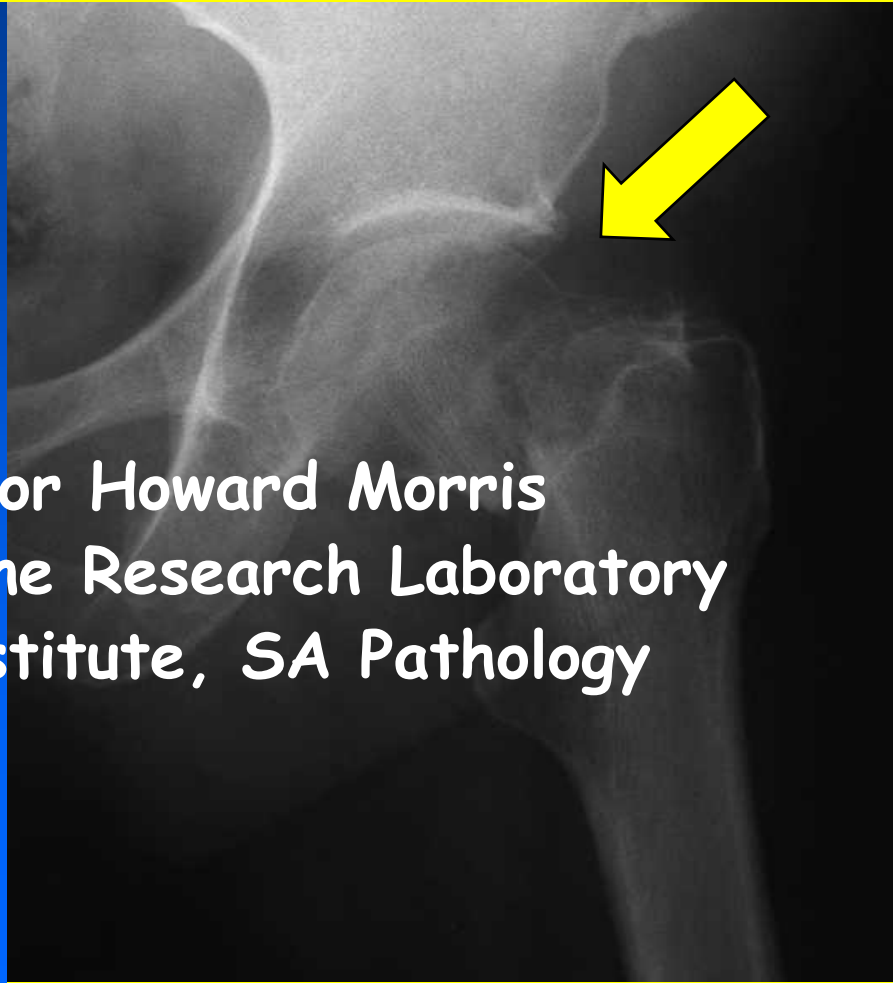


Vitamin D in Bone Development, Bone Health and Cancer Prevention

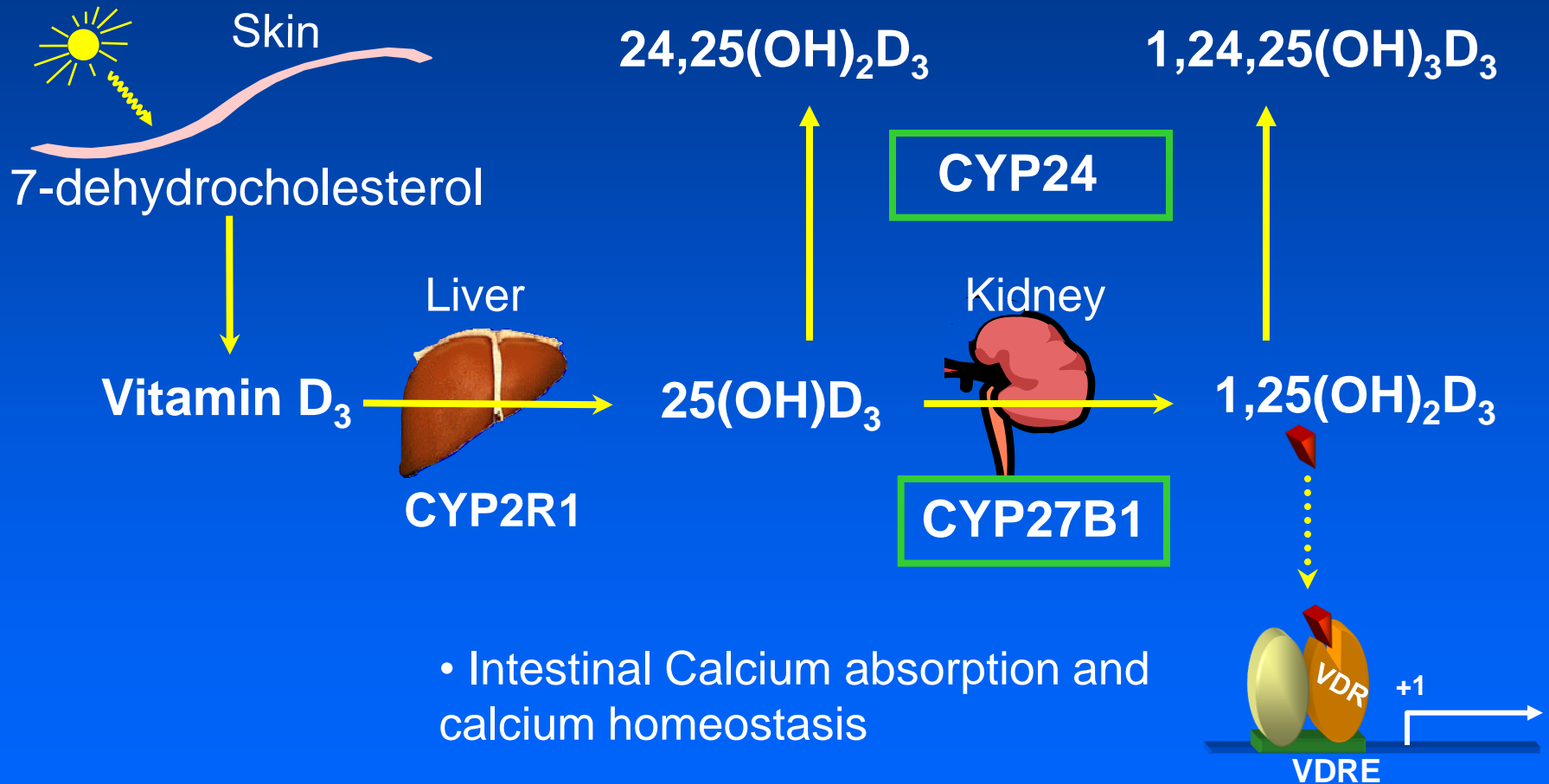


Professor Howard Morris
Endocrine Bone Research Laboratory
Hanson Institute, SA Pathology

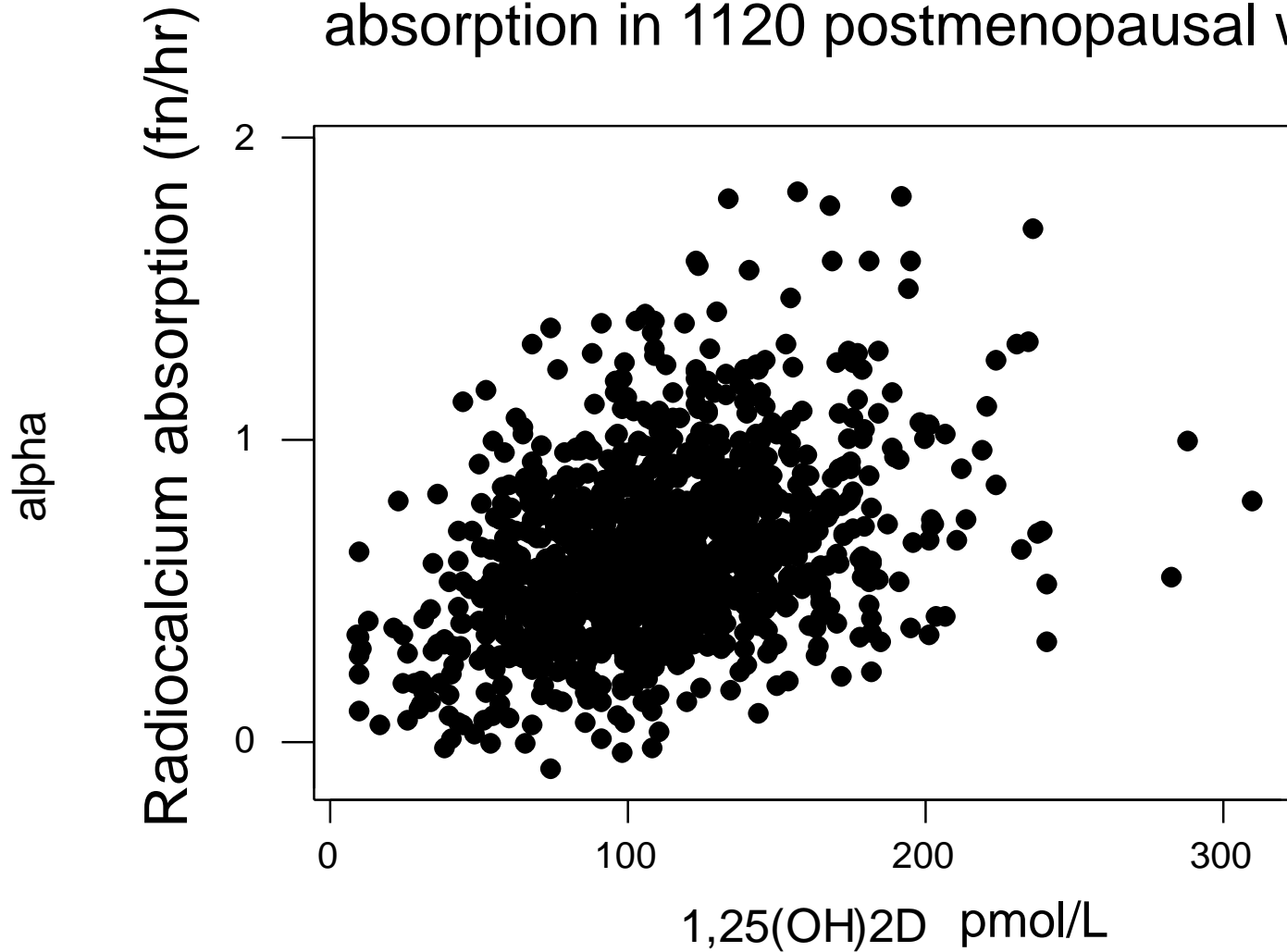
Vitamin D Responsive Genes: 913 unique genes expressed by Squamous Carcinoma Cell line

- Microarray analyses of SCC25 +/- 10 nM 1,25D (Affymetrix Hu133A chip) identified regulation of expression of 913 genes (734 stimulated and 179 repressed expression)
- Genome-wide *in silico* screen of DR3 and ER6 VDRE's conserved between human & mouse genomes indicated 3062 vitamin D responsive genes (sub-set of 156; 126 induced and 31 repressed ie ~80% of genes are up-regulated)

Vitamin D metabolism: The endocrine system



Relationship between serum 1,25D and calcium absorption in 1120 postmenopausal women

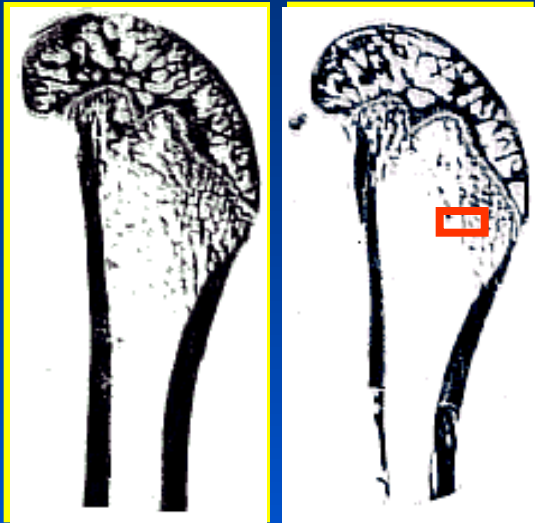


Need et al unpublished data

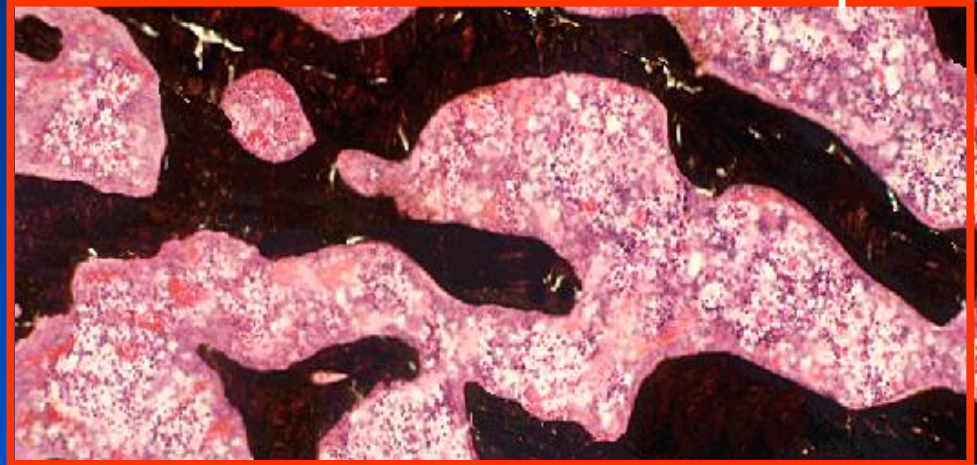
Effects of Vitamin D & Calcium on Bone

Vit D (+) Vit D (-)

1% Ca

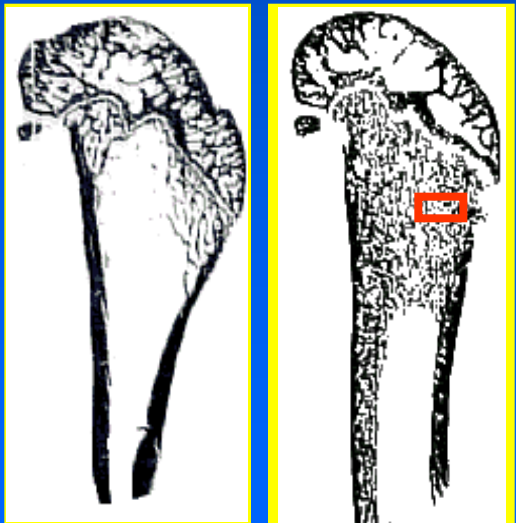


10 x
→

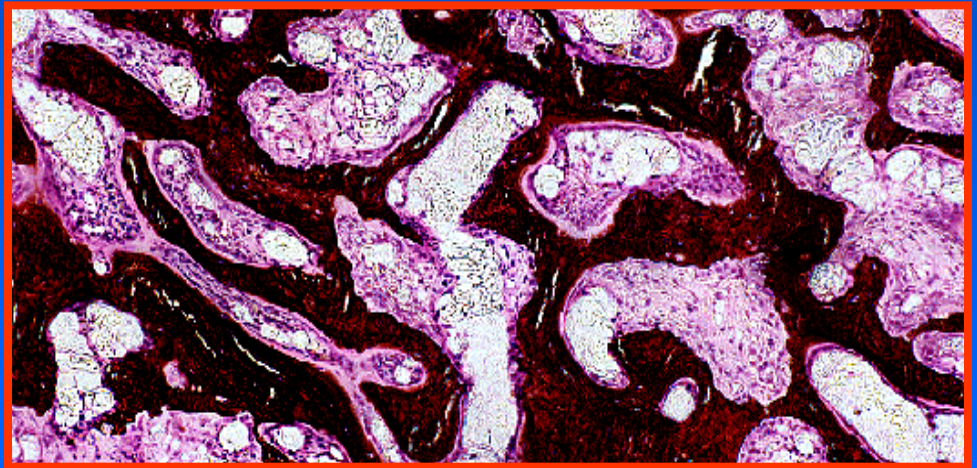


Osteopenia

0.1% Ca



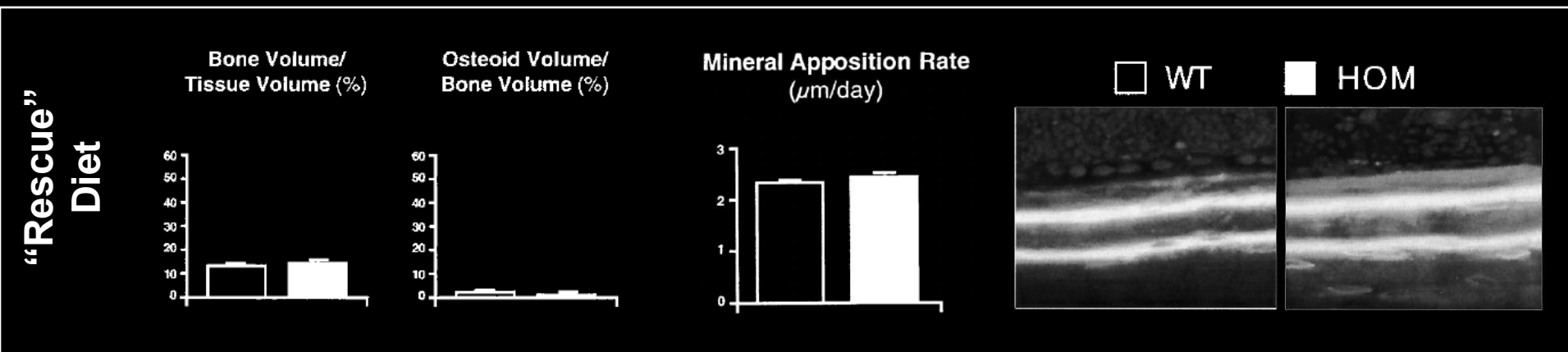
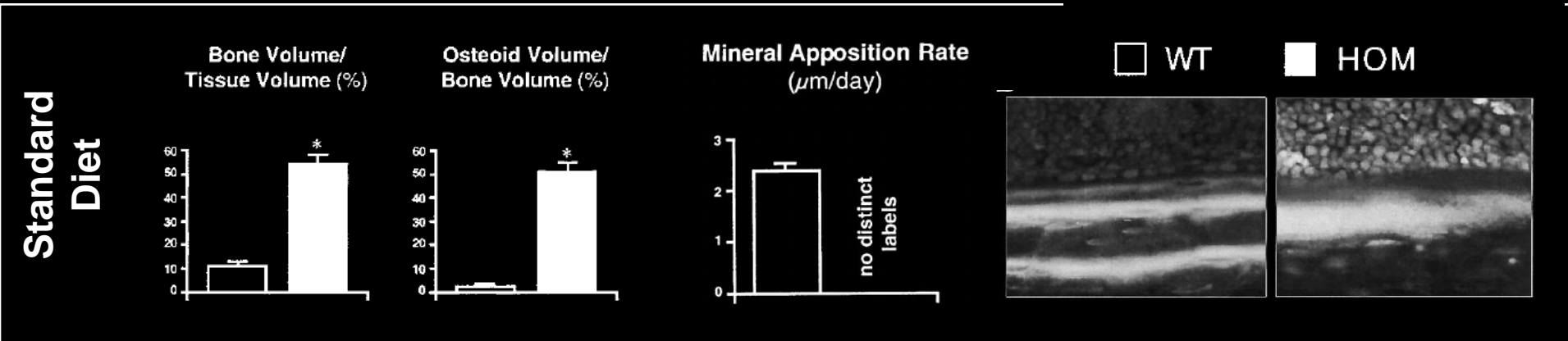
10 x
→



Osteomalacia

Iida et al 2004

VDR-KO MOUSE - EFFECTS OF A Hi Calcium "RESCUE" DIET



WT HOM

- fed 3w mice until 10w of age

Standard Diet - 1% Ca, 0.6% Phosphorus

Amling et al 1999

"Rescue Diet" - 2% Ca, 1.25% Ph, 20% Lactose, 2200IU/kg D3

Vitamin D Deficiency in Rats

Severe vitamin D deficiency leads to osteomalacia
Less severe vitamin D depletion leads to osteopenia



Serum 25D

10 nmol/L

20 nmol/L

115 nmol/L

Ca

hypo

norm

norm

PTH

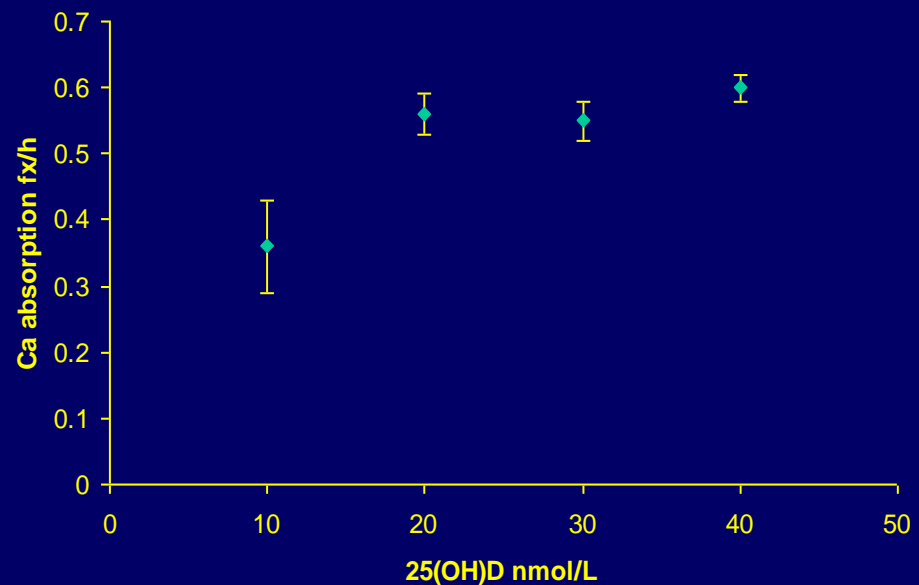
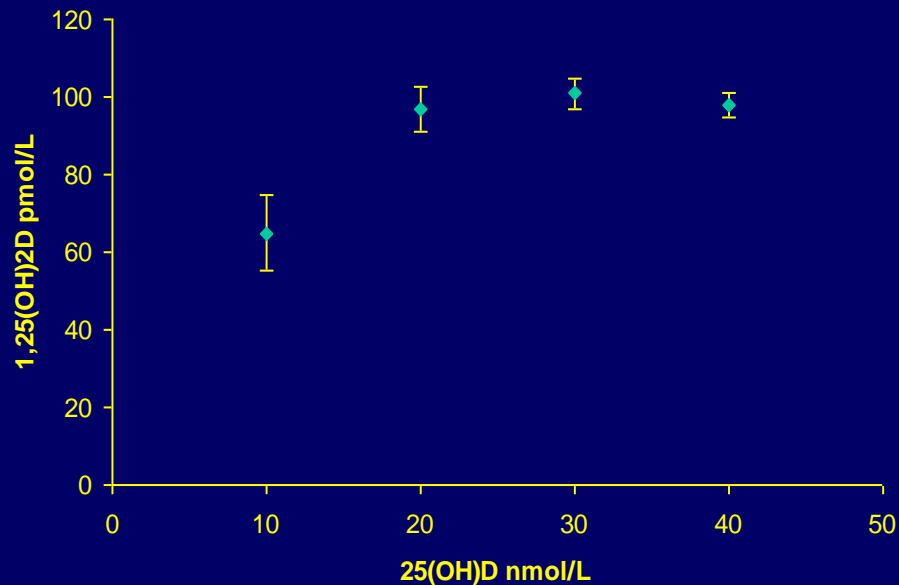
hyper

norm

norm

Anderson et al J Bone Miner Res 2008

Serum 1,25D levels and intestinal calcium absorption in 319 patients with low vitamin D status - levels below 20 nmol/L reduce 1,25D and calcium absorption



Hip fracture patients provide new insights into requirements for vitamin D

Fractures cost the Australian healthcare system some \$8 billion annually from direct and indirect costs of which most are associated with hip fractures.

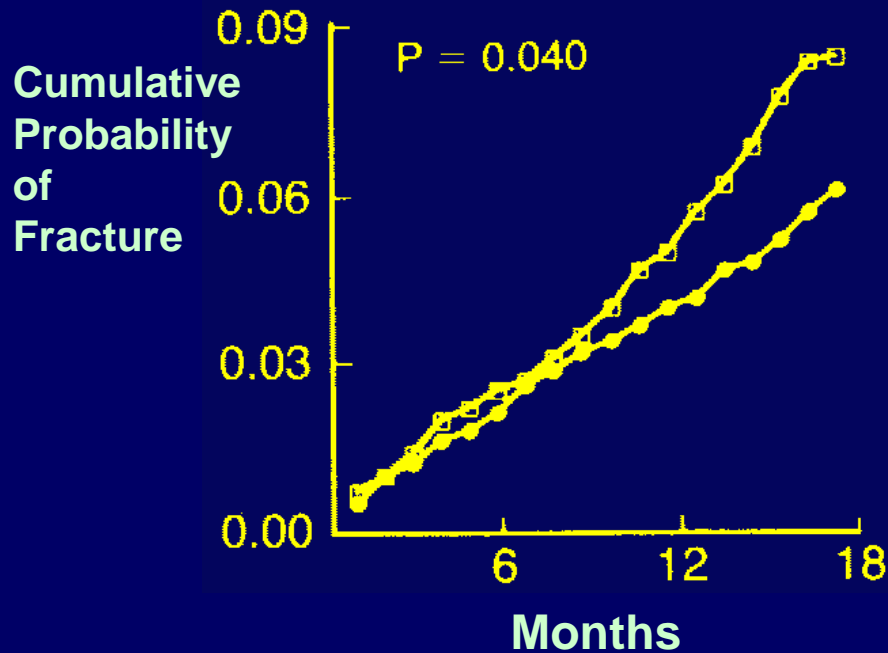
A reduction of hip fractures by 20% would save the healthcare system about \$1 billion annually.

Vitamin D and calcium supplementation for the elderly can reduce the risk of hip fracture by 30%

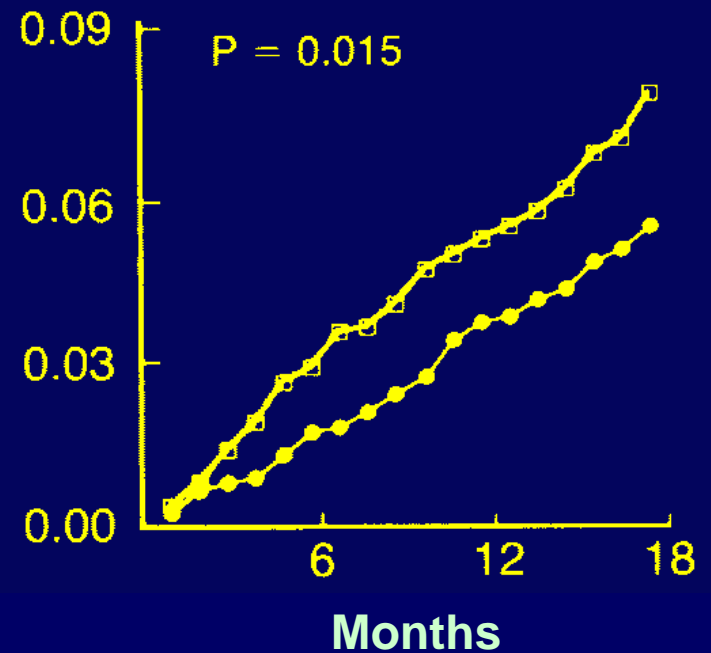


Vitamin D and Calcium Prevent Hip Fractures in Elderly Women

Hip Fractures

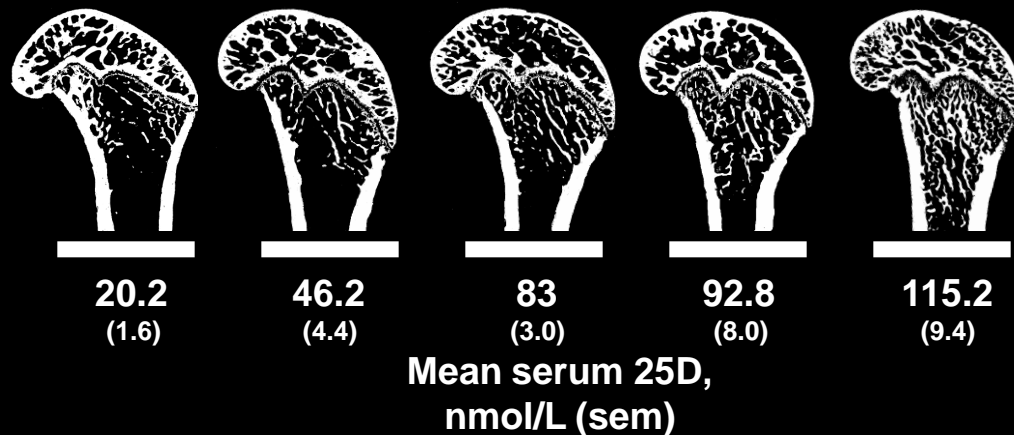
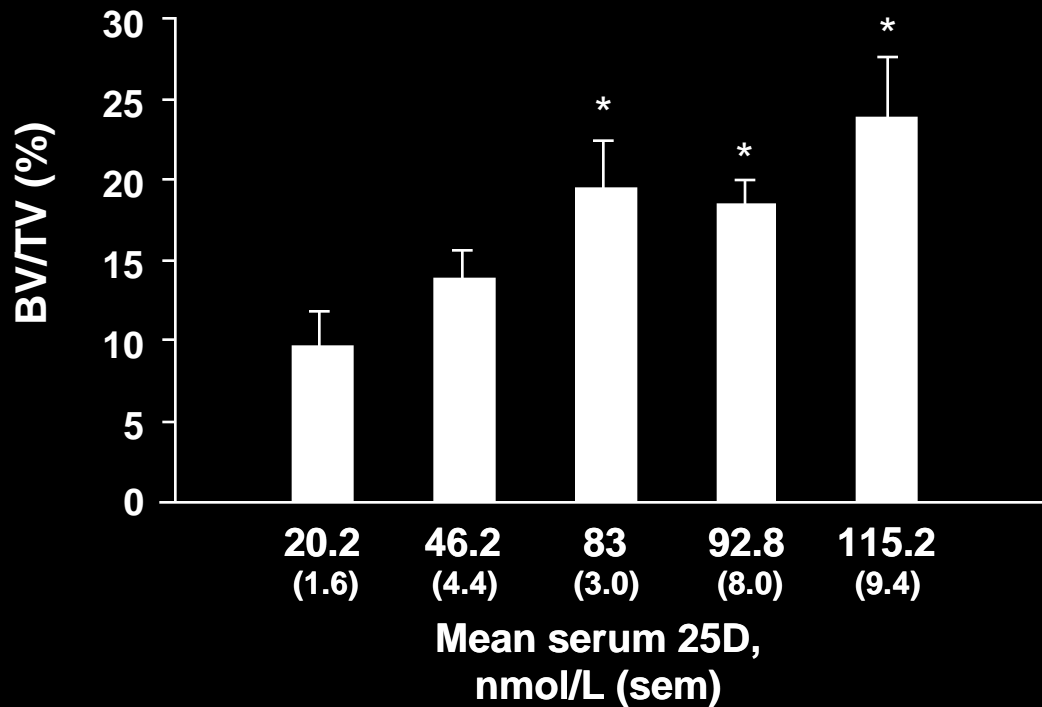
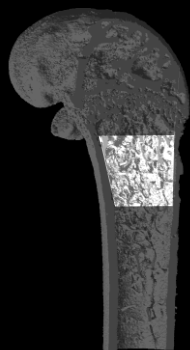


Other Non-vertebral Fractures

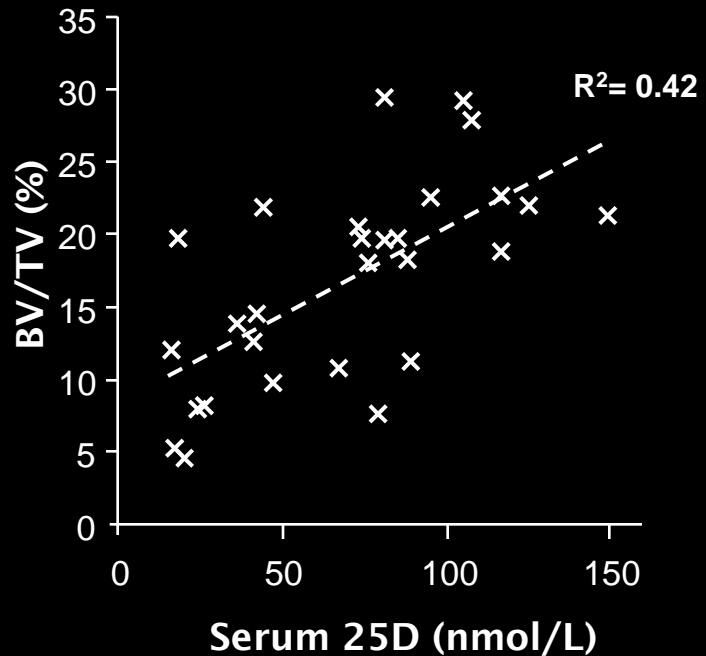


Bone loss occurs with 25D's below 80nmol/L

Trabecular mineral volume in distal femoral metaphysis



BV/TV is positively associated with serum 25D (not associated with 1,25D or PTH levels)

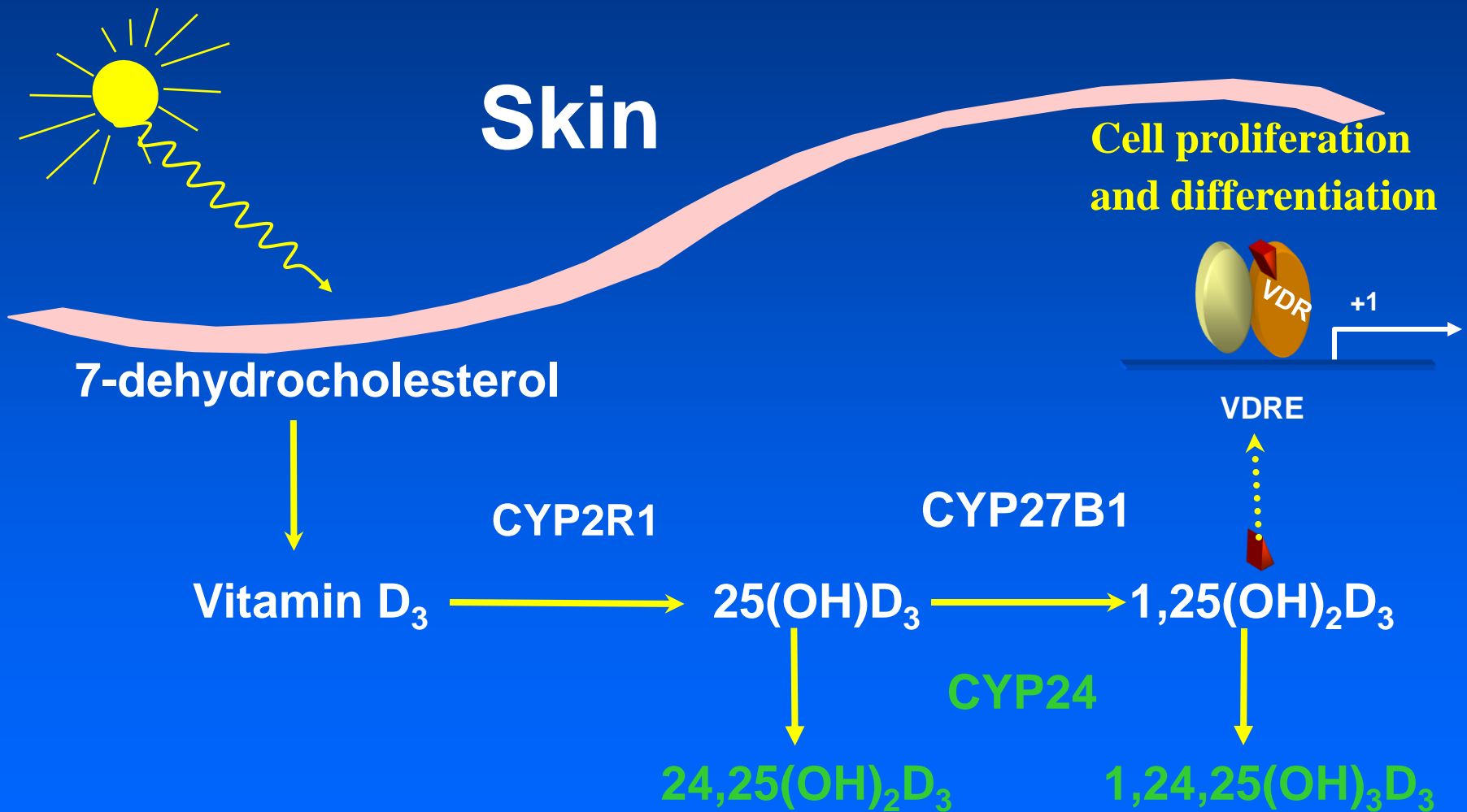


Multiple linear regression equations for serum 25D, 1,25D and PTH as determinants of trabecular bone volume (BV/TV) in the distal femoral metaphysis.

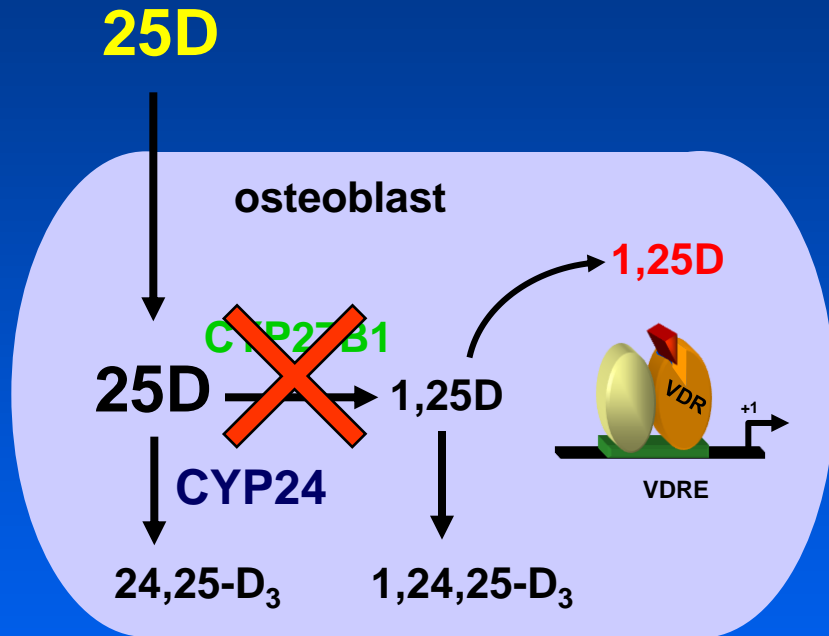
Independent Variable	Equation	R ²	P value
Serum 25D	BV/TV = + 0.09 x 25D	0.60	0.004
+ Serum 1,25D	+ 0.02 x 1,25D	0.28	NS
+ Serum PTH	- 0.21 x PTH + 7.9	0.17	NS
		Multiple R ² = 0.62	

25D, 25 hydroxyvitamin D₃; 1,25D, 1,25 dihydroxyvitamin D₃; PTH, parathyroid hormone.

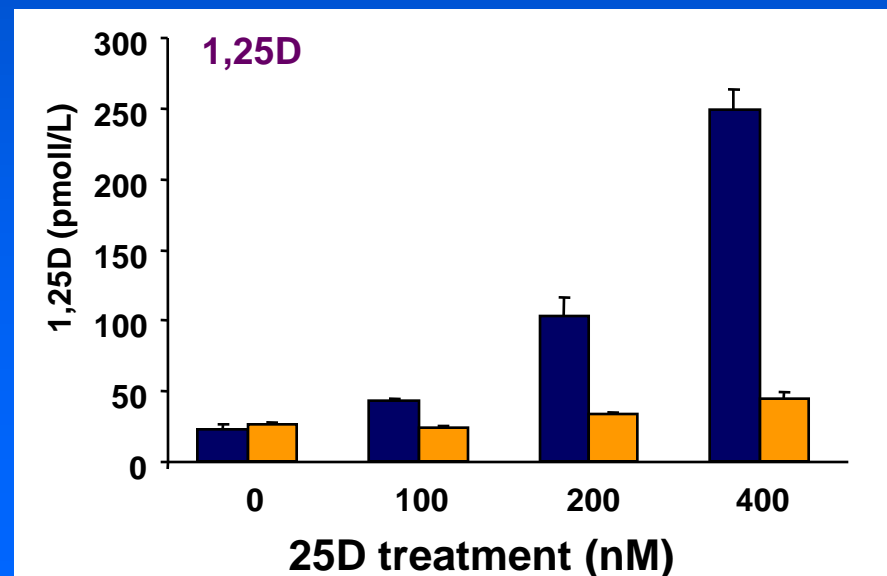
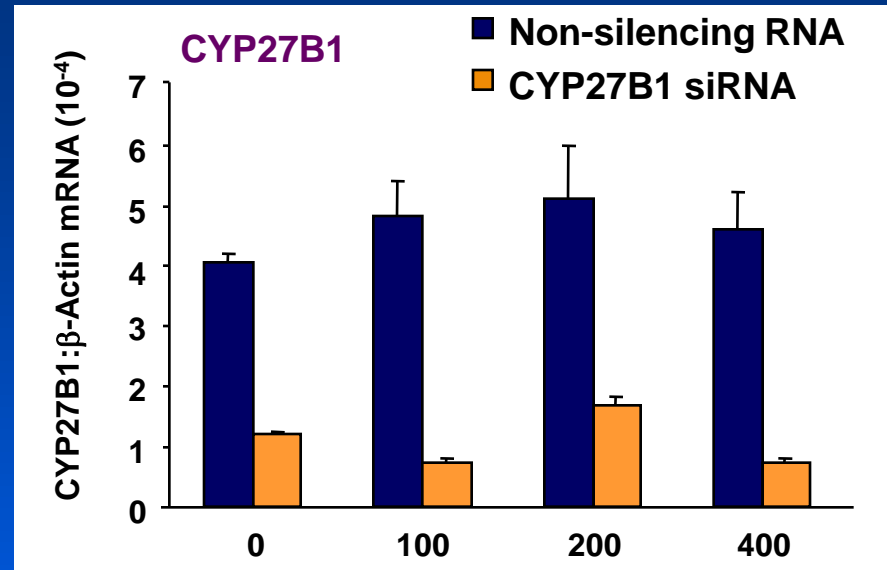
Vitamin D Metabolism: the autocrine/ paracrine system



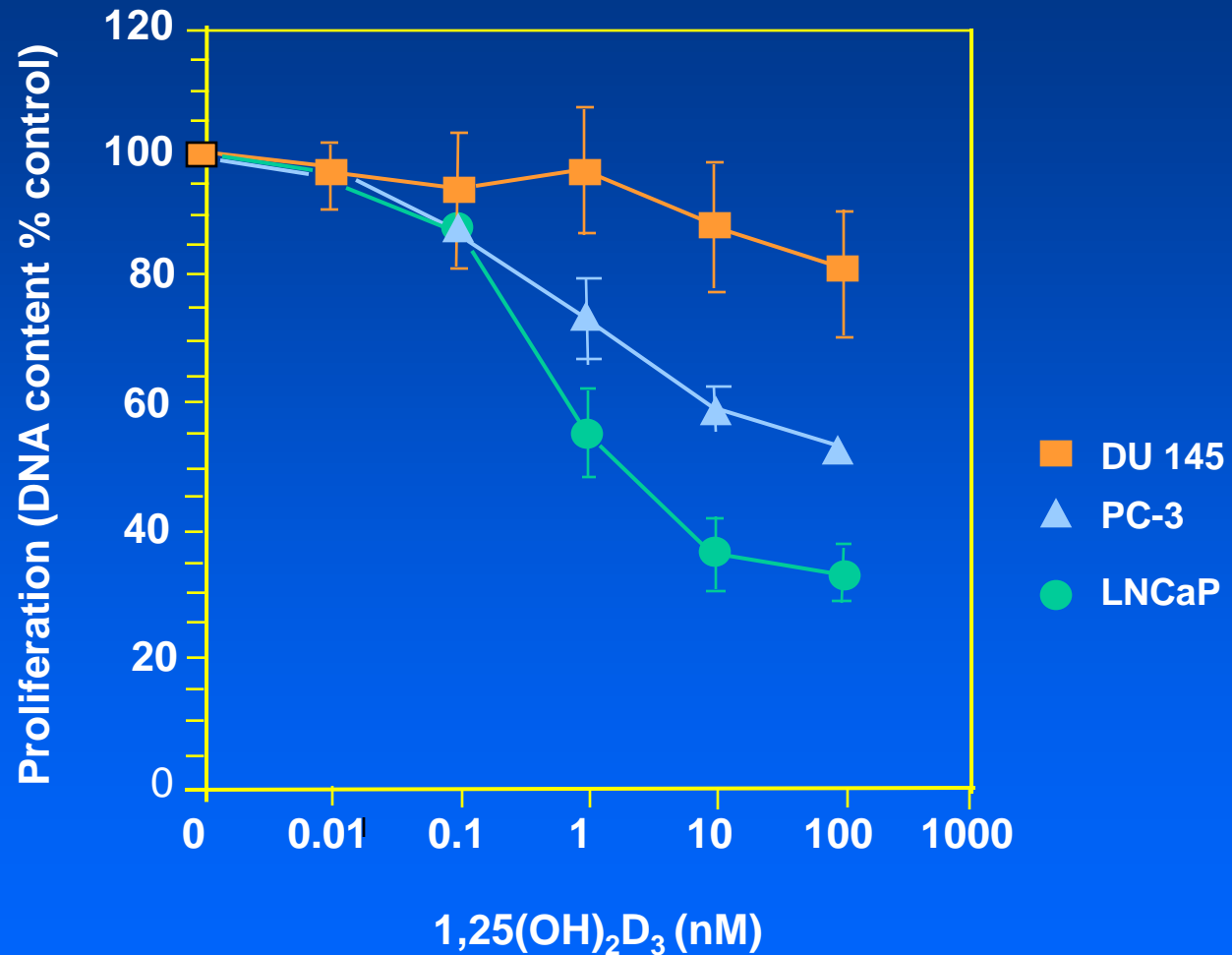
Knock-down of CYP27B1 mRNA in HOS cells by RNAi



Atkins et al Bone 2007



Active vitamin D (125D) inhibits growth of human prostate cancer cell lines



Skowronski et al., *Endocrinology* 1993

Solar UV-B exposure and cancer incidence (1)

Data collected on 3 million cancer incidences ('98 to '02), 3 million cancer deaths ('93 to '02) and daily satellite-measured UV-B exposure;

Continental US non-hispanic white subjects;

Data corrected for age, poverty, income, smoking, alcohol consumption, outdoor occupation, urban/rural residency, and air quality

Relative risk calculated between latitudes 48°N and 32°N

Boscoe and Schymura BMC Cancer 2006; 6: 264

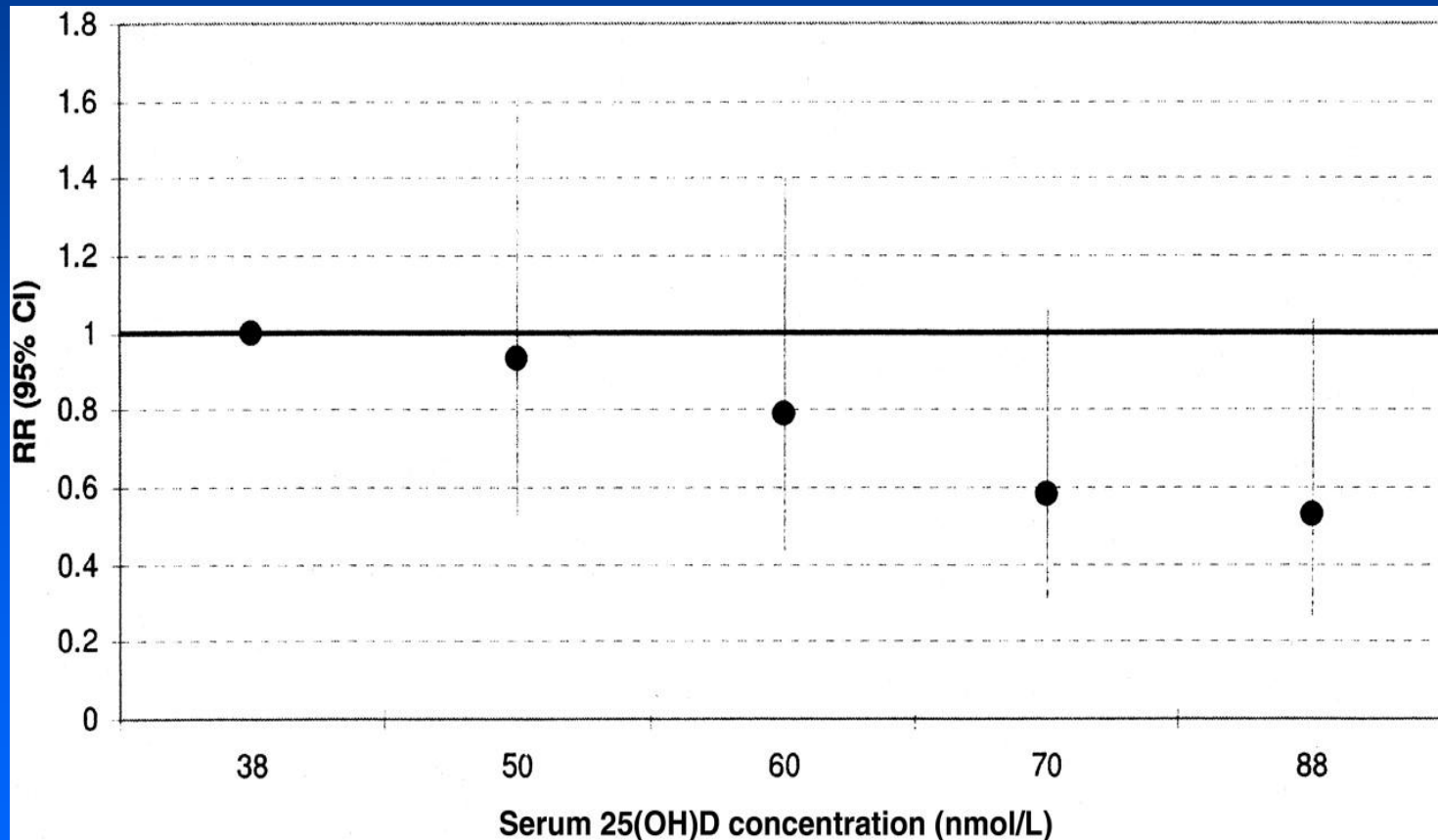
Solar UV-B exposure and cancer incidence

Cancer sites with strongest evidence – RR (95% CI)

	<u>Incidence</u>	<u>Mortality</u>
Oesophagus (M)	1.27 (1.21-1.34)	1.36 (1.31-1.41)
Stomach	1.42 (1.35-1.49)	1.31 (1.26-1.36)
Colon	1.11 (1.08-1.13)	1.27 (1.24-1.30)
Rectum	1.27 (1.23-1.32)	1.53 (1.45-1.60)
Gallbladder (F)	1.86 (1.66-2.09)	1.98 (1.82-2.16)
Uterus	1.49 (1.45-1.53)	1.52 (1.46-1.58)
Vulva	1.18 (1.09-1.29)	1.93 (1.72-2.17)
Prostate	1.20 (1.19-1.22)	1.17 (1.15-1.19)
Bladder	1.13 (1.10-1.16)	1.24 (1.20-1.28)
Hodgkin lymphoma	1.16 (1.04-1.29)	1.14 (1.00-1.30)
Myeloma	1.19 (1.12-1.27)	1.16 (1.11-1.22)

Boscoe and Schymura BMC Cancer 2006; 6: 264

Vitamin D status required to reduce the risk of colon cancer: Data from the Nurses Health Study



Bischoff-Ferrari H et al Am J Clin Nutr 2006; 84: 18-28

Conclusions:

- Vitamin D endocrine activity regulates intestinal calcium and phosphate absorption protecting against rickets/osteomalacia for bone development
- Bone and many other cell types are capable of activating vitamin D to regulate activities to optimise health
- A 25D serum level of 80 nmol/L or greater is necessary for optimal bone structure. Evidence is suggestive for similar levels for optimal health.