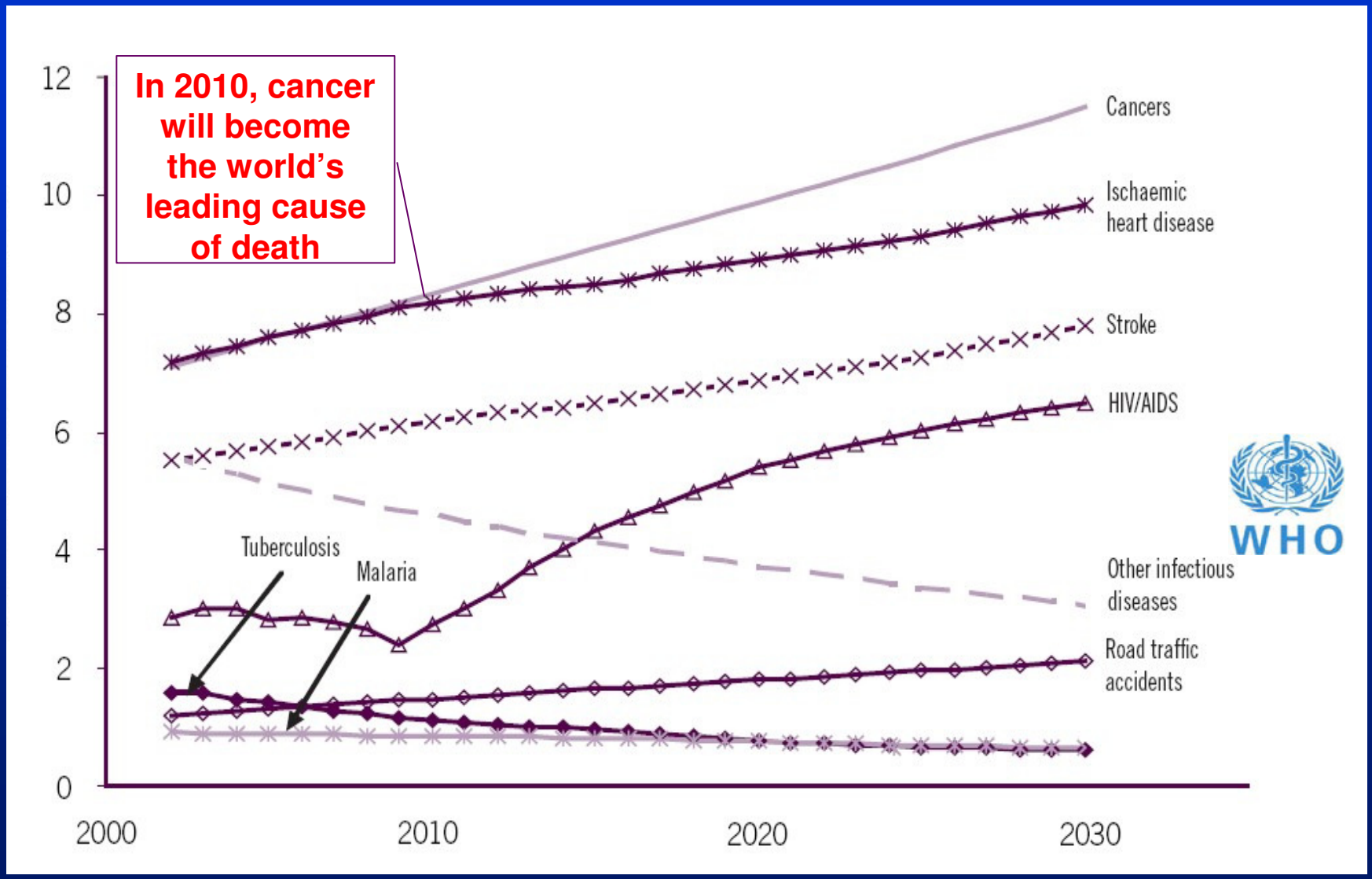
The World Is Changing: Projected Deaths



By **2020**, cancer **could kill**

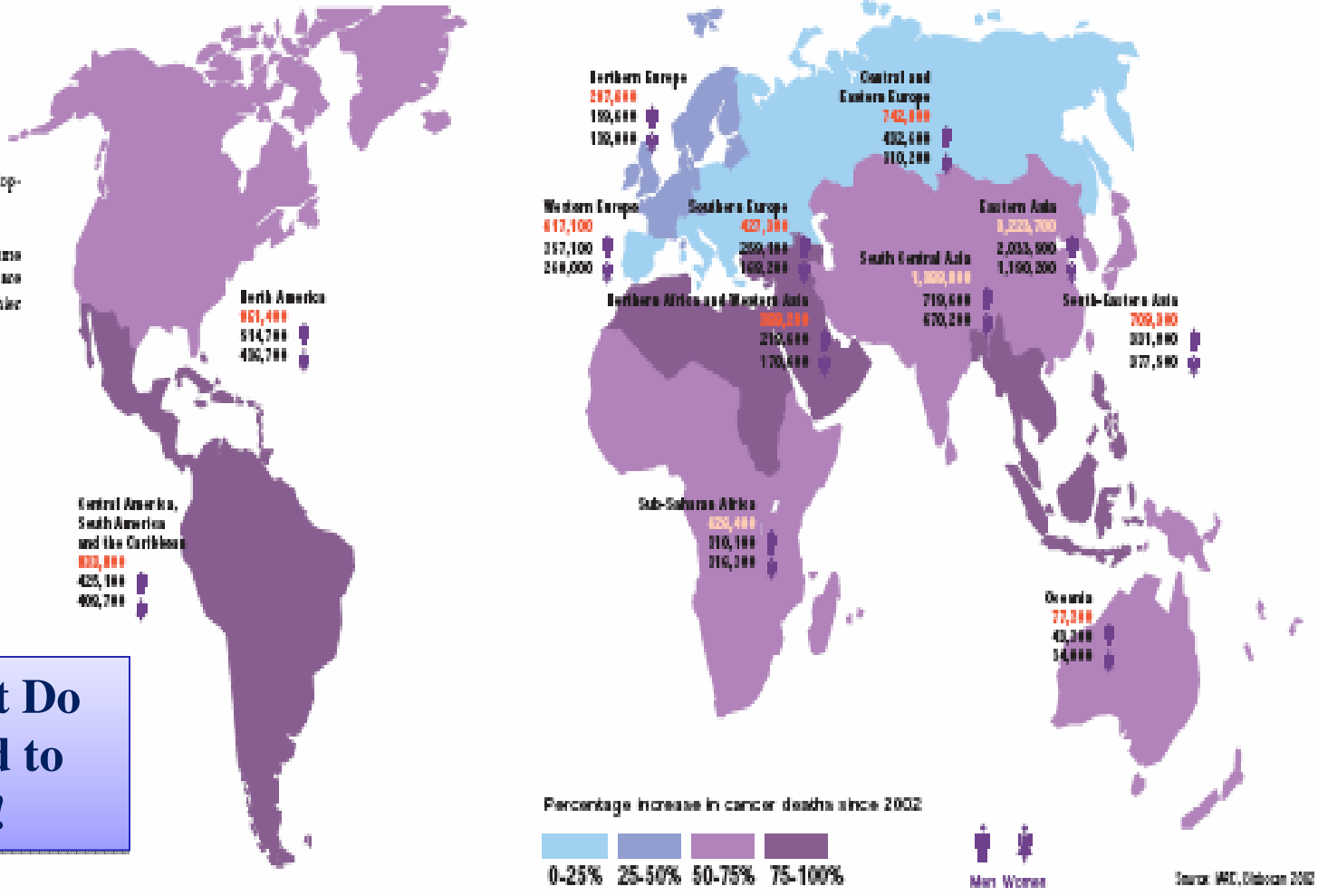
10.3 million

people per year unless we act

Trends

The biggest rates of increase are in developing and newly industrialized countries.

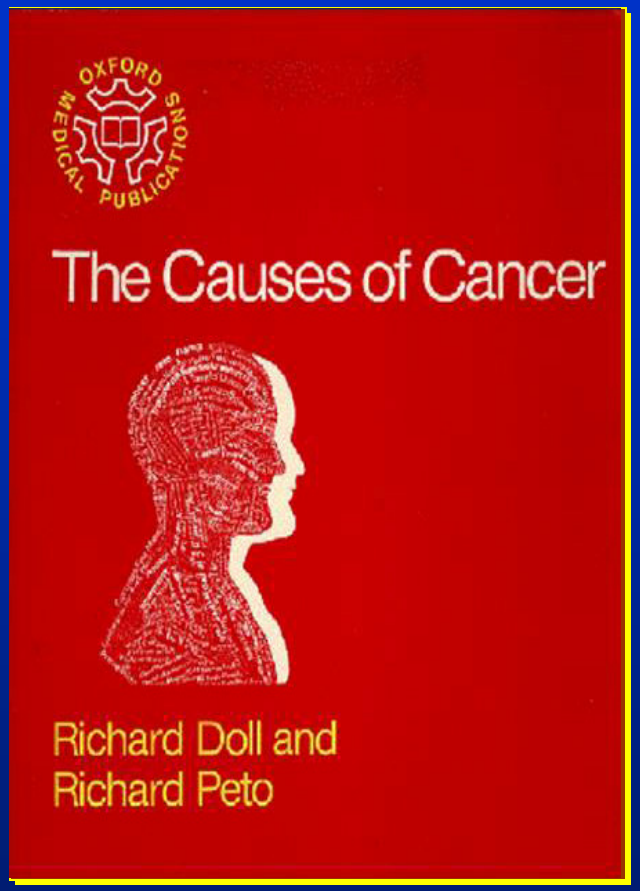
The relative increase is smallest in some Western countries where populations are rejecting tobacco and adopting healthier lifestyles.

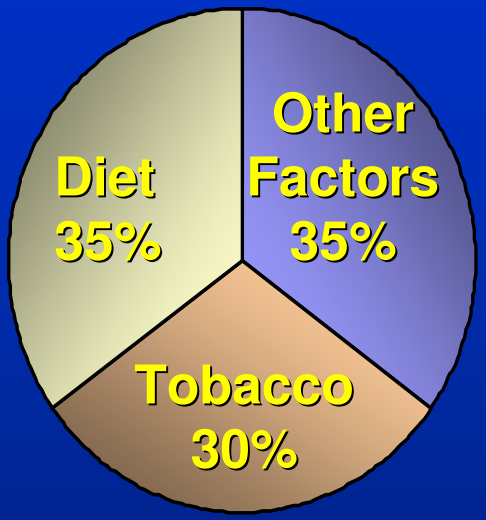


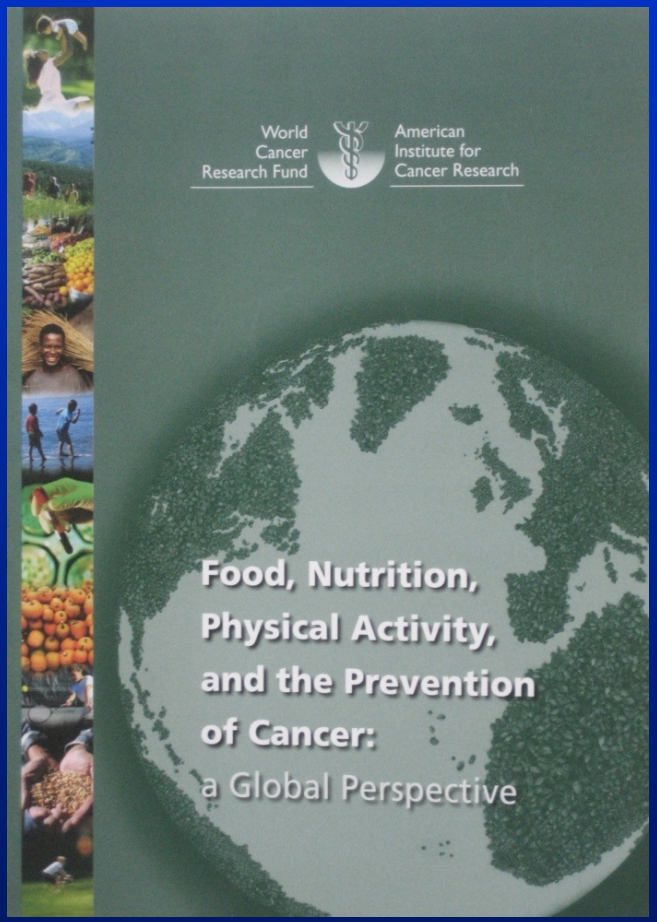
If Prevent Do Not Need to Treat!

Dr. Lee Jong-wook, Director General WHO

It has been estimated that about 1/3 of all cancer deaths may be attributable to dietary factors.







The Causes of Cancer – Richard Doll & Richard Peto, 1981

WCRF/AICR Report - Released Nov. 1-2, 2007

msnbc

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Vitamin D shown to cut cancer risk in women

Major study suggests supplement wards off several types of cancer

Forbes

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ncer risk'

How Strong is the Evidence that vitamin D may have a role in cancer?

American Cancer Society

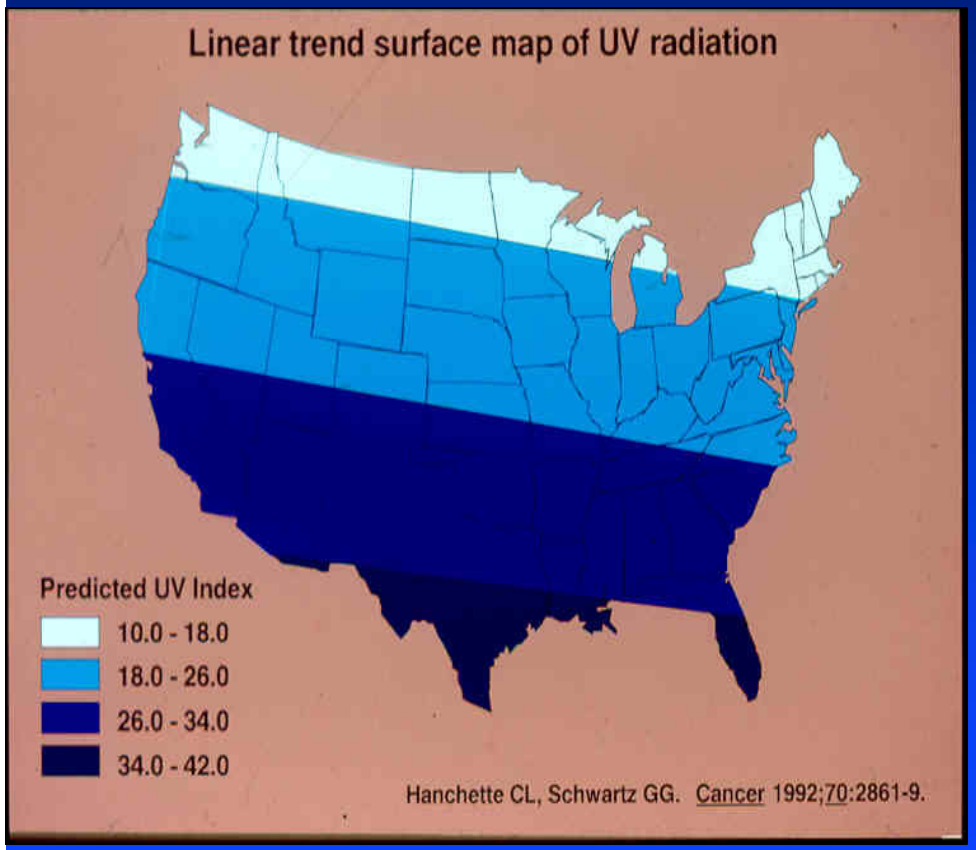
Study Sees Link Between Vitamin D, Breast Cancer Prognosis

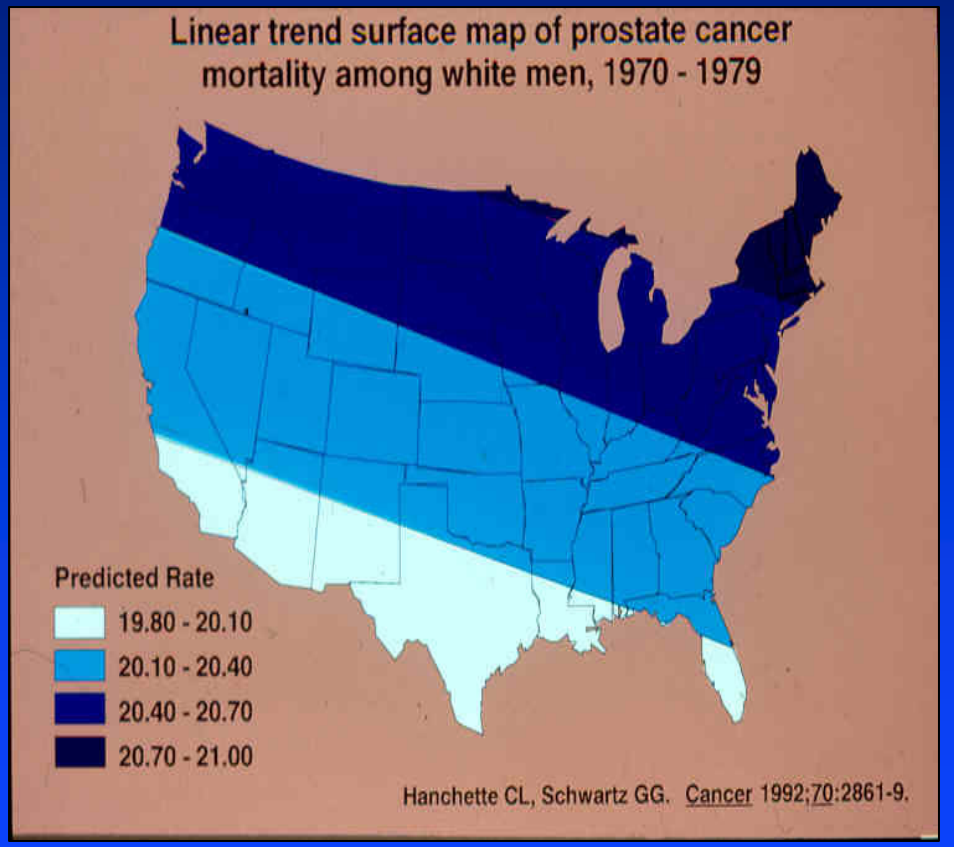
Cancer Resource Center

Home > Health > CancerPreventionAndTreatment

Vitamin D May Cut Cancer Risk

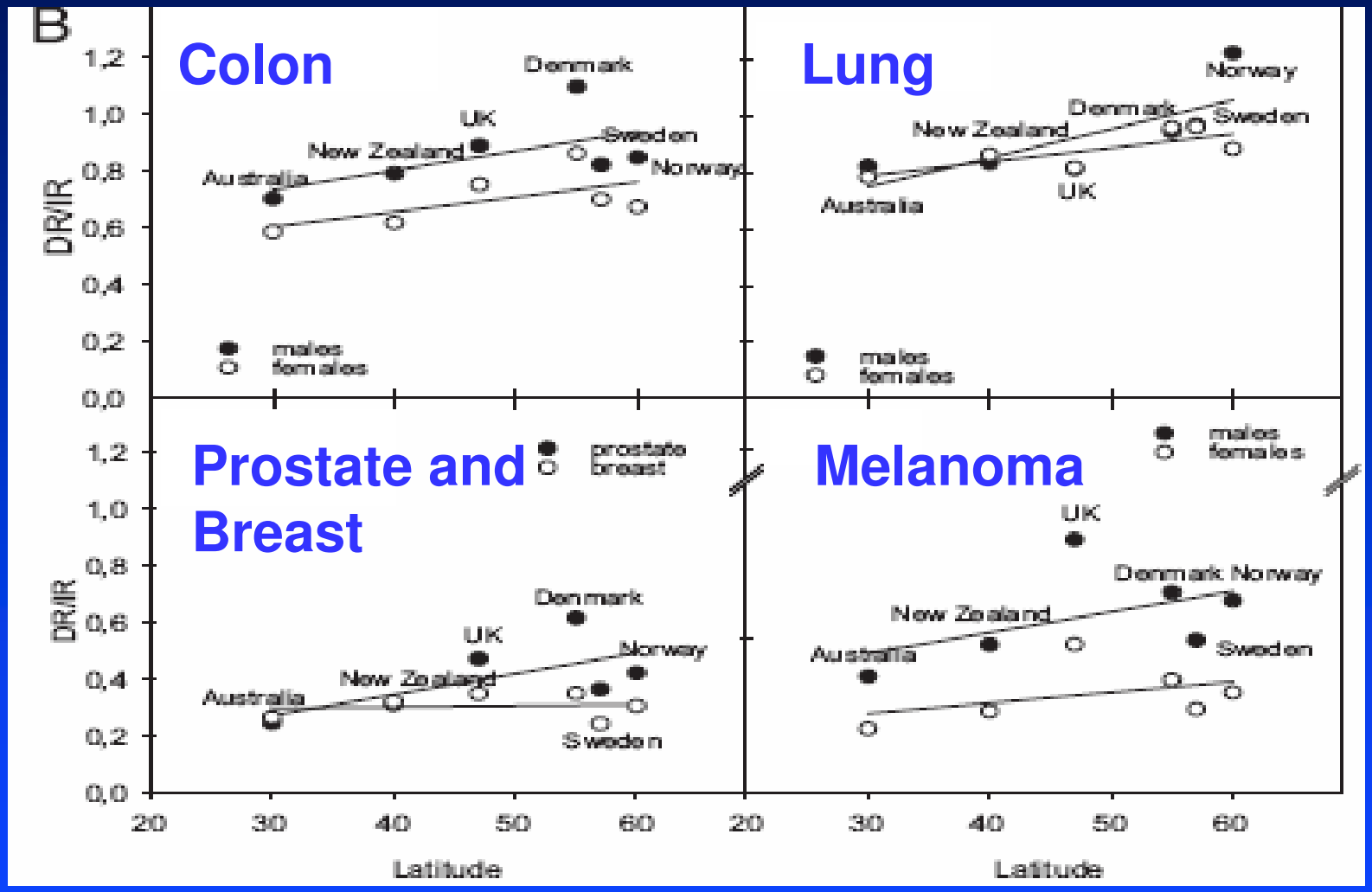
Age-Adjusted Prostate Cancer Mortality Rates (Whites) and Ultraviolet Radiation in 3073 U.S. Counties





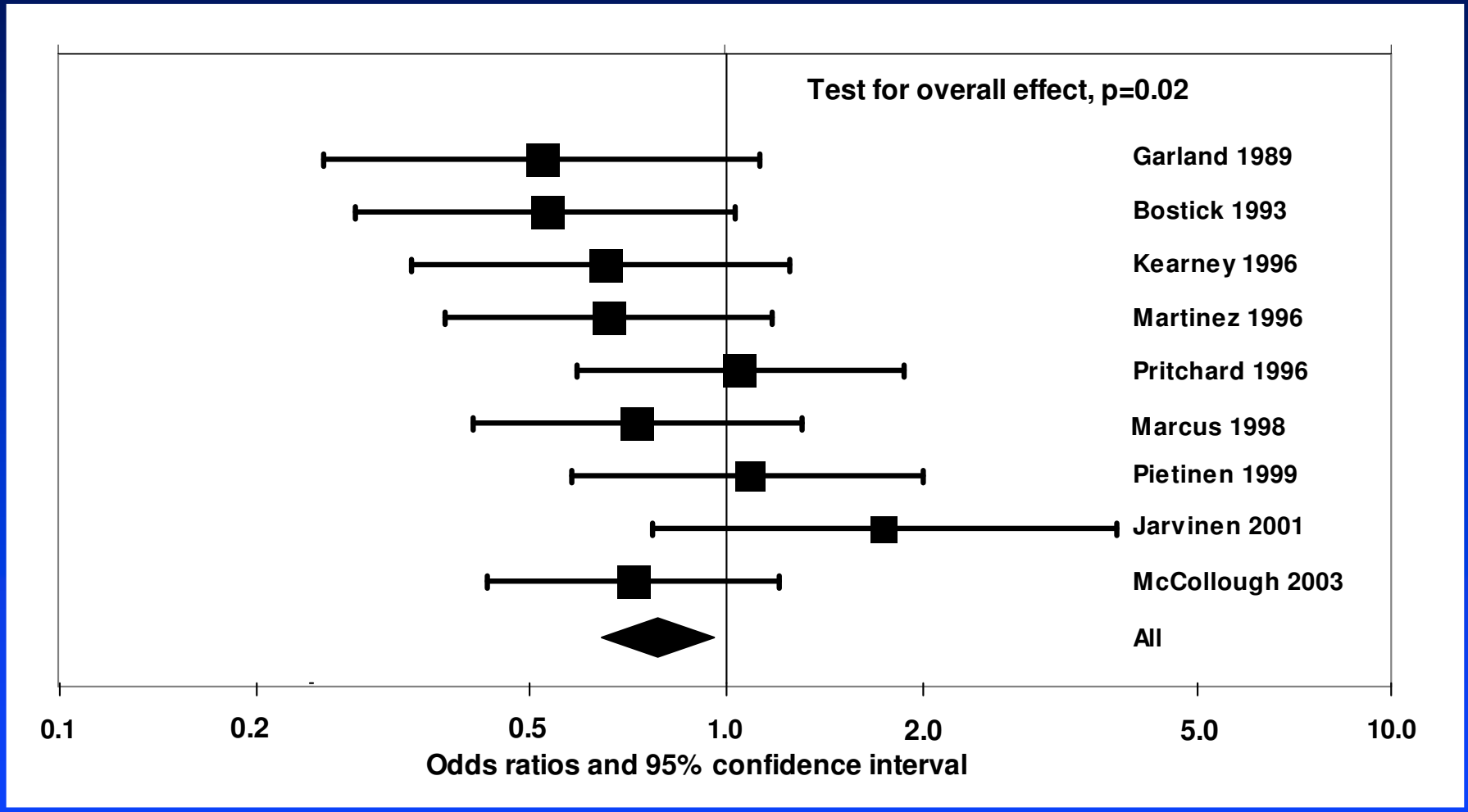
Hanchette and Schwartz, Cancer 70:261-9, 1992

Cancer Mortality and Latitude



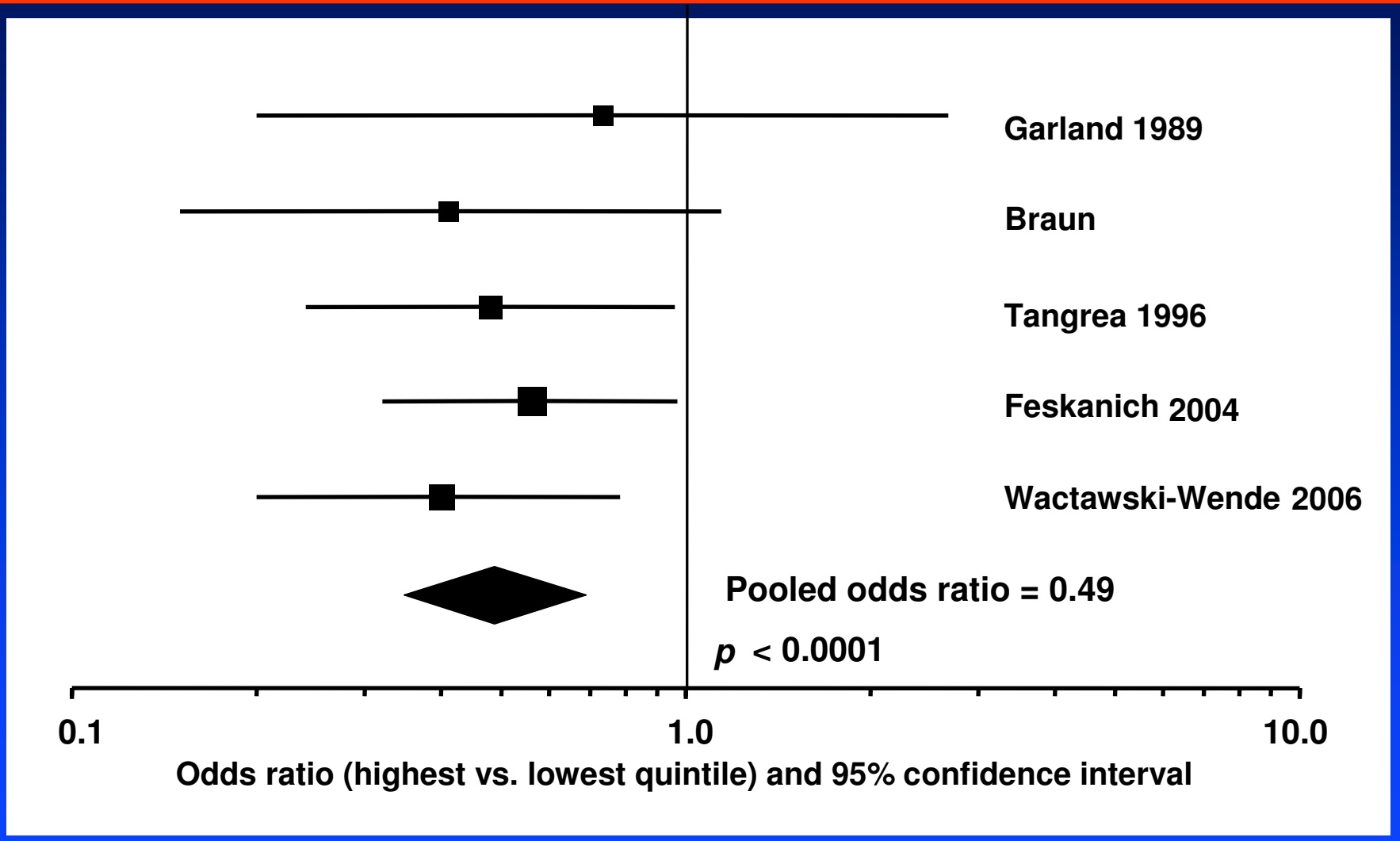
Moan J et al. PNAS 105: 668-673, 2008

Dietary Vitamin D and Colorectal Cancer



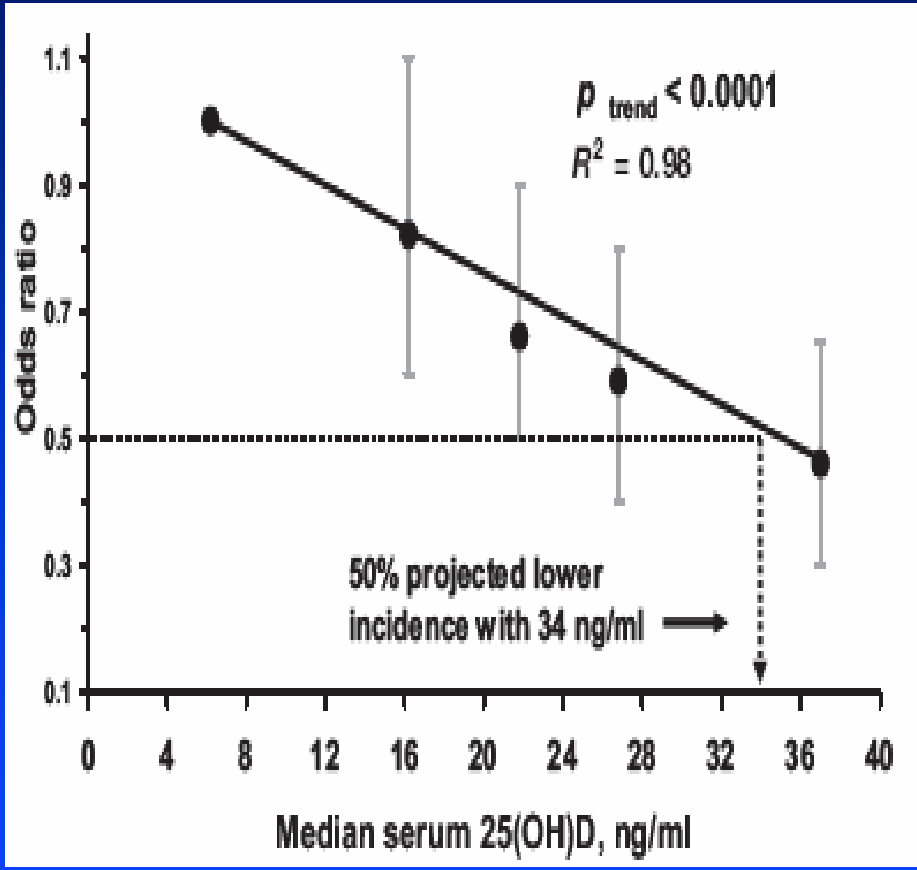
Gorham E., et al. J Steroid Biochem Mol Biol. 97:179-94, 2005

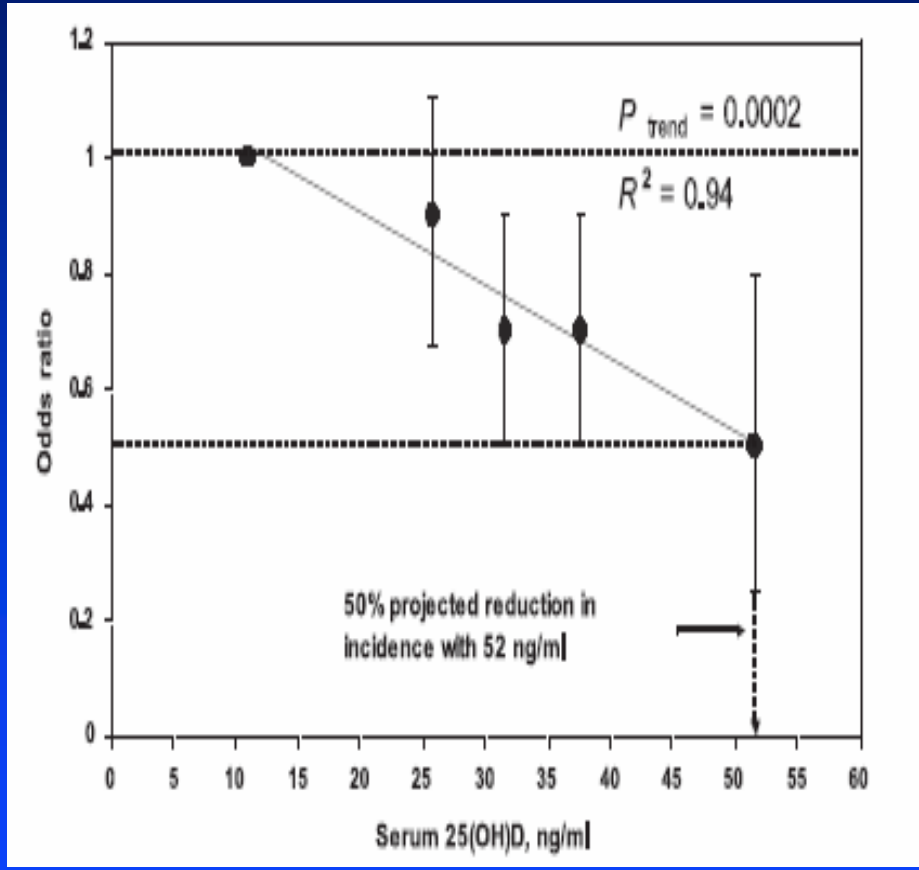
Serum 25(OH)D and Colorectal Cancer Risk



Gorham E., et al. J Steroid Biochem Mol Biol. 97:179-94, 2005

Serum 25(OH)D and Risk of Colorectal and Breast Cancer

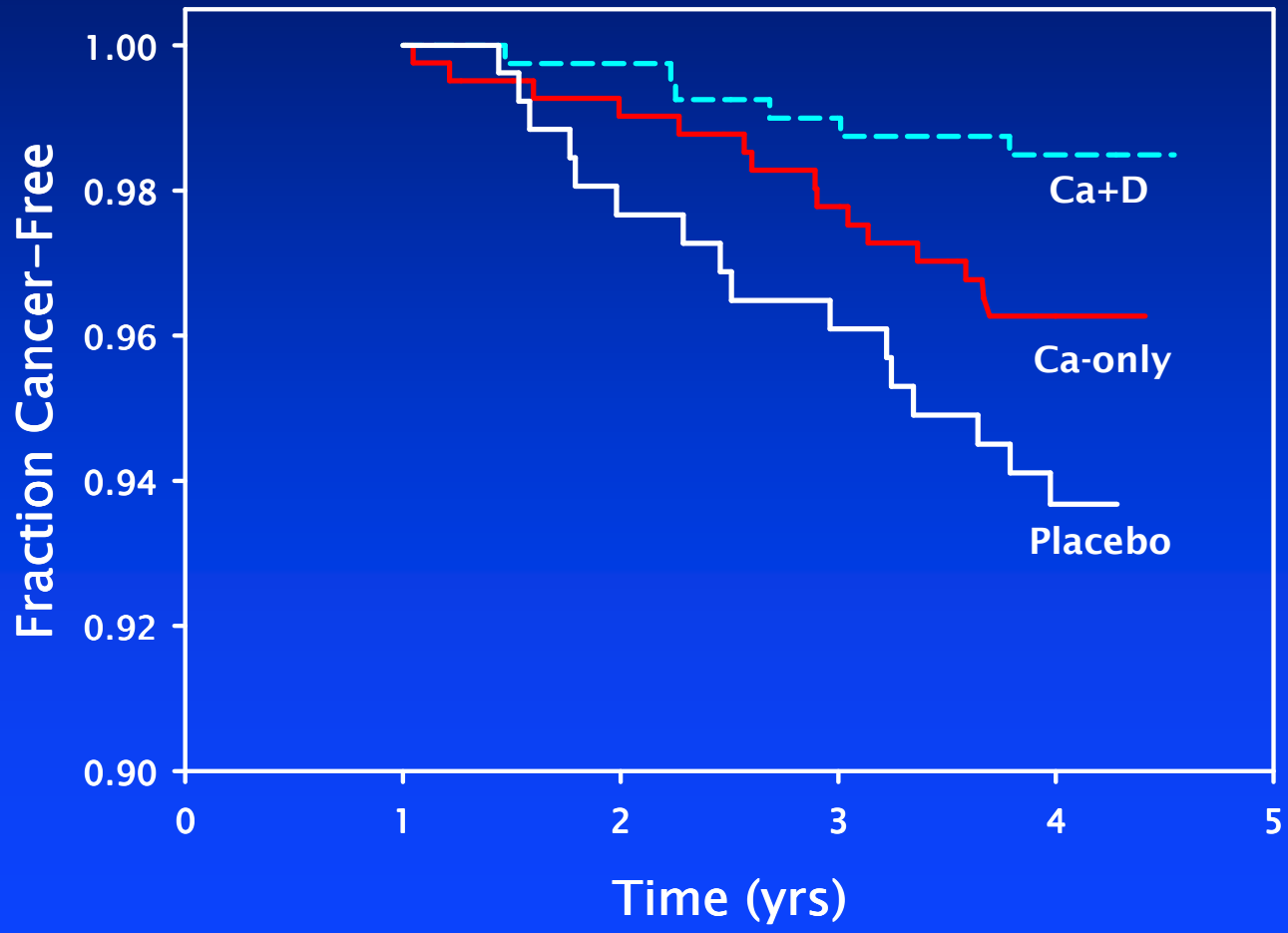




Garland et al. Nutr. Rev 65:S91-95, 2007

Vitamin D and Cancer Incidence

1179 Healthy women, 66±7 yrs, 4 yr study, Calcium (1400 mg/d), Vitamin D_3 (1100 IU/d)



RR = 0.232

Lappe et al. Am. J. Clin. Nutr. 85:1586-1591, 2007

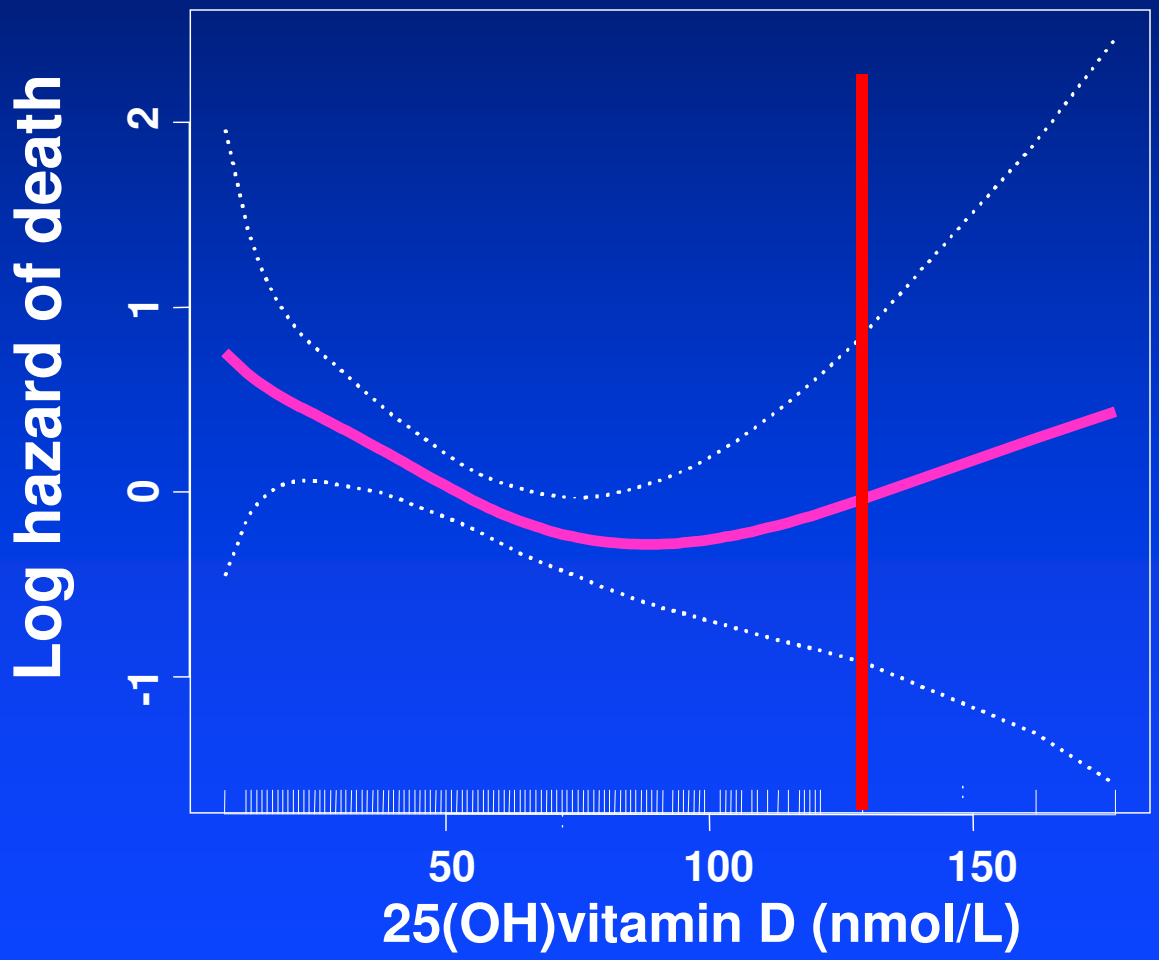
Cancers By Primary Site

Site	Placebo	Calcium	Calcium+D
Breast	7	6	4
Colon	2	0	0
Lung	3	2	1
Blood	4	4	2
Uterus	0	1	0
Other	2	2	1
Total	18	15	8

Lappe et al. Am. J. Clin. Nutr. 85:1586-1591, 2007

Vitamin D Status and Mortality in Breast Cancer Patients

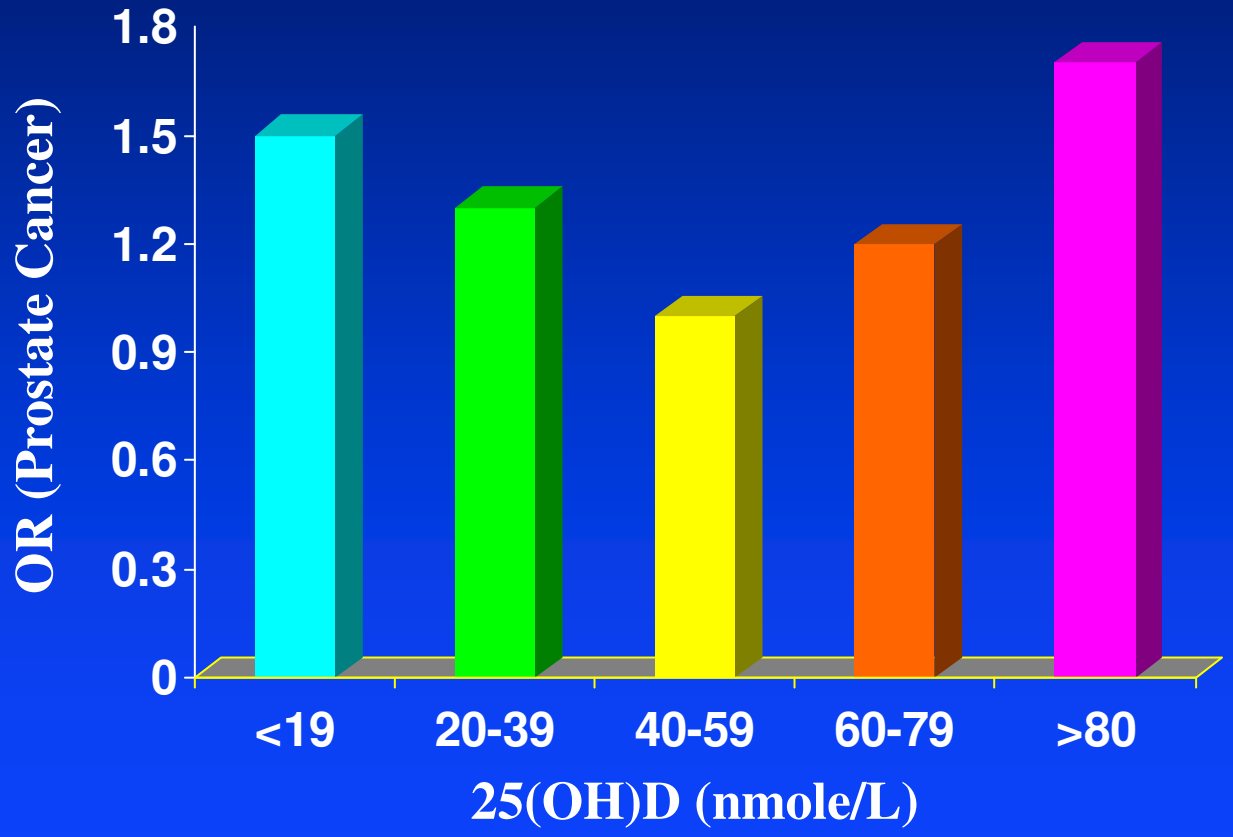
512 women, early stage breast cancer, Toronto, 11.6 year follow-up



Goodwin et al., J. Clin Oncol.23: 3755-3763, 2009

Serum 25(OH)D and Prostate Cancer Risk

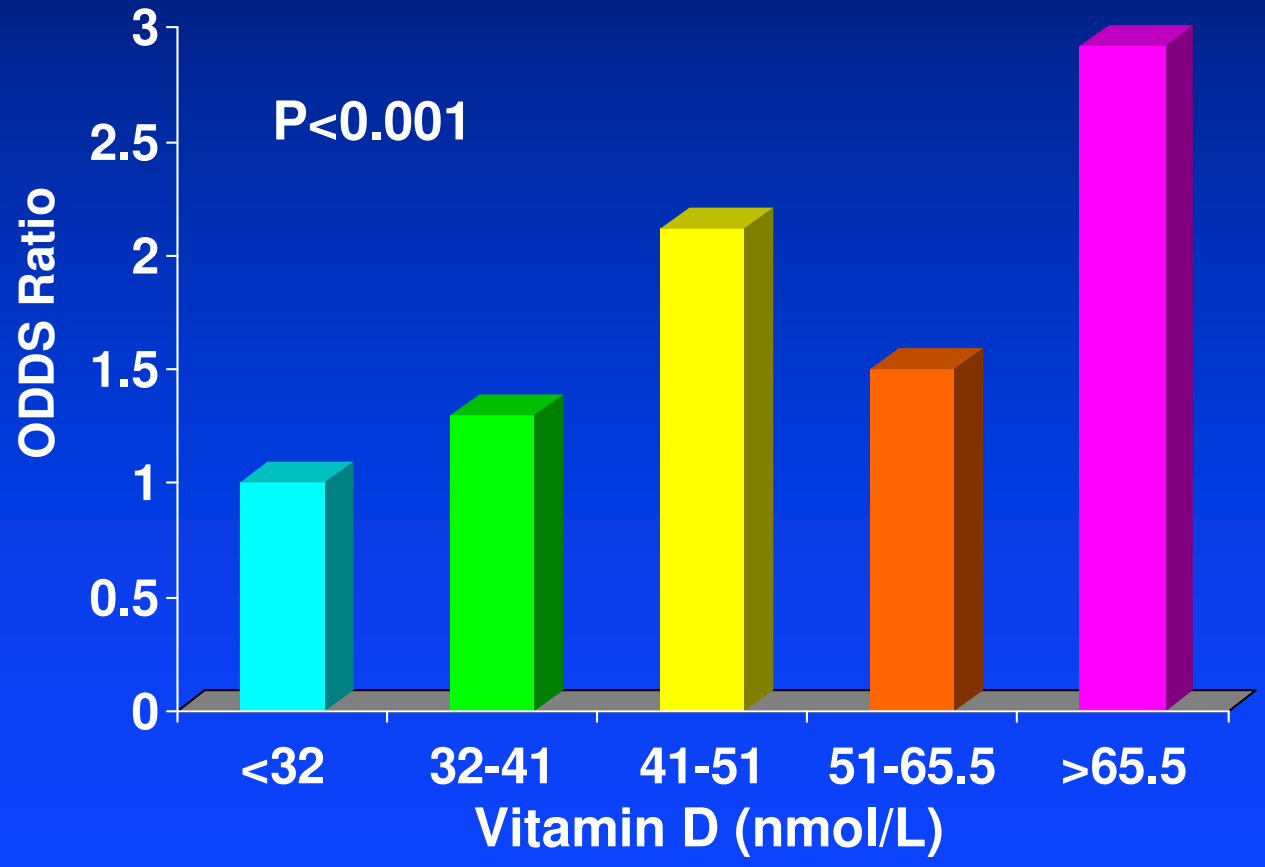
Nested Case-Control Study in Nordic Men (622 cases and 1451 controls)



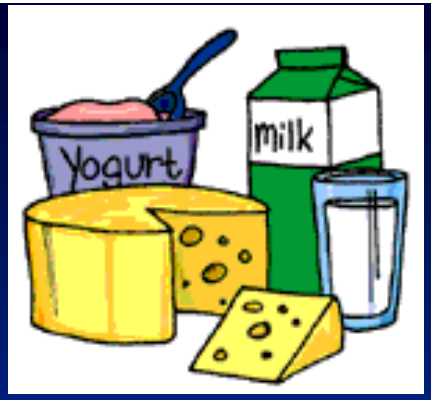
Tuohimaa et al. Int J Cancer 108: 104-108, 2004

Serum 25(OH)D and Pancreatic Cancer

200 cases and 400 controls from the ATBC study of Finnish Male Smokers



Stolzenberg-Solomon et al. Cancer Res 66:10213-9, 2006



Vitamin D_3

Liver

$25(OH)D_3$

Kidney

$24,25(OH)_2D_3$

Cyp 24

$25(OH)D_3$

$1,25(OH)_2D_3$

1α hydroxylase

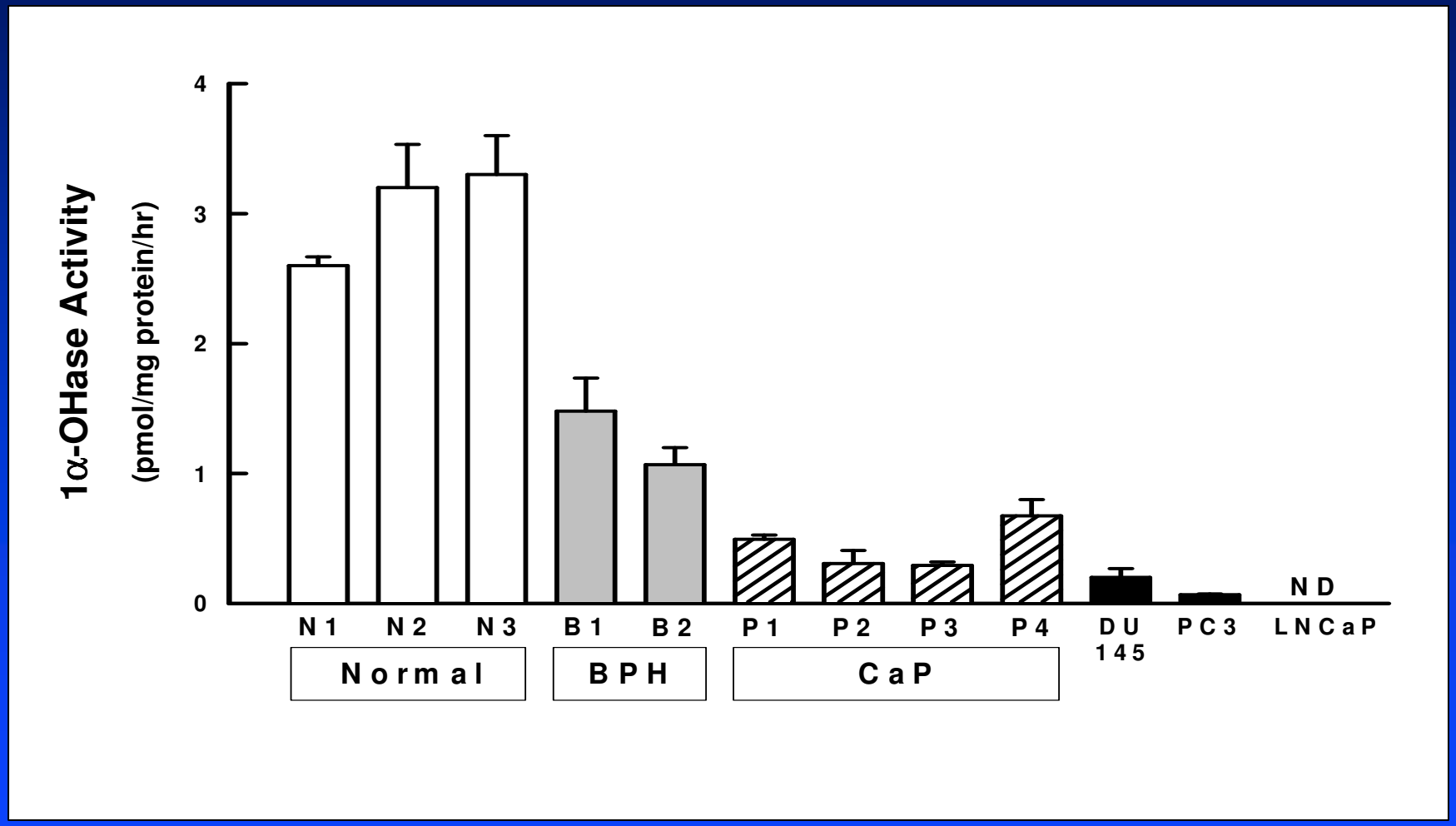
Prostate

Colon

Breast

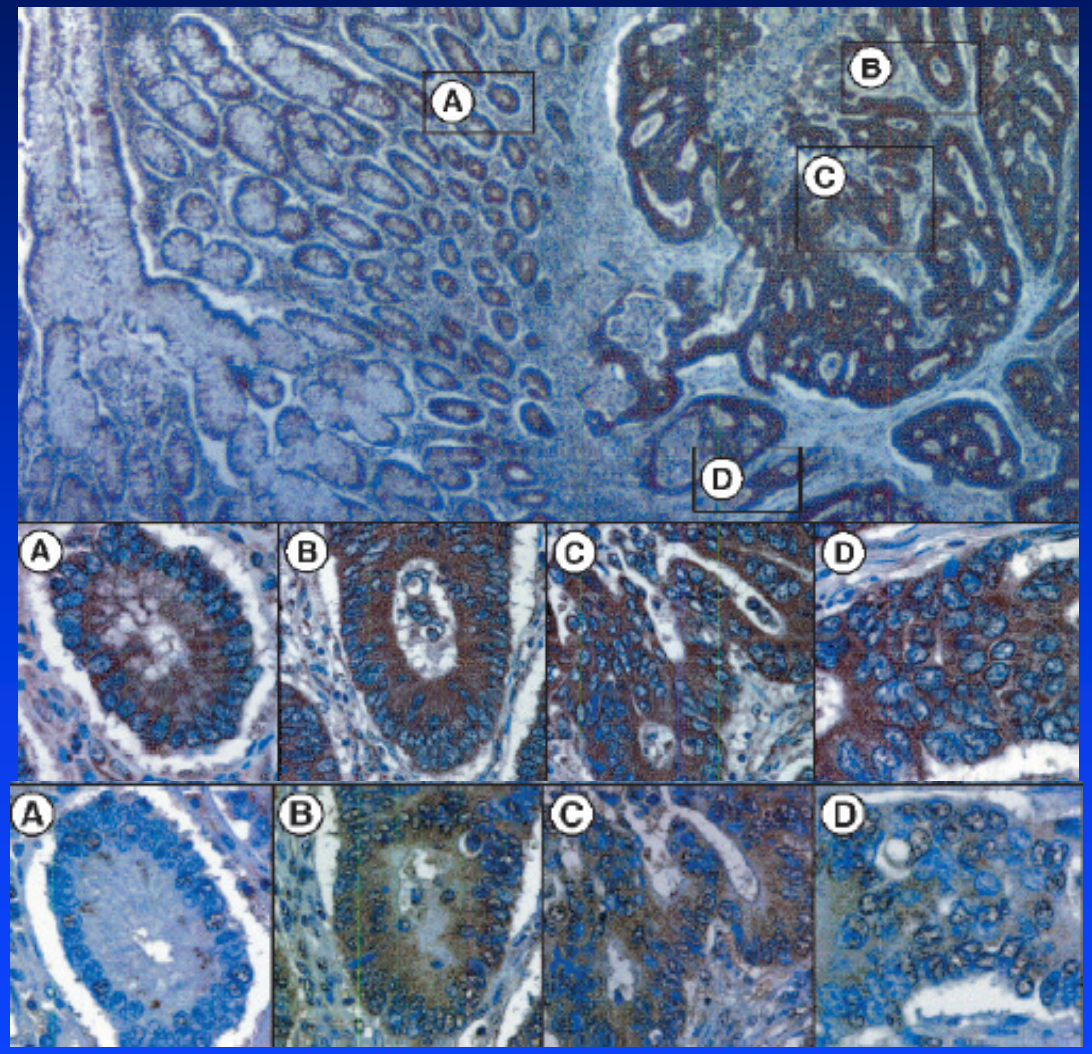
Bones

1-α-Hydroxylase Activity is Reduced in Prostate Cancer



Whitlatch et al., *J Steroid Biochem Mol Biol* 2002;81:135-140.

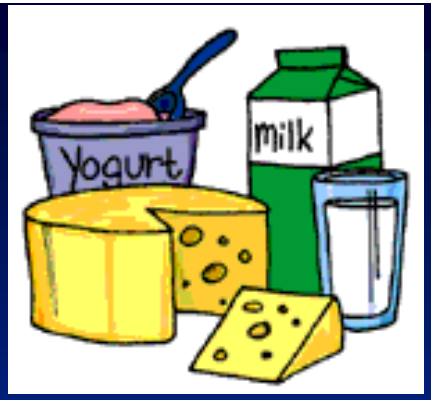
Expression of 1✂Hydroxylase and VDR in Human Colon Tissue



1✂-hydroxylase

Vitamin D Receptor

Matusiak et al. Cancer Epidemiol Biomark Prev 14:2370-2376, 2005



Vitamin D_3

Kidney

Liver

$24,25(OH)_2D_3$

Cyp 24

$25(OH)D_3$

$1,25(OH)_2D_3$

1α hydroxylase

Prostate
Colon
Breast
Bones

$25(OH)D_3$

Target cell nucleus

$1,25(OH)_2D_3$

Retinoid X receptor

VDR

VDRE

Transcription

Effects of VDR ablation on chemically-induced carcinogenesis

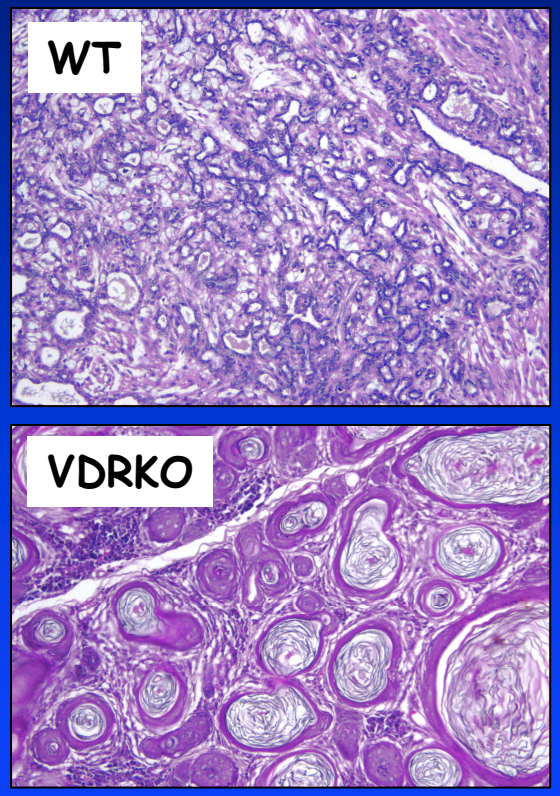
DMBA:

- ↑ mammary hyperplasias in VDRKO mice
- ↑ hormone independent mammary carcinomas in VDRKO mice
- Skin papillomas developed in VDRKO but not WT mice
- ↑ Lymphomas in VDRKO mice
- Tumor incidence in ovary, liver, lung, uterus unaffected by VDR

AOM:

- ↑ aberrant crypt foci (ACF) in VDRKO mice

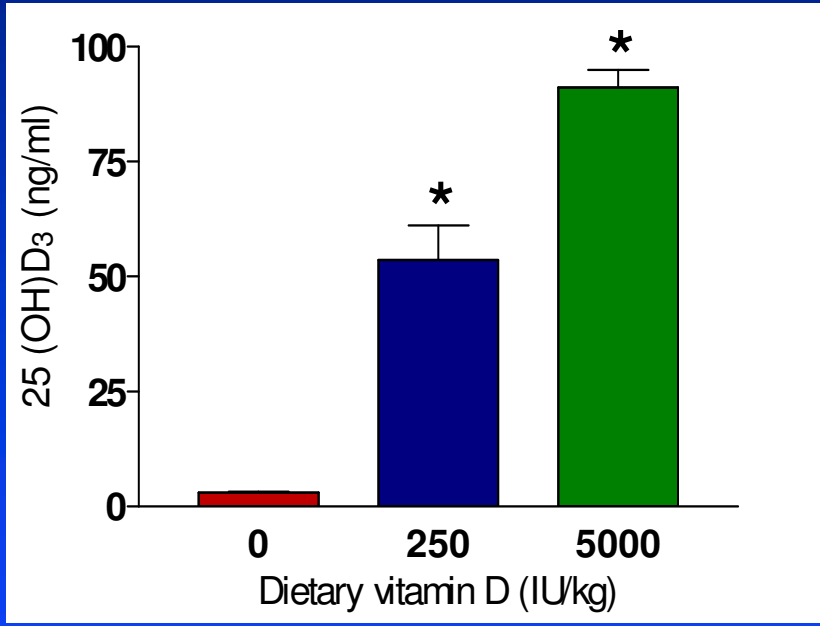
Tumor Morphology



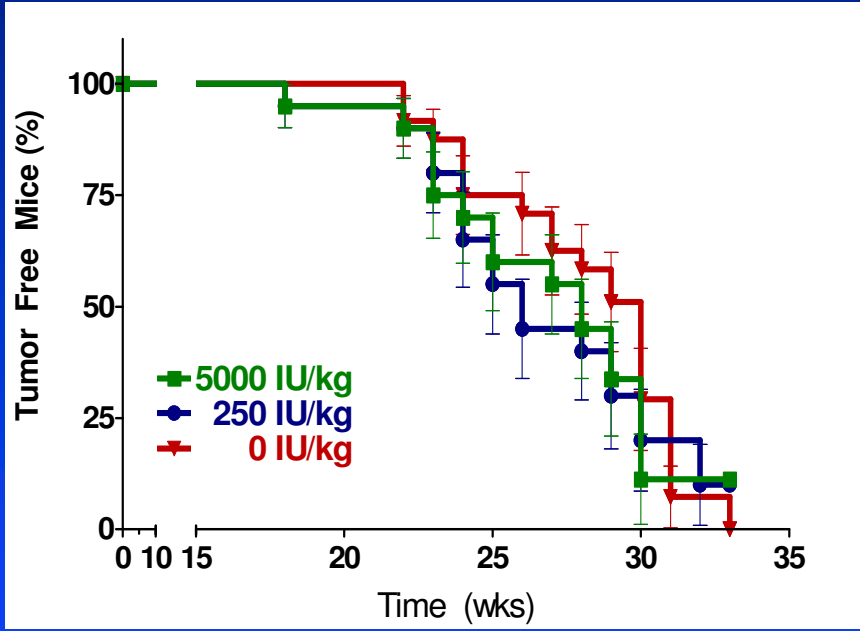
Zinser et al, J. Steroid Biochem Mol. Biol. 97:153-64, 2005

Effect of Dietary Vitamin D in VDR Knockout Animals

Serum 25(OH)D_3

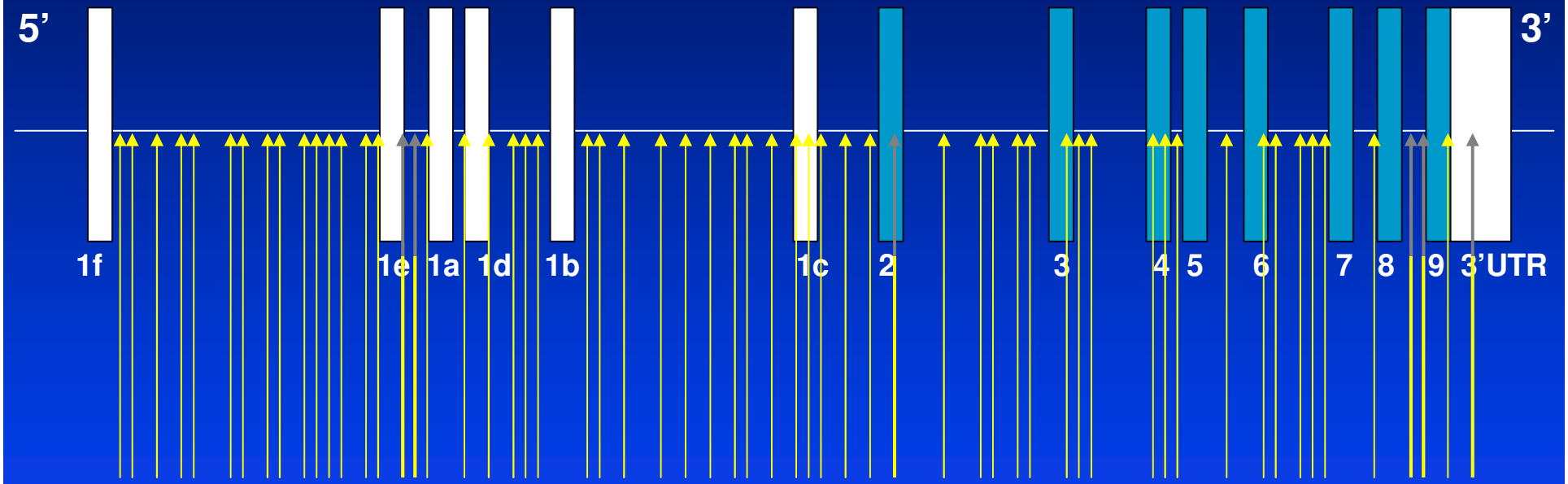


Tumor Development



Zinser & Welsh, personal communication

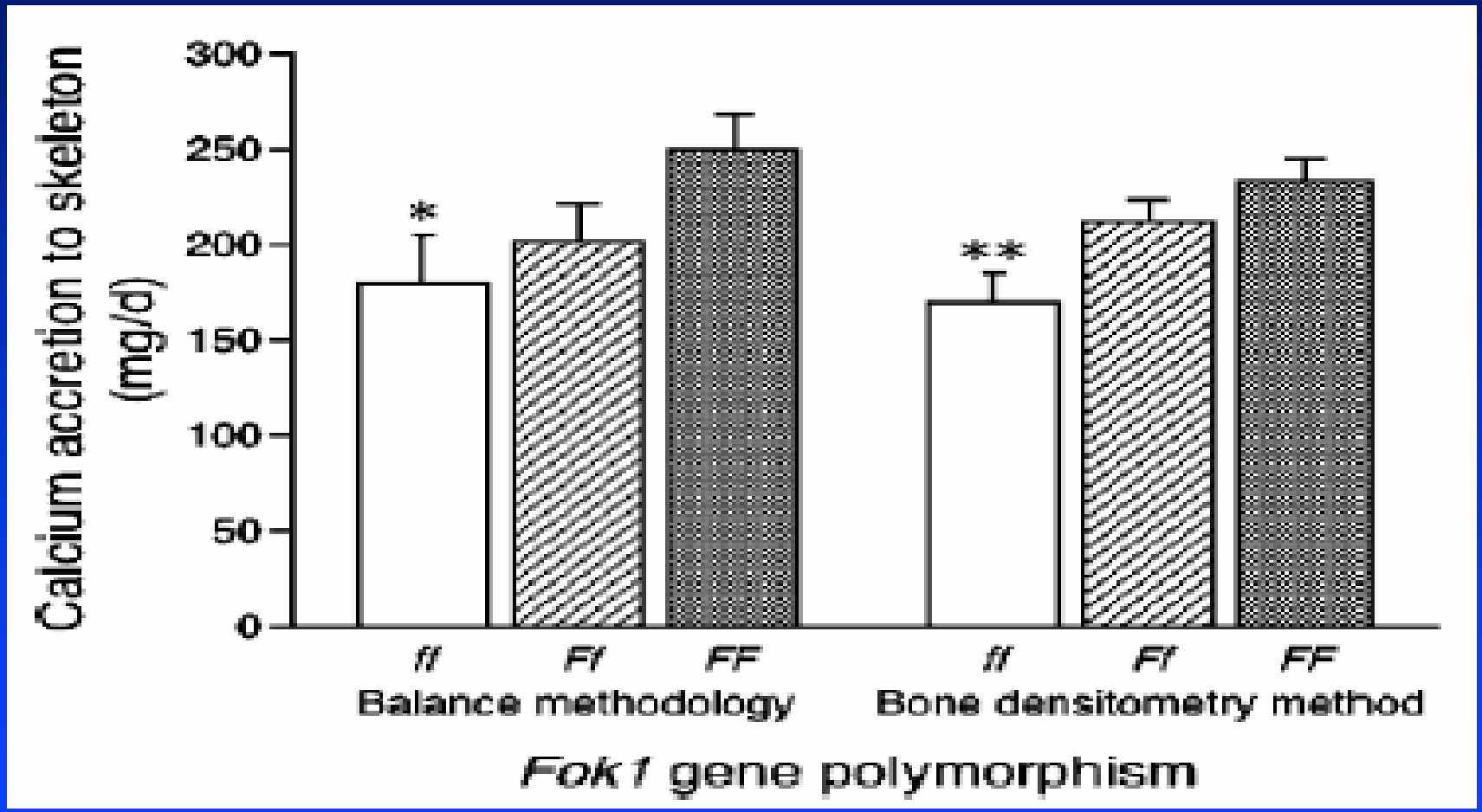
Single Nucleotide Polymorphisms in the VDR gene



Human VDR >470 reported SNPs
Distribution and frequency varies among ethnic groups

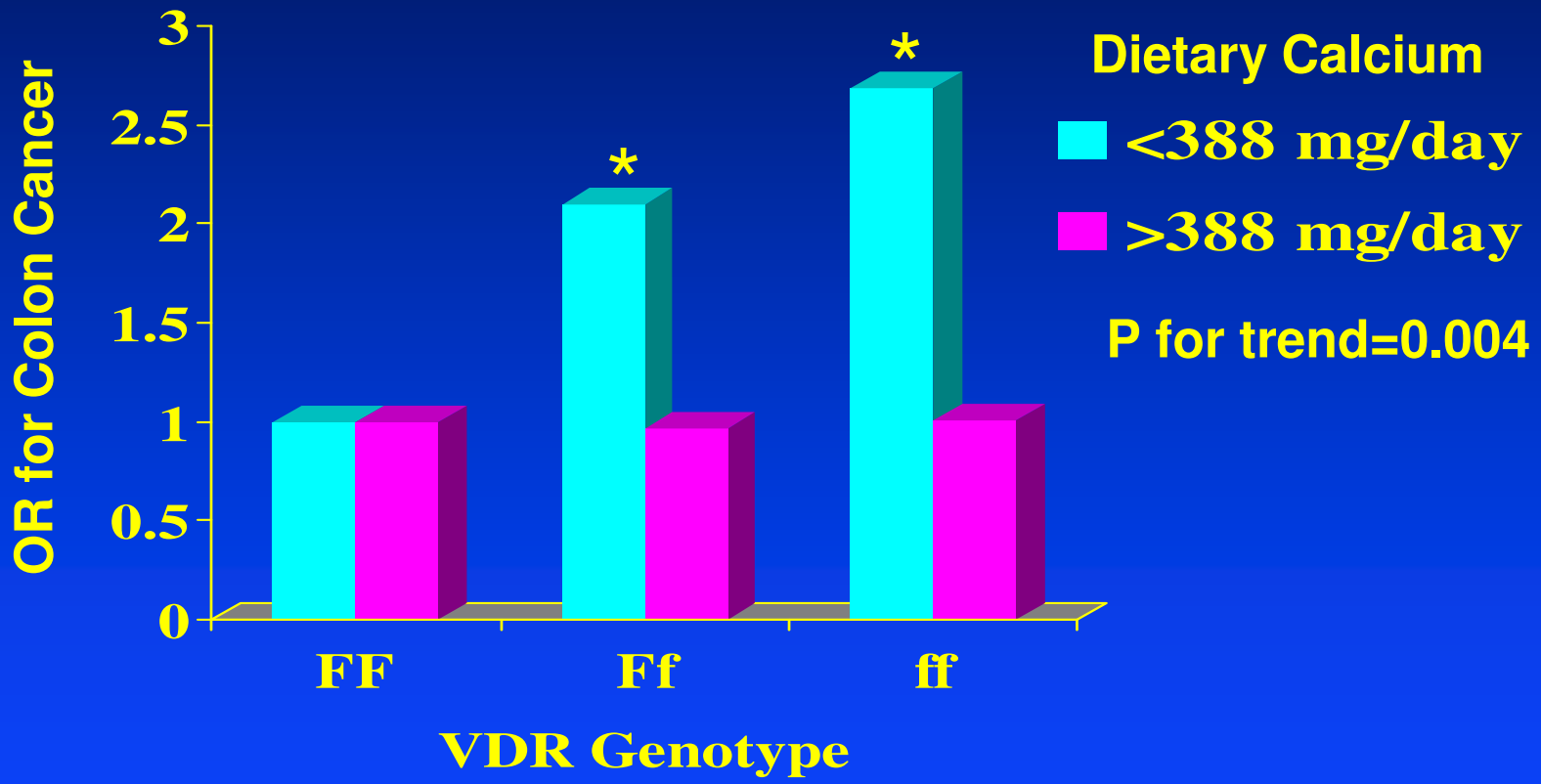
These polymorphisms may alter 1,25 Vitamin D function and thereby affect cancer risk

VDR *FokI* Polymorphism Affects Calcium Metabolism



Abrams et al. J. Bone Mineral Res. 20: 945-953, 2005

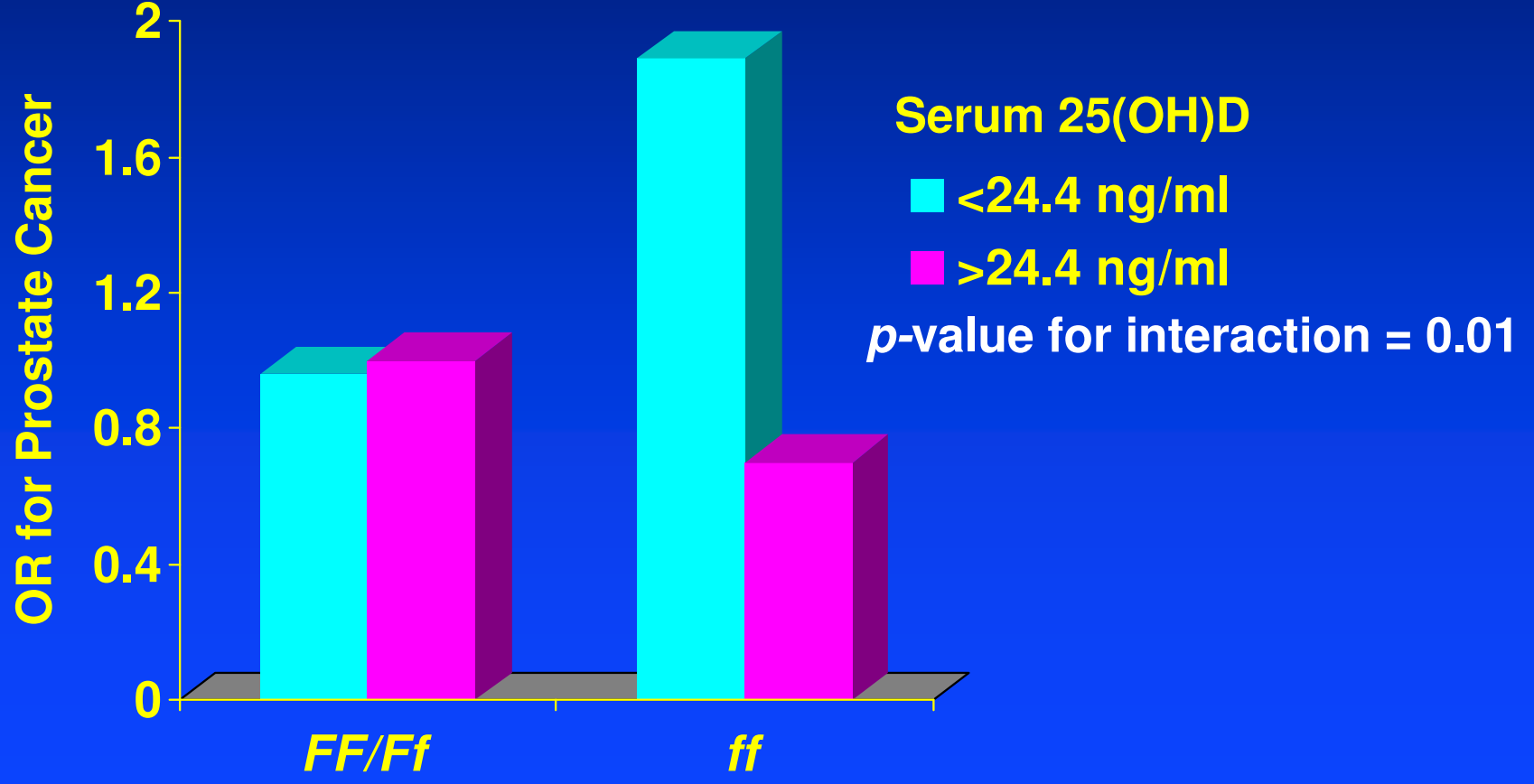
Dietary Calcium, VDR *FokI* Genotype and Colon Cancer Risk



Wong et al. Carcinogenesis, 24: 1091-1095, 2003

Vitamin D Status, VDR *FokI* Genotype and Prostate Cancer Risk

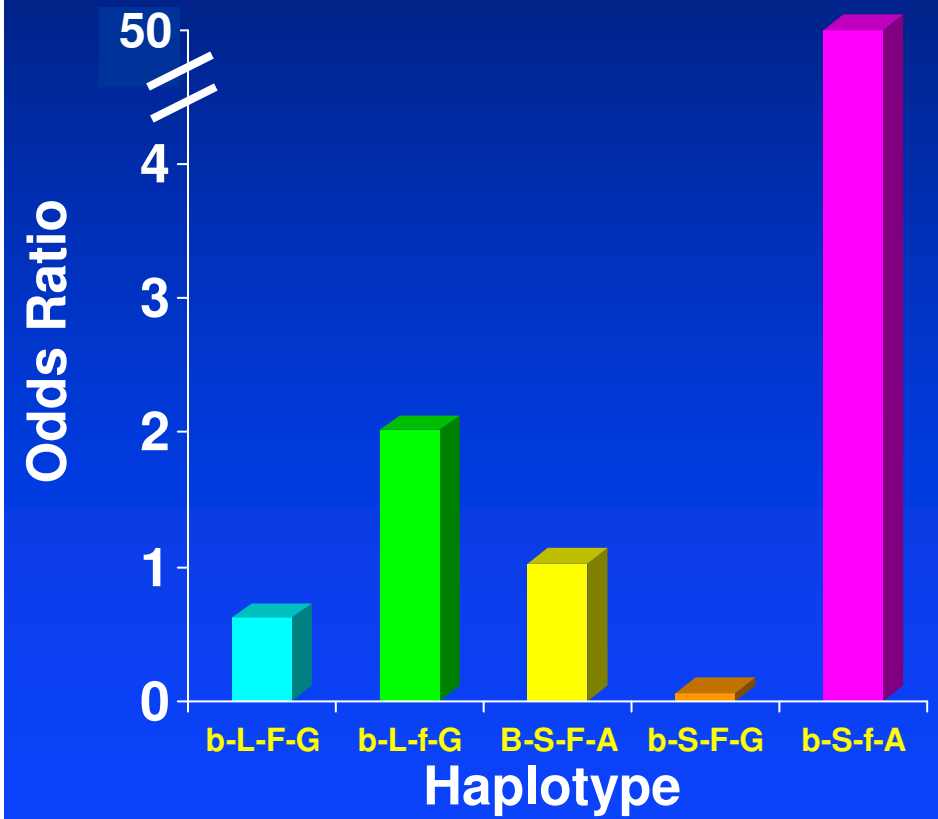
1,066 prostate cancer cases and 1,618 age-matched controls from the Physician's Health Study



Li et al. PLoS Medicine 4:562-571, 2007

Haplotypes in the VDR Gene Influence Colon Cancer Risk

Bsml **(b or B), poly (A) S or L, *Fok I* (f or F) and CDX2 (G or A); 1574 cases and 1970 controls**

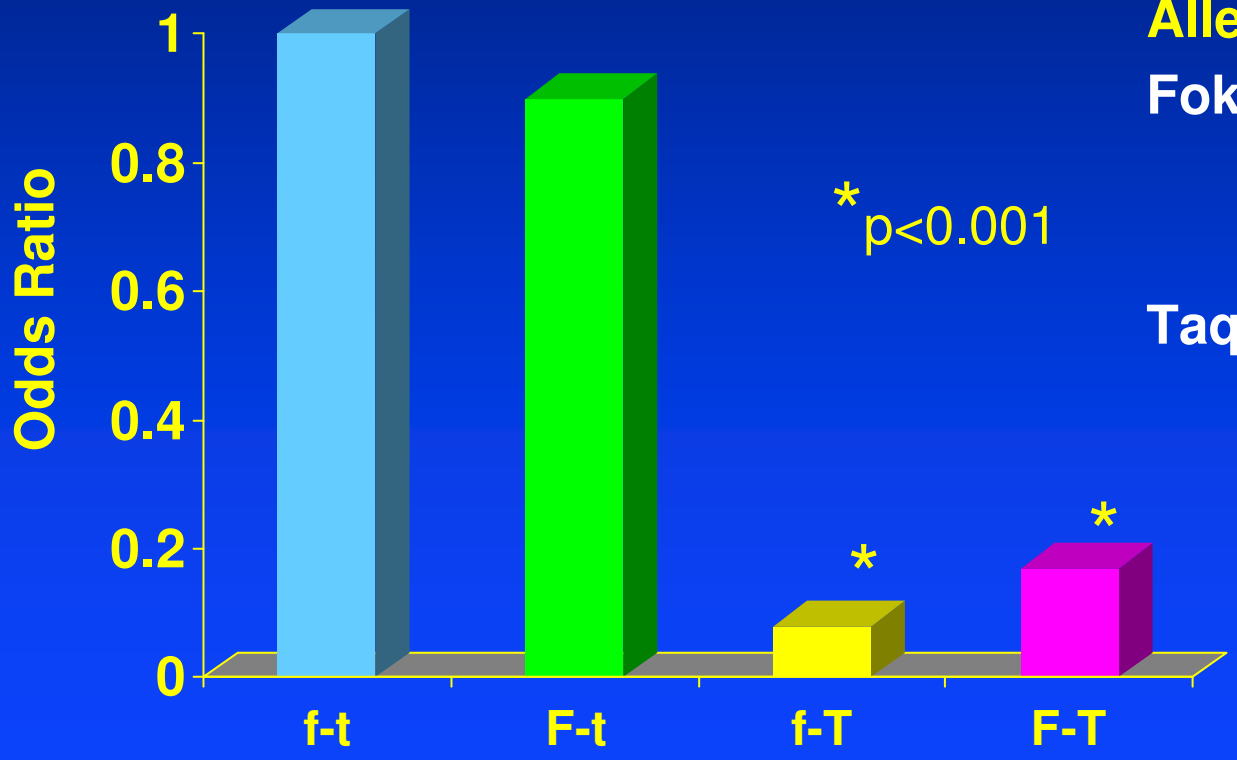


- **Haplotype frequencies varied by ethnic group**
- **OR for colon cancer varied from 0.06 to 51.12 depending on haplotype**

Slattery et al. Cancer Epidemiol Barmark Prev. 16:2752-5, 2007

VDR Haplotypes and Bladder Cancer Risk in India

130 patients with bladder cancer and 346 controls in Northern India analyzed for Taq-1 and Fok-1 polymorphisms

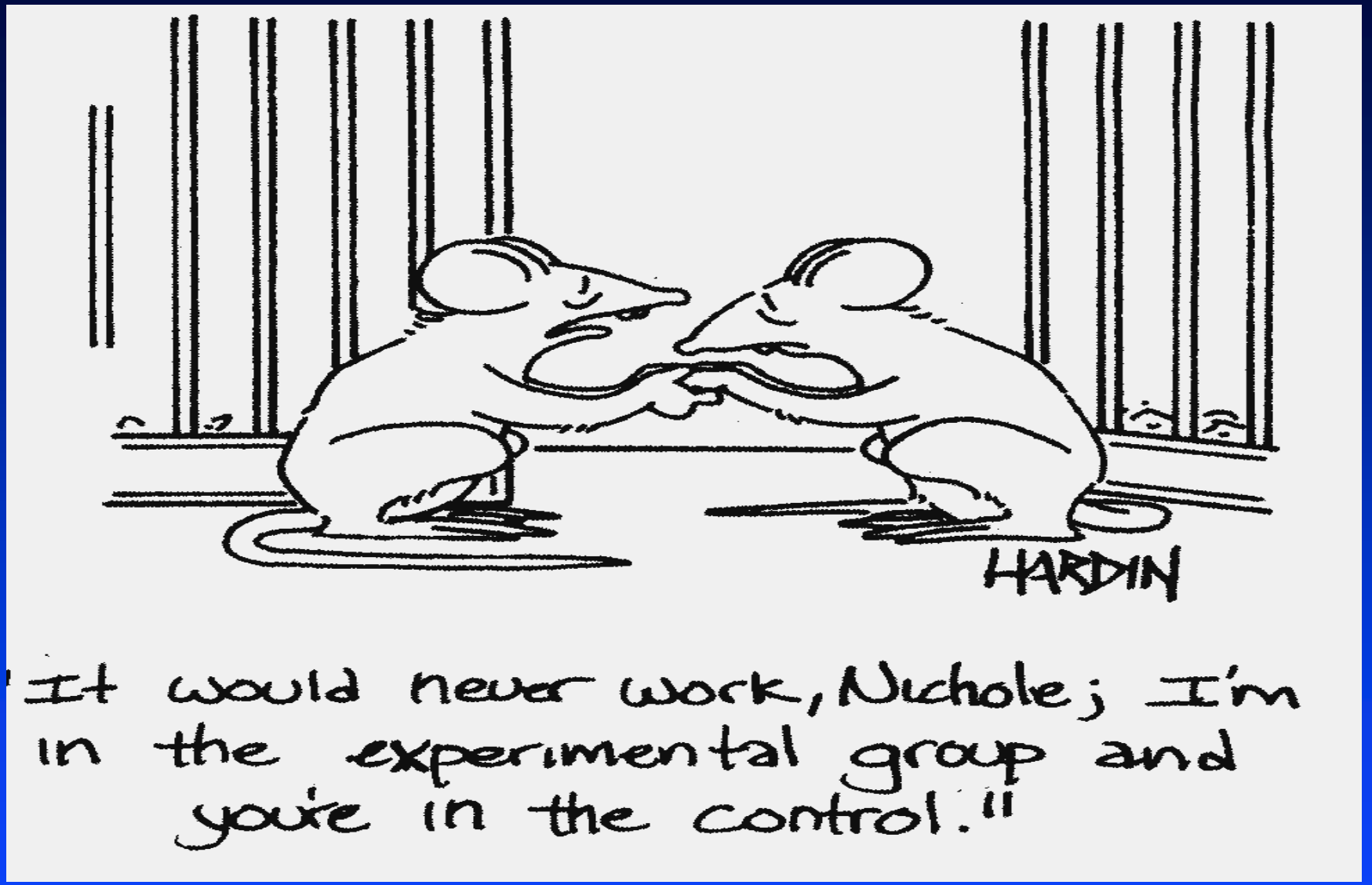


Allele frequencies in India:

Fok-1:	FF 44%
	Ff 49%
	ff 7%
Taq-1	TT 49%
	Tt 40%
	tt 11%

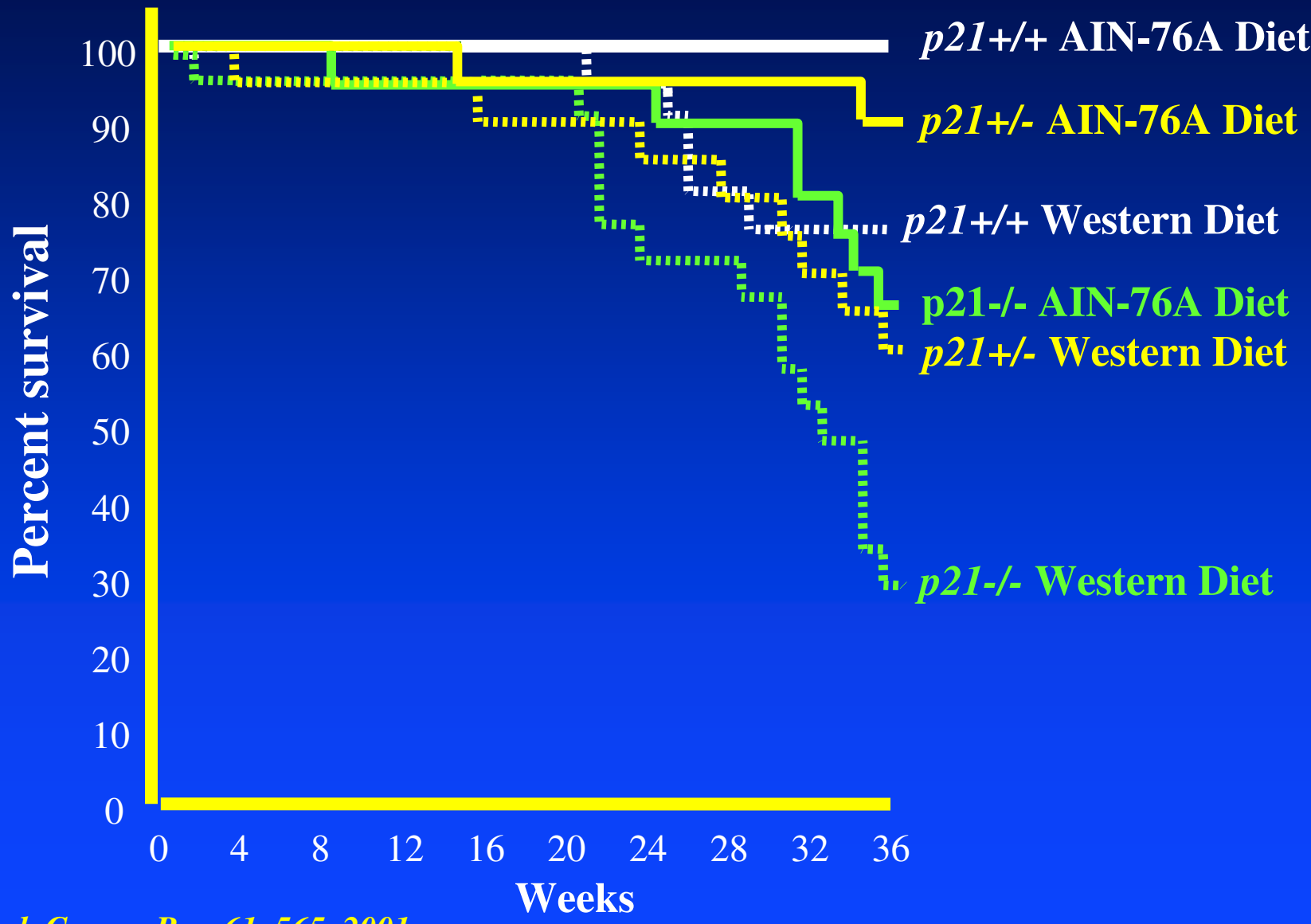
Mittal et al. BJU International 99: 933-937, 2007

One Size Does Not Fit All! Genetic Background May Determine Who Will Respond to Vitamin D for Cancer Prevention



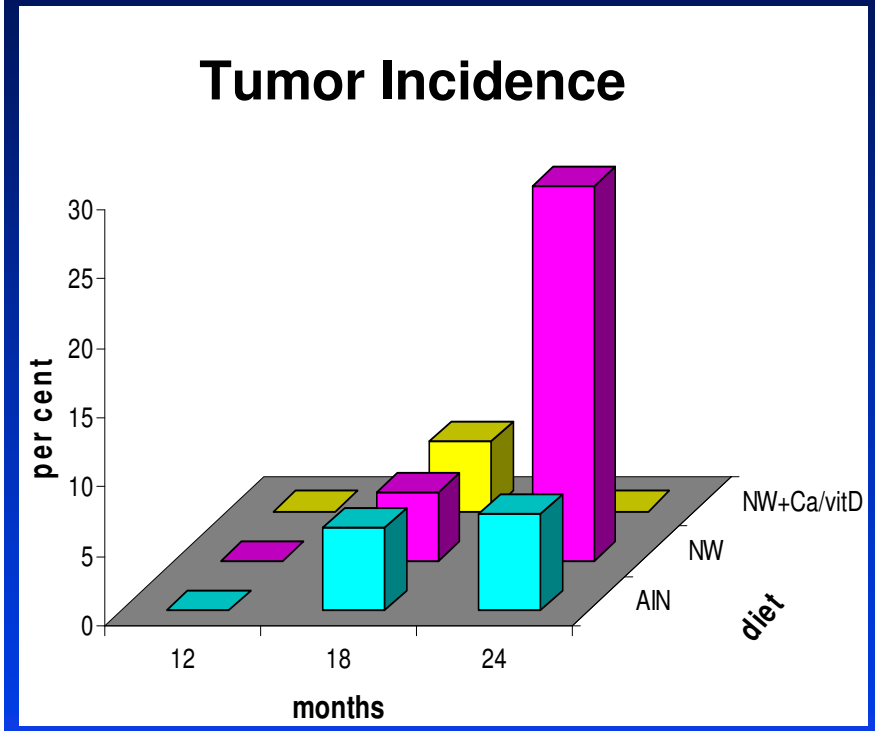
Animal Models Are Providing Fundamental Clues About Vitamin D and Cancer Risk

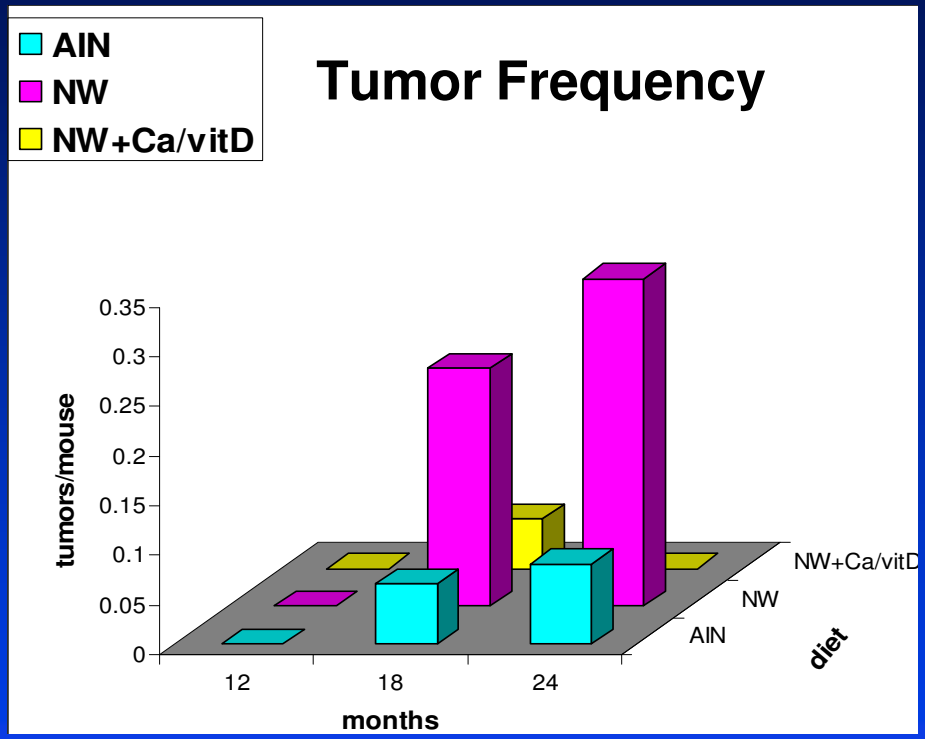
Gene-Nutrient Interactions and Colon Cancer



Yang et al, Cancer Res. 61, 565, 2001

A Western-Style Diet Induces Malignant Neoplasms in the Colon of Normal Mice

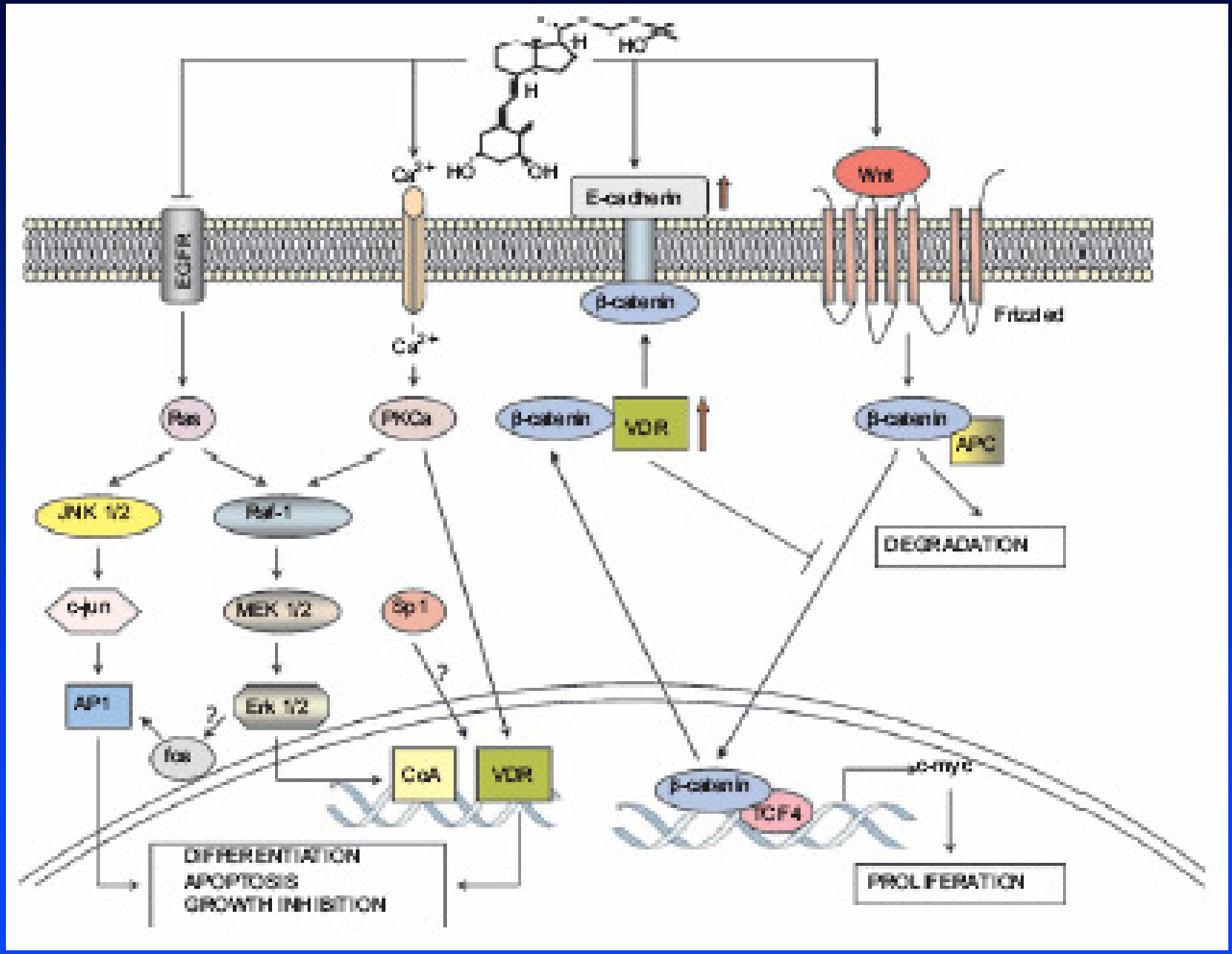




Approximately 25% of the mice develop a single tumor …..this is a new mouse model of sporadic colon cancer, which represents the vast majority of human colon cancer

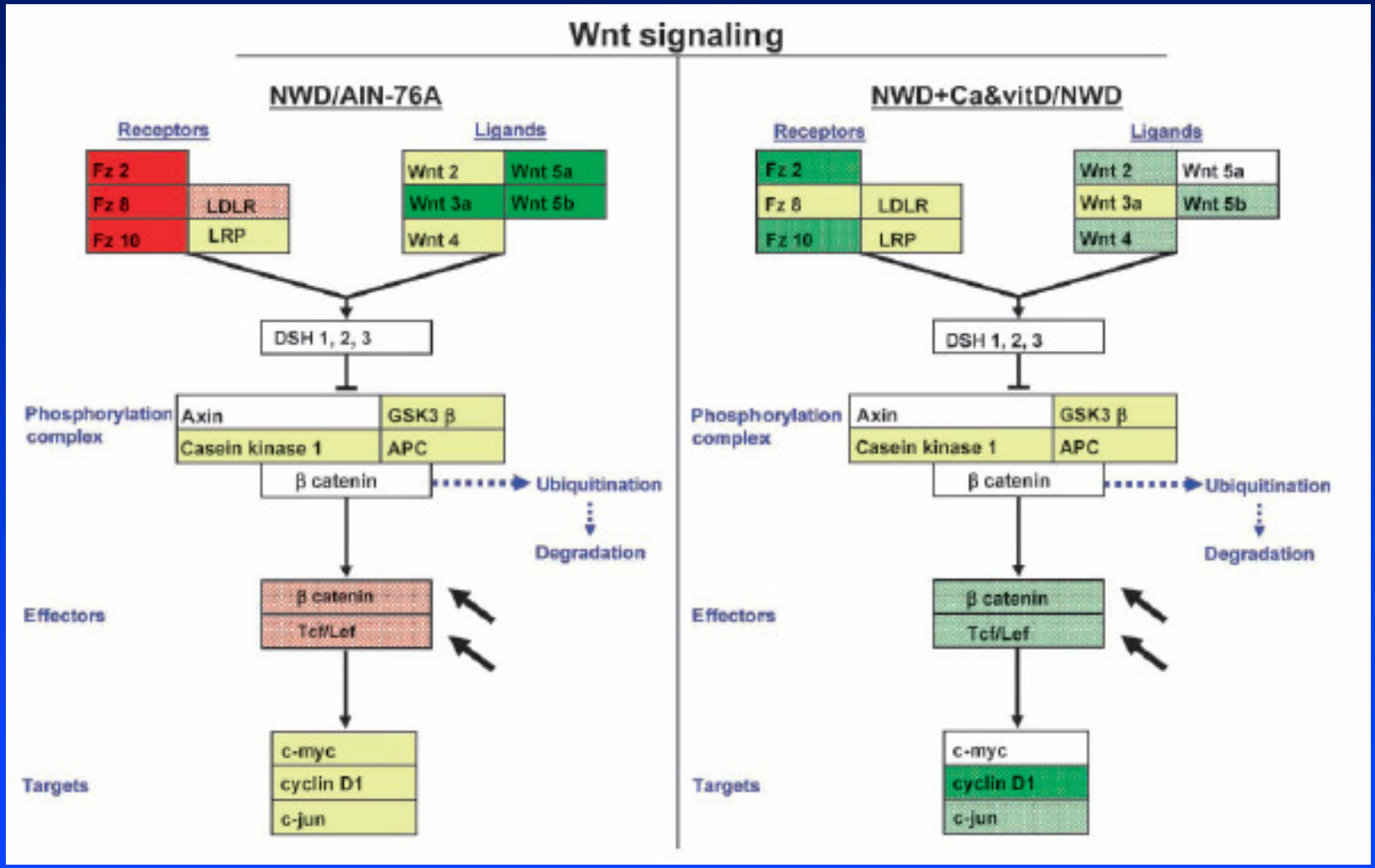
Supplementation with vitamin D and calcium inhibits tumor formation

Yang et al. J Nutr. 2005;135:2710-4.



Gocek E. Critical Reviews Clin. Lab Sci. 46: 190-209, 2009

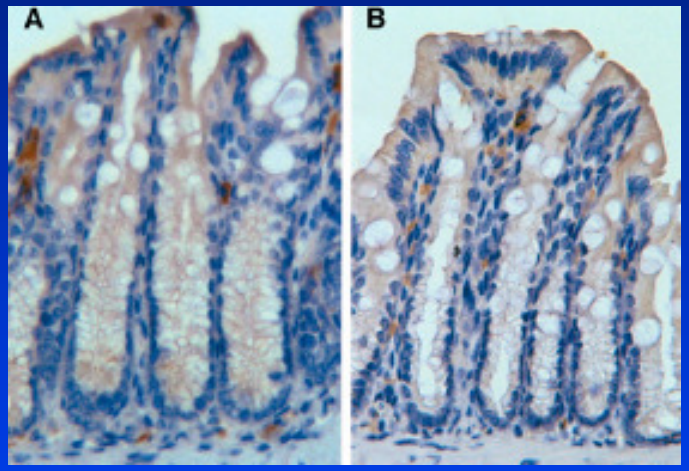
Vitamin D and Calcium Modulate Wnt Signaling



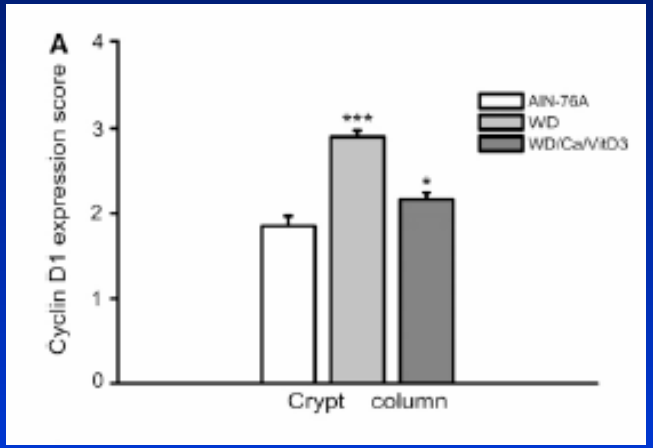
Yang et al. Cancer Research 68: 7803-7810, 2008

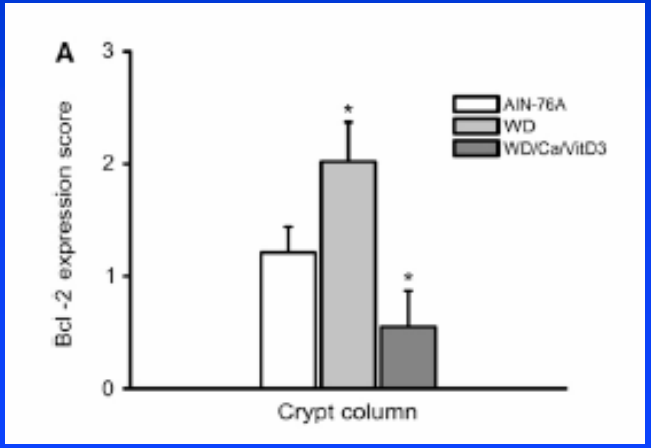
Dietary Vitamin D and Calcium Modulate Cell Proliferation and Apoptosis in the Colon

Cyclin D1 Expression



Western Diet **Western/D/Ca**

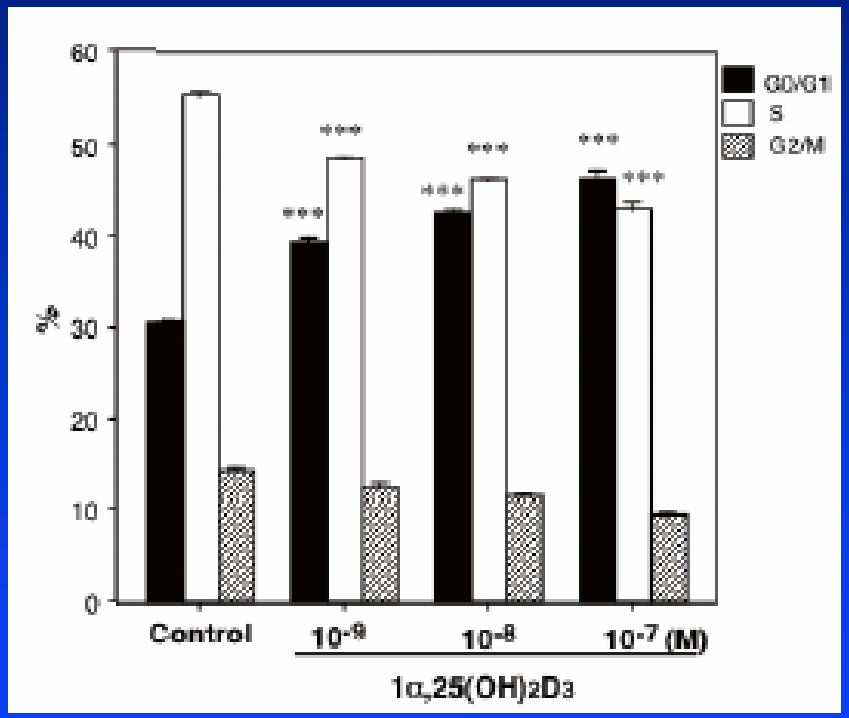


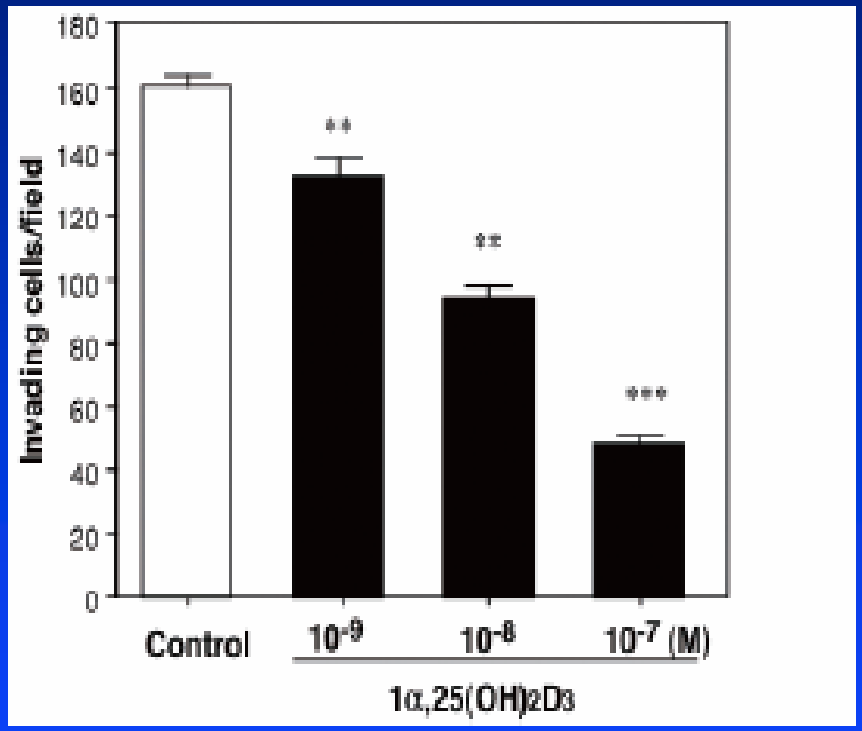


Yang K et al. J. Nutrition 138: 1658-1663, 2008

Vitamin D Inhibits Cancer Cell Proliferation and Metastasis

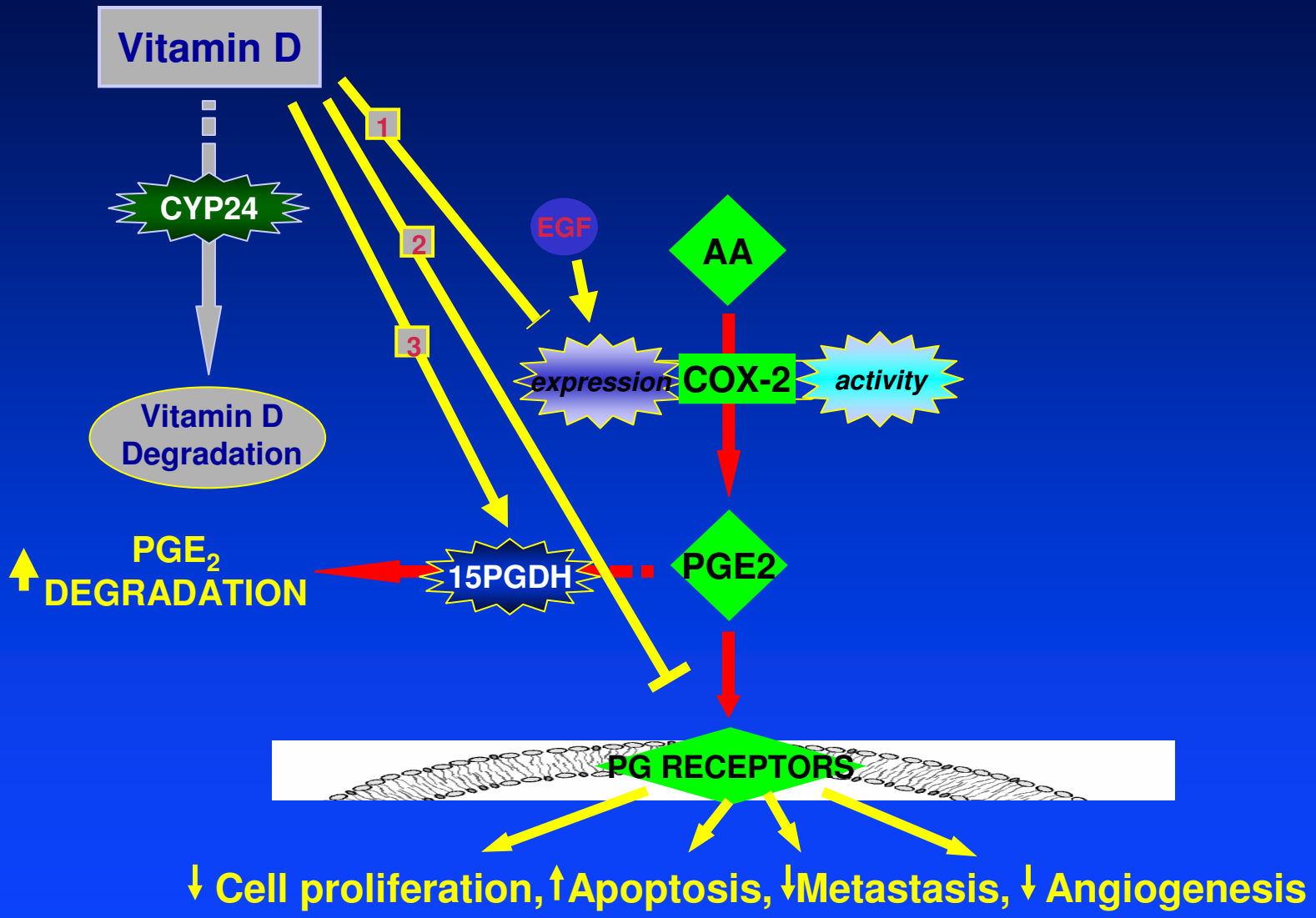
Lewis Lung Carcinoma Cells





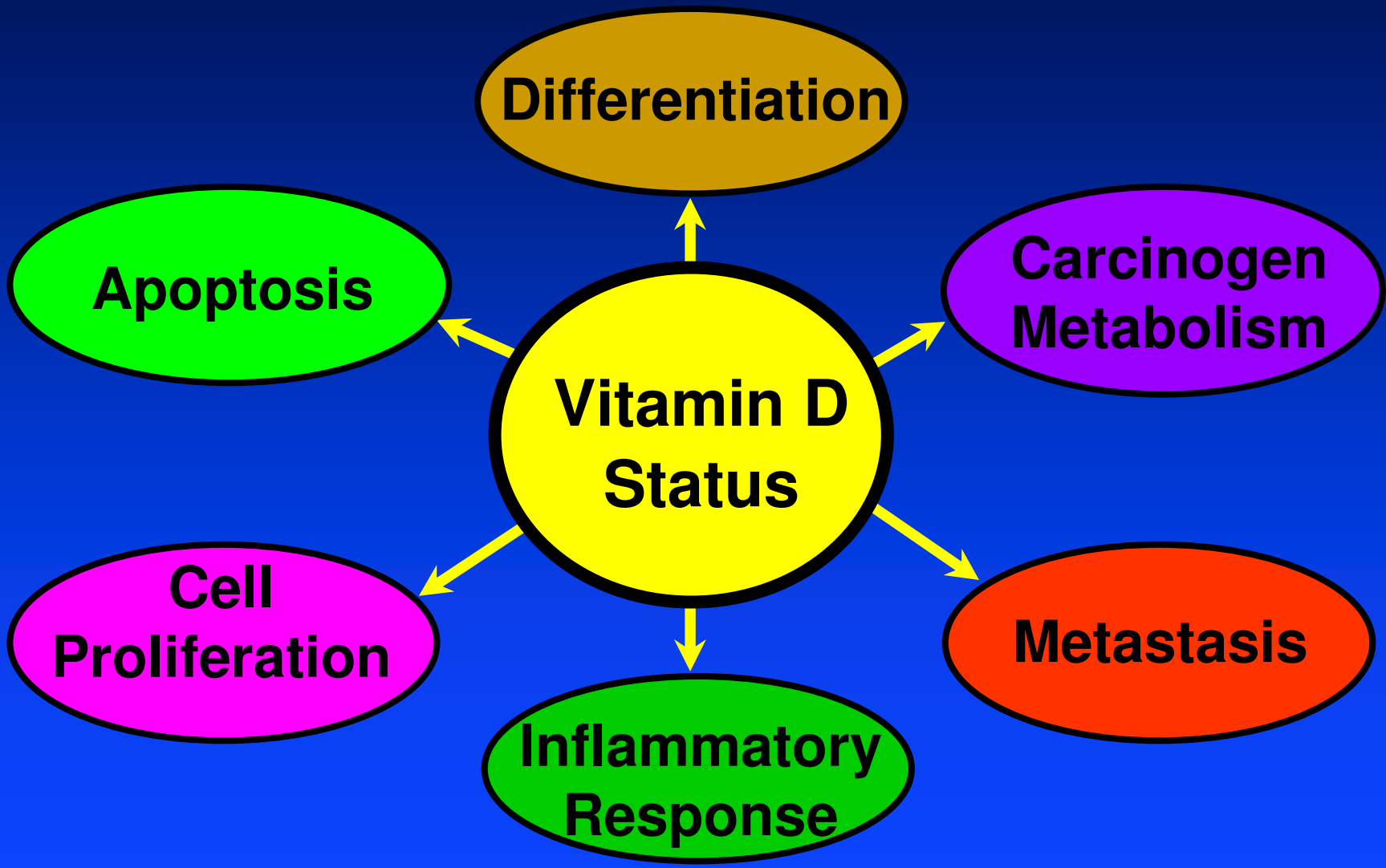
Nakagawa et al. Carcinogenesis, 26:429-440, 2005

Vitamin D Modifies Prostaglandin Metabolism



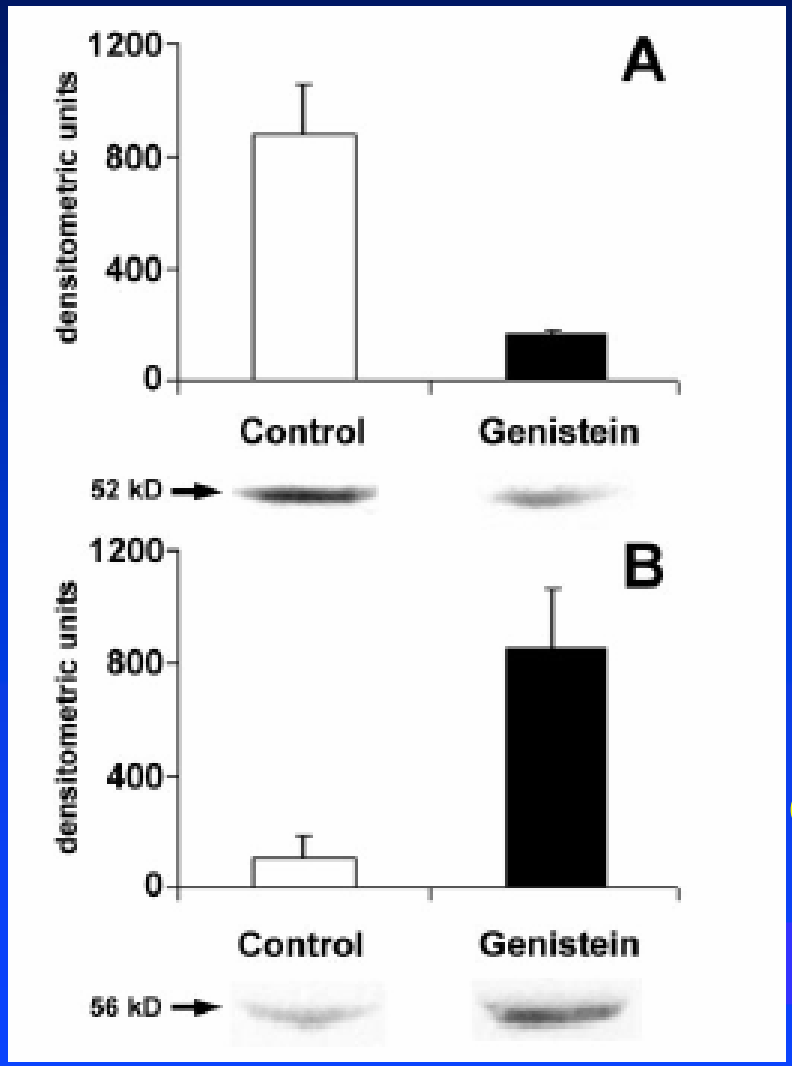
Moreno J et al. Anticancer Res 2006

Vitamin D May Influence Genetic Events Associated with Several Cancer Processes



Other Dietary components and Environmental Factors May Determine the Response to Vitamin D

Dietary Genistein Influences CYP24 and 1✂Hydroxylase Expression in Mouse Colon



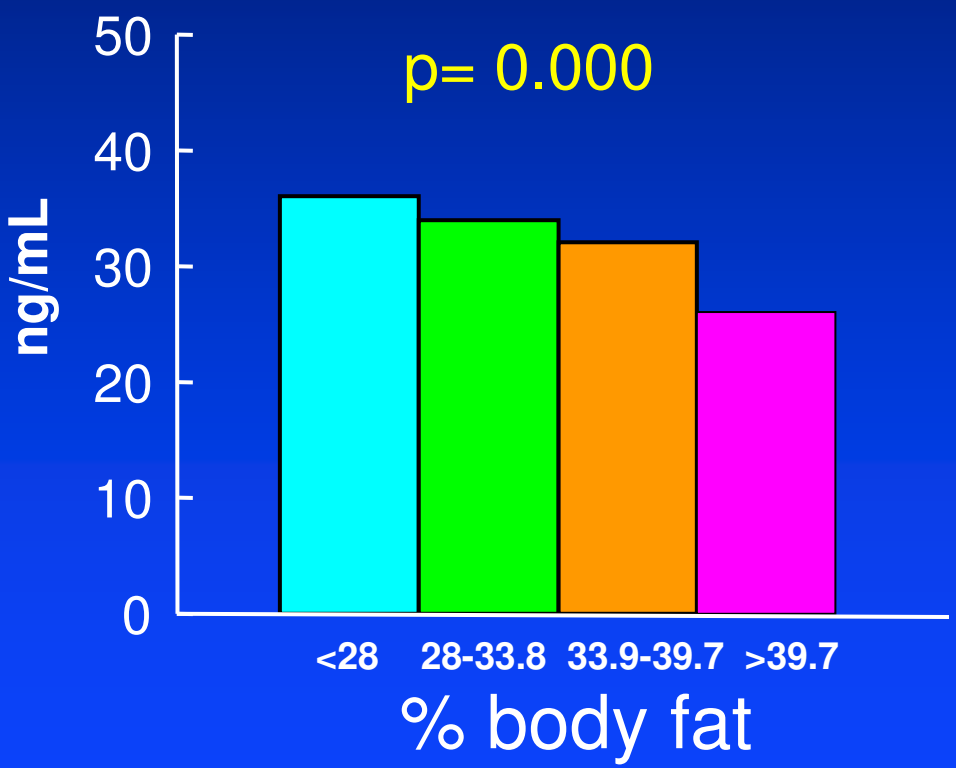
CYP24

1✂Hydroxylase

Cross HS et al. J. Nutrition 134: 1207s-1212s, 2004

Effect of Body Fat on Serum 25(OH)D Concentrations

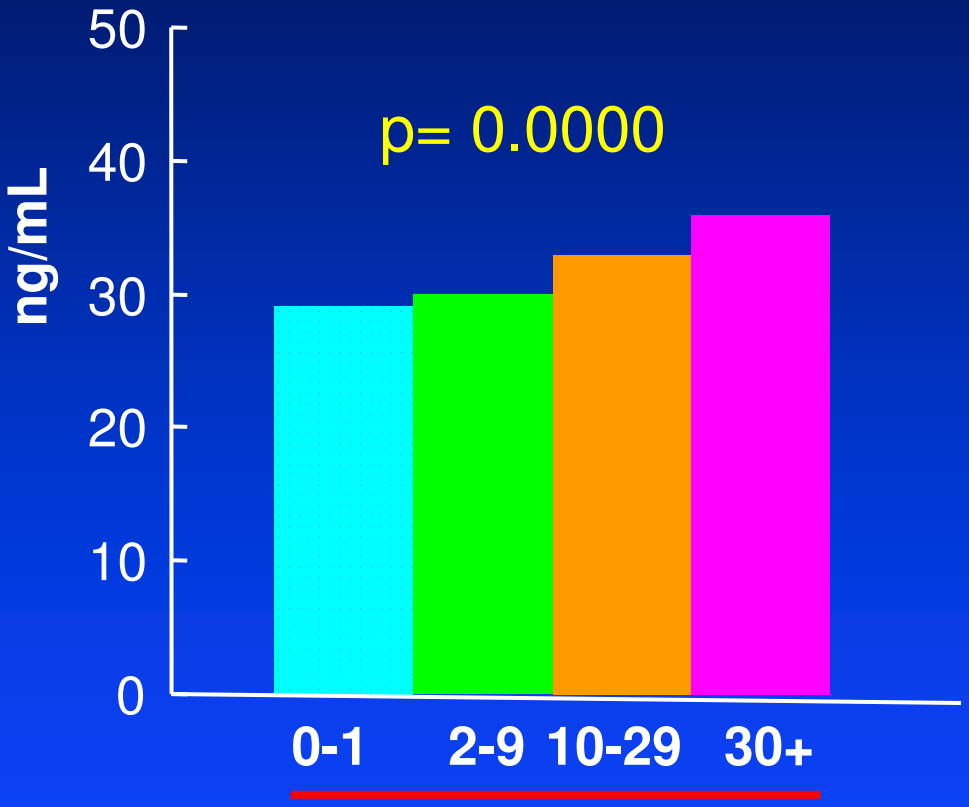
Non-Hispanic White Women, aged 20-49, NHANES III Study



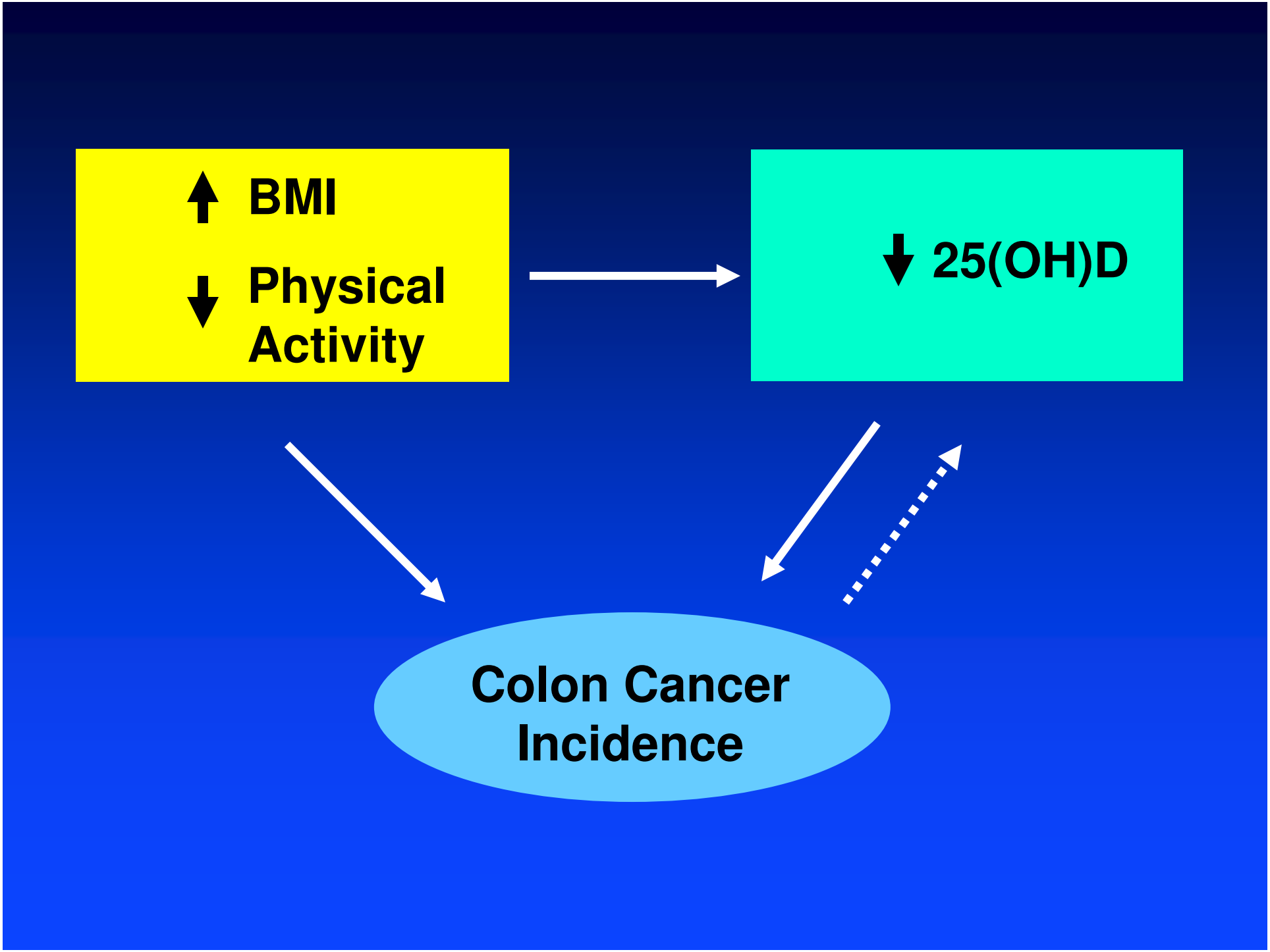
Looker, Nutr. Rev. 65:S124-125, 2007

Effect of Physical Activity on Serum 25(OH)D Concentrations

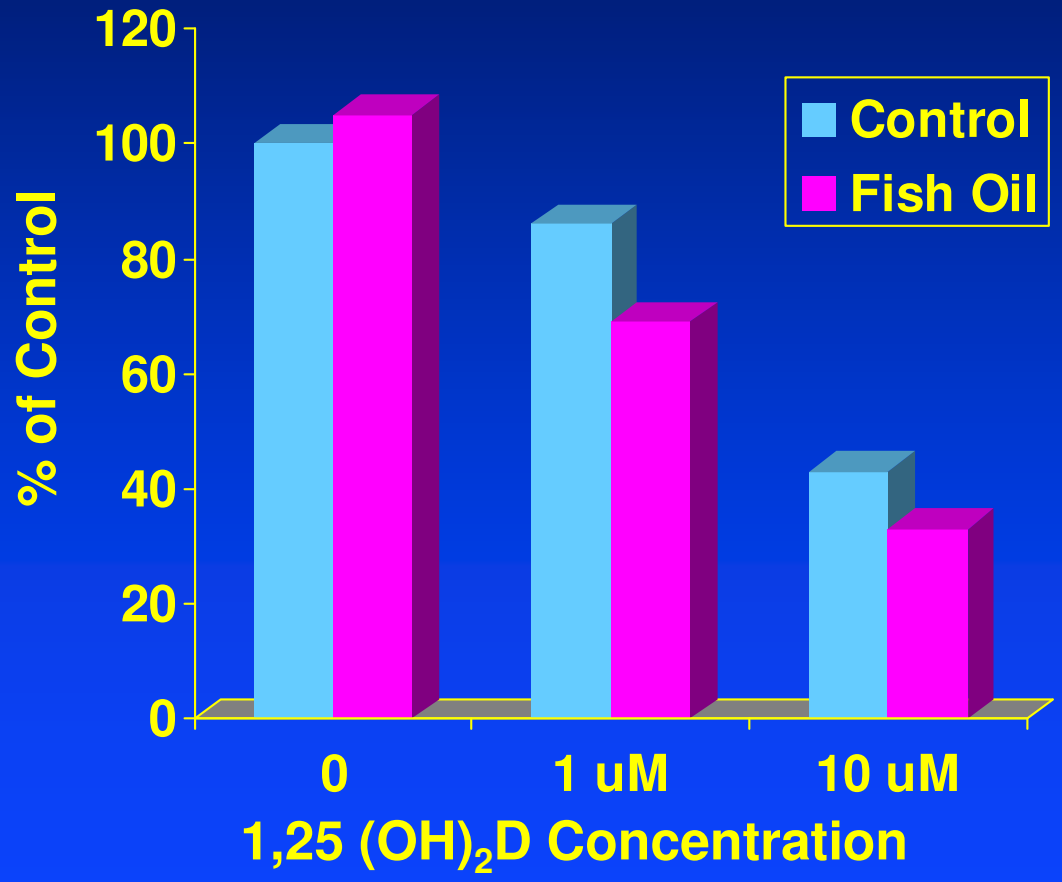
Non-Hispanic White Women, aged 20-49, NHANES III Study



Looker, Nutr. Rev. 65:S124-125, 2007


BMI
Physical Activity
25(OH)D
Colon Cancer Incidence

Fish Oil Enhances the Cell Growth Inhibition of 1,25 $(OH)_2D$ in Liver Cancer Cells



Chiang KC et al. Anticancer Res. 29: 3591-3596, 2009

VITAL (VITamin D and OmegA-3 Trial)

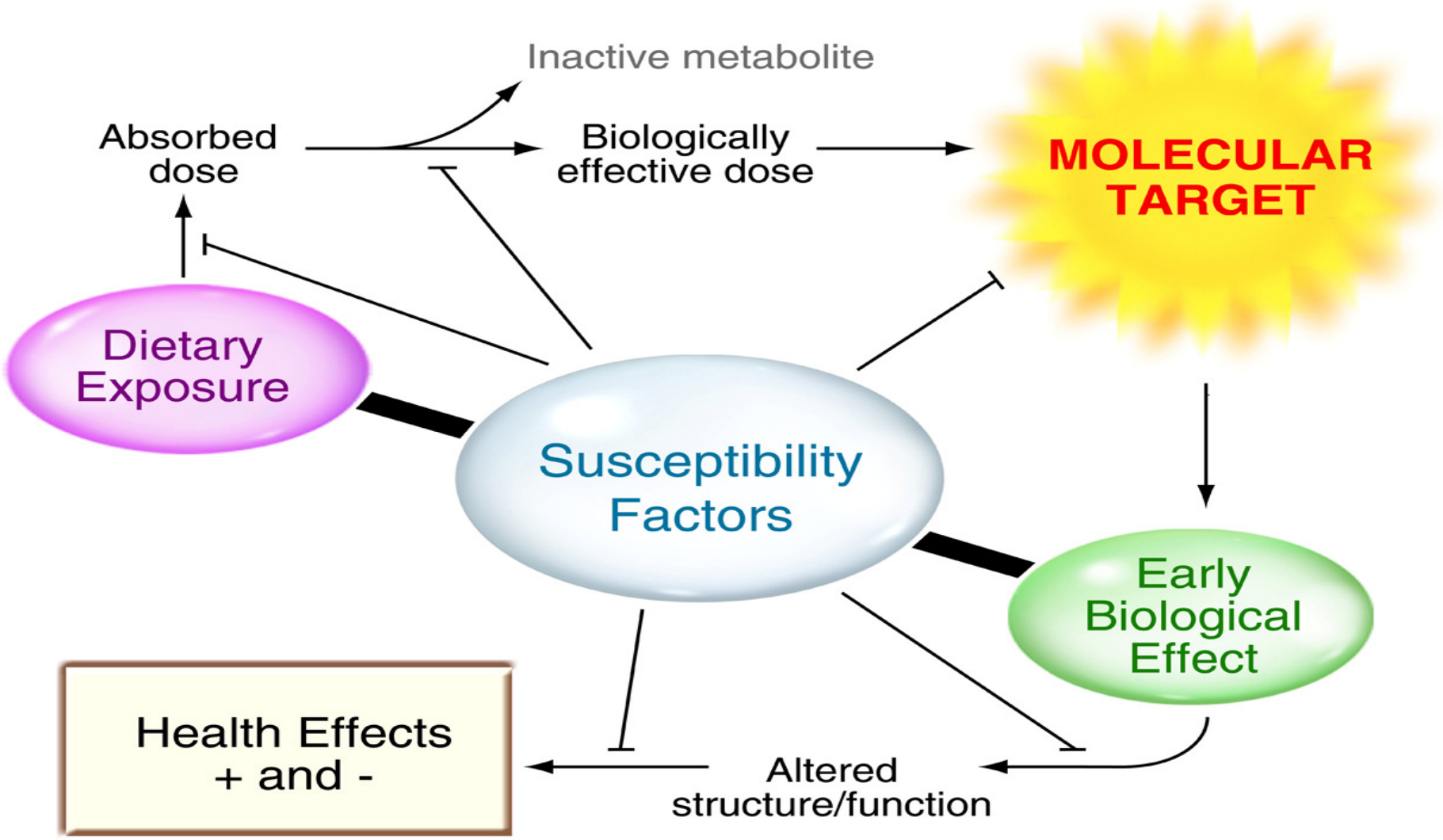
Randomized, Double-Blind, Placebo Controlled Study

20,000 men, age ≥ 60 and women ≥65 years

Placebo	**Vitamin D (2000 IU)**
Fish Oil (1000 mg)	**Vitamin D and Fish Oil**

Principal Investigators: **Drs. JoAnn Manson and Julie Buring**

Research Needs: Better Biomarkers



Just when I knew all of life's answers, They changed all the questions!!