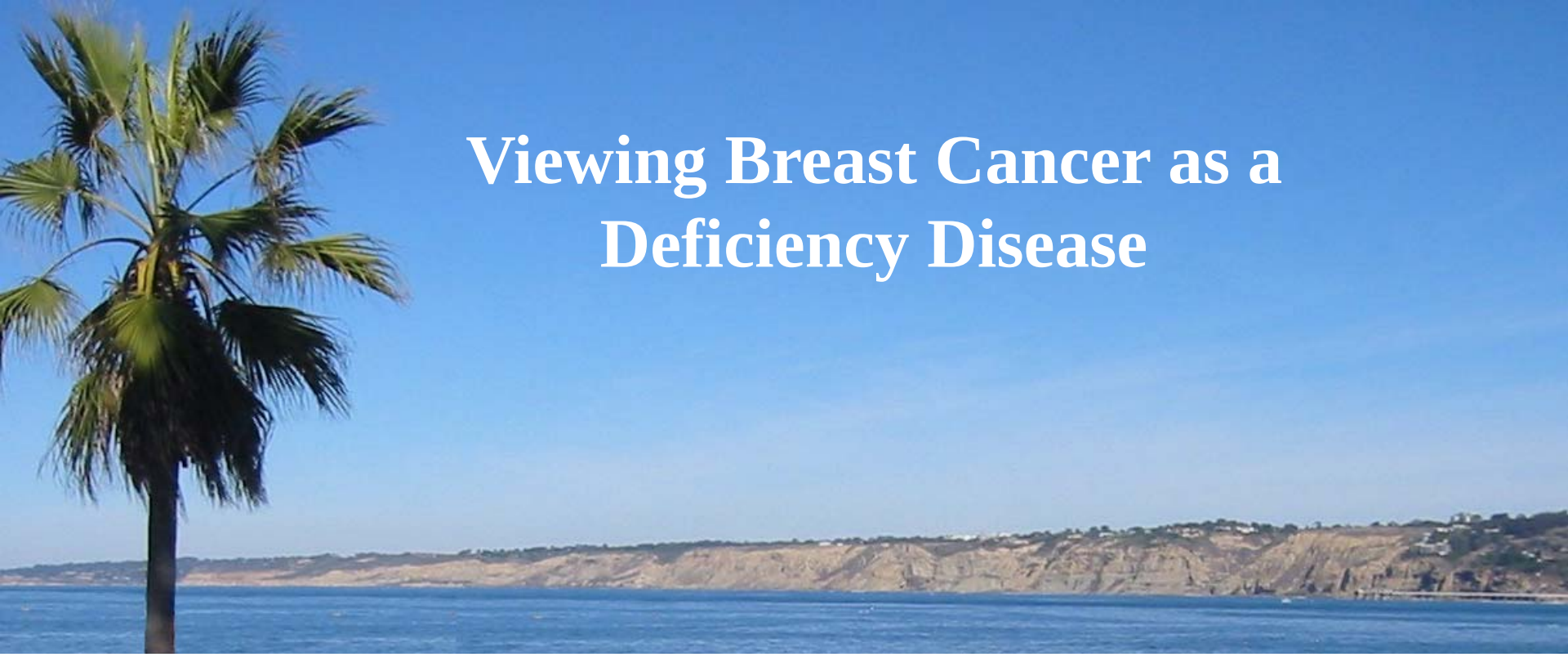

Viewing Breast Cancer as a Deficiency Disease

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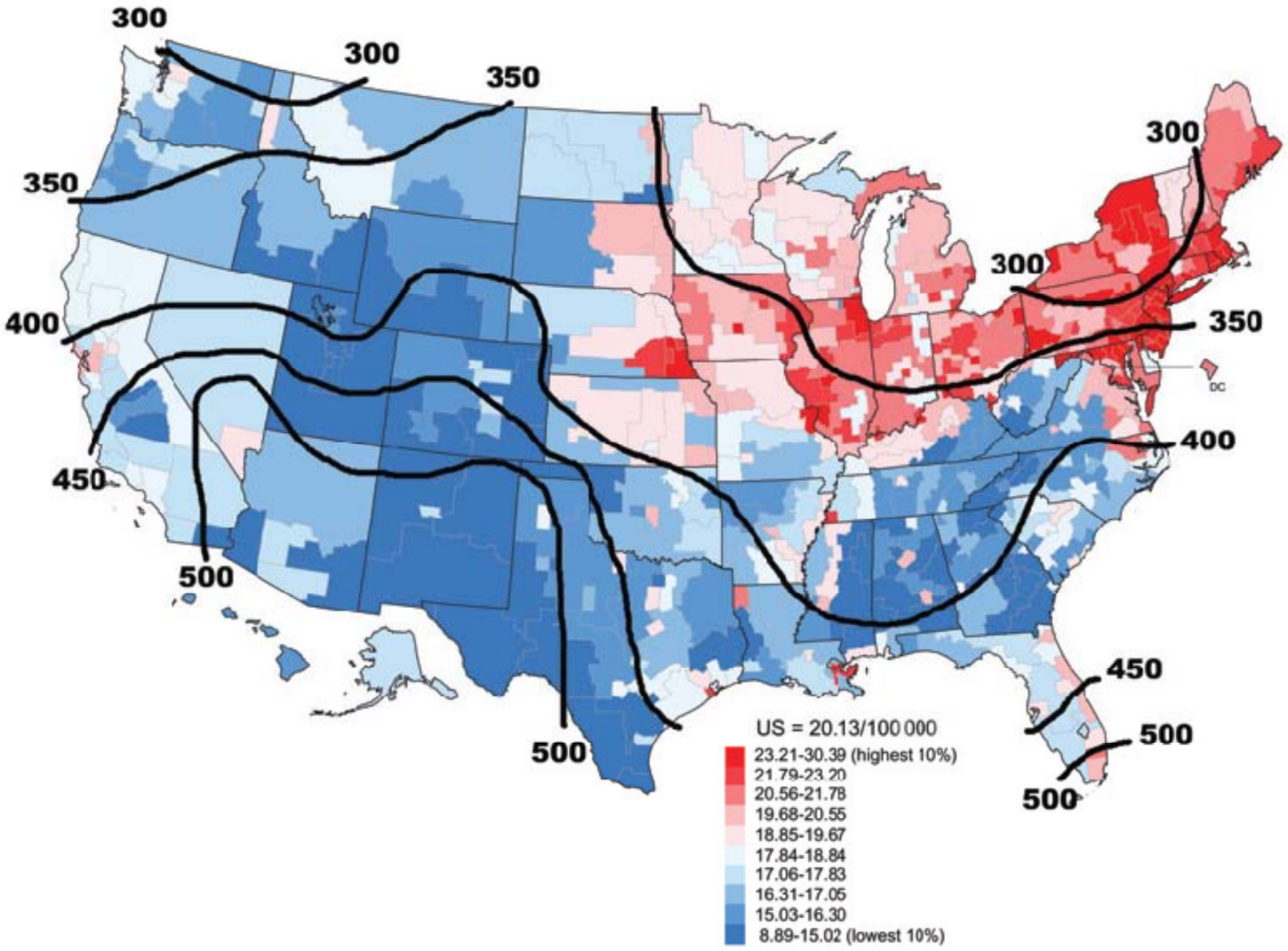
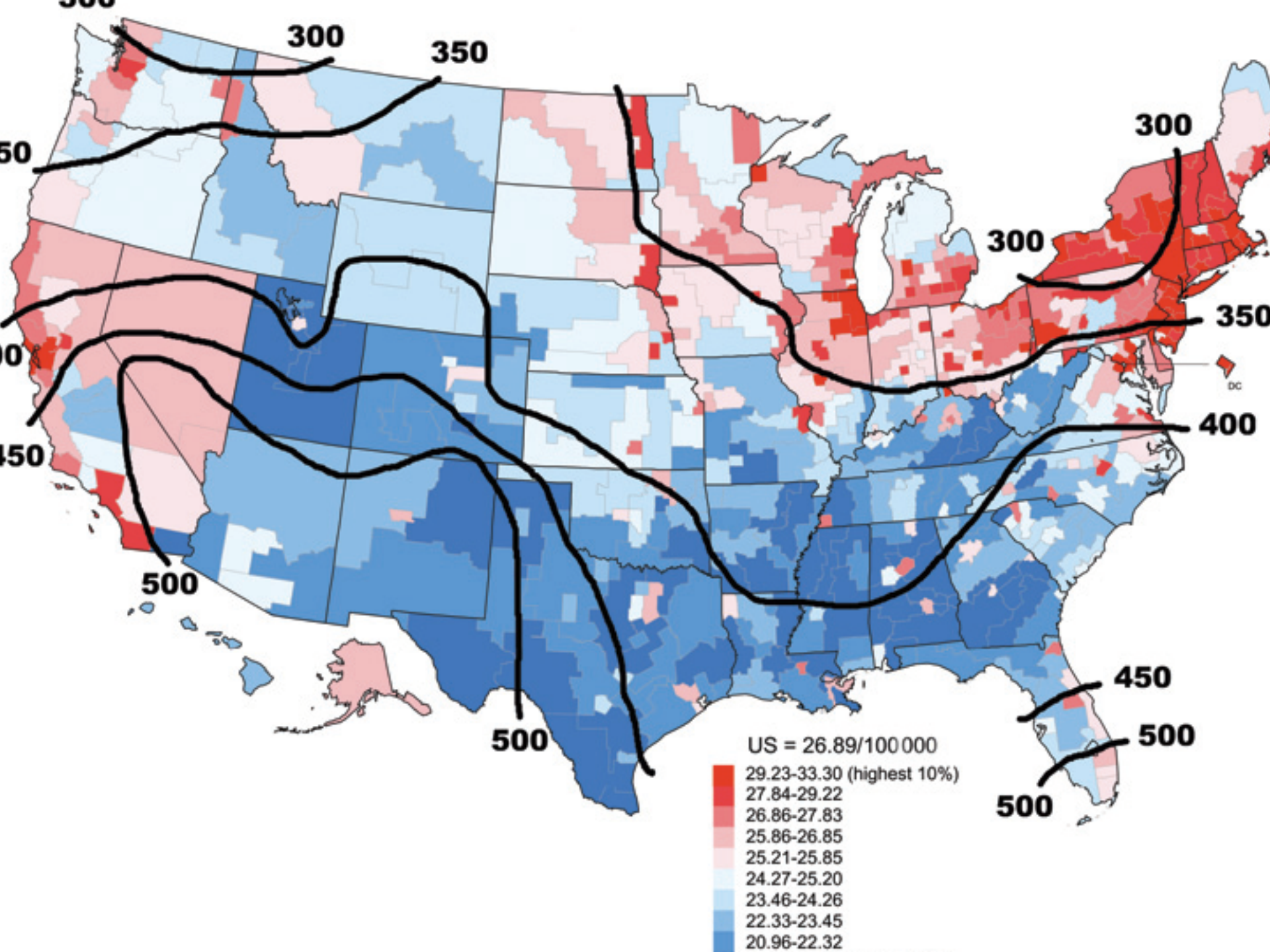
November 3, 2009

Diagnosis and Treatment of Vitamin D Deficiency
University of Toronto Faculty Club

Disclosure

I have no actual or potential conflict of interest in relation to this program.


300
300
350
350
300
400
300
350
DC
400
450
500
450
500
500
US = 20.13/100 000
23.21-30.39 (highest 10%)
21.79-23.20
20.56-21.78
19.68-20.55
18.85-19.67
17.84-18.84
17.06-17.83
16.31-17.05
15.03-16.30
8.89-15.02 (lowest 10%)


300
350
300
300
350
400
450
500
500
450
500
500
DC
US = 26.89/100 000
29.23-33.30 (highest 10%)
27.84-29.22
26.86-27.83
25.86-26.85
25.21-25.85
24.27-25.20
23.46-24.26
22.33-23.45
20.96-22.32

“All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.”

--Schopenhauer

Role of UVB and Latitude for Vitamin D

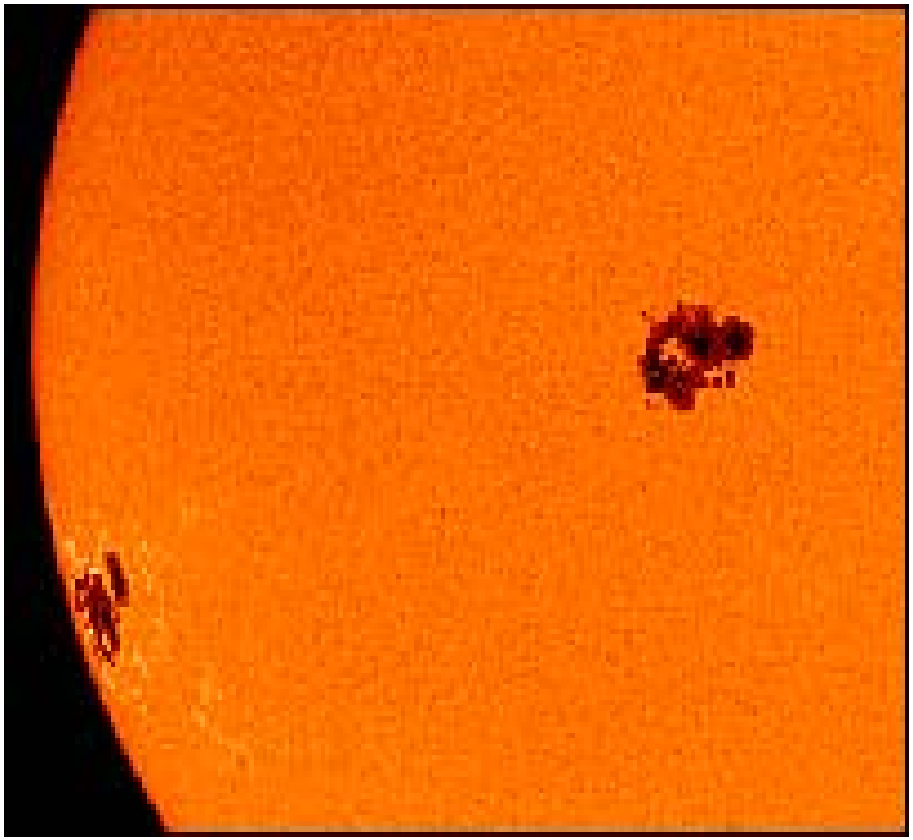


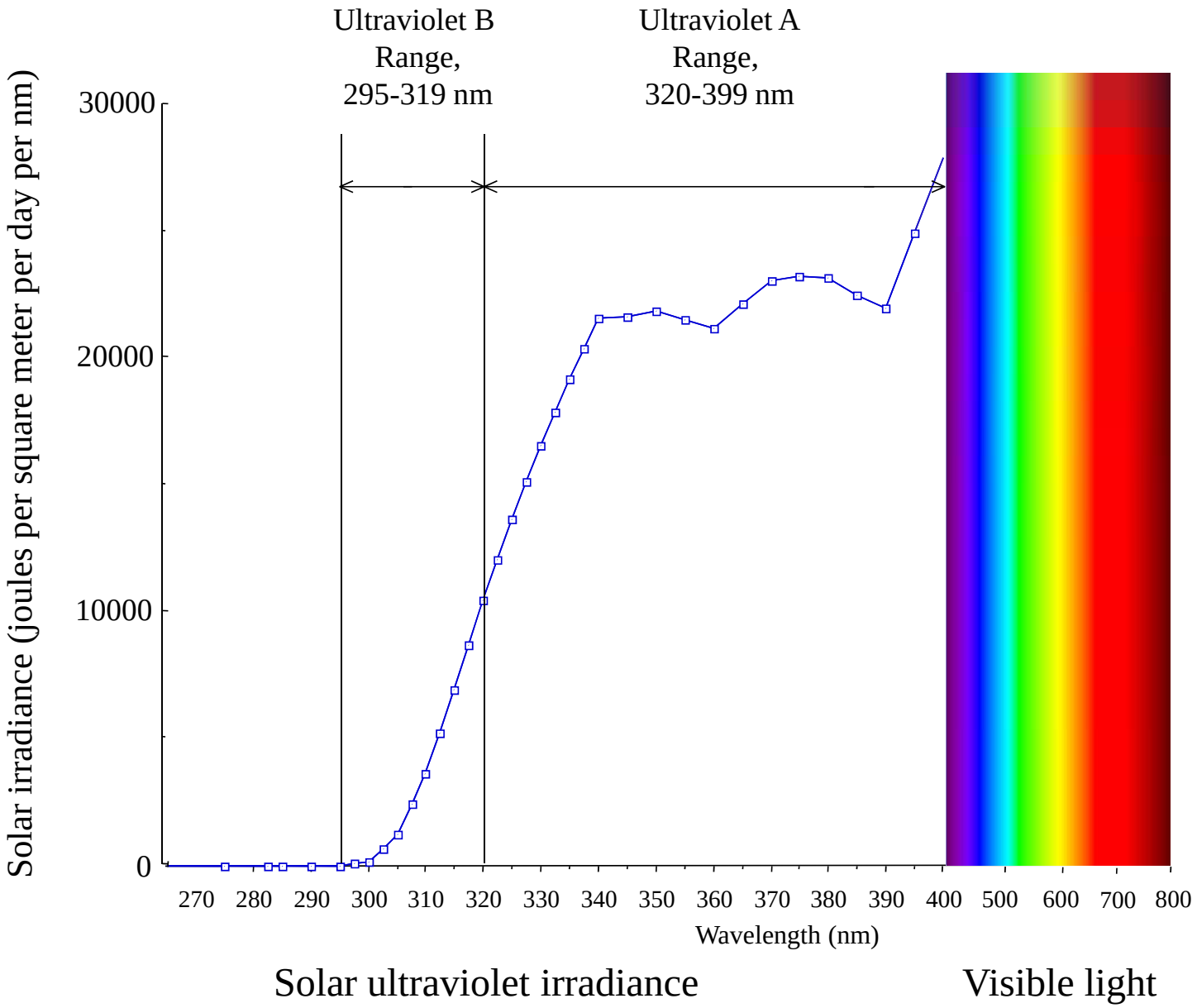
Photo: Stanford Univ.

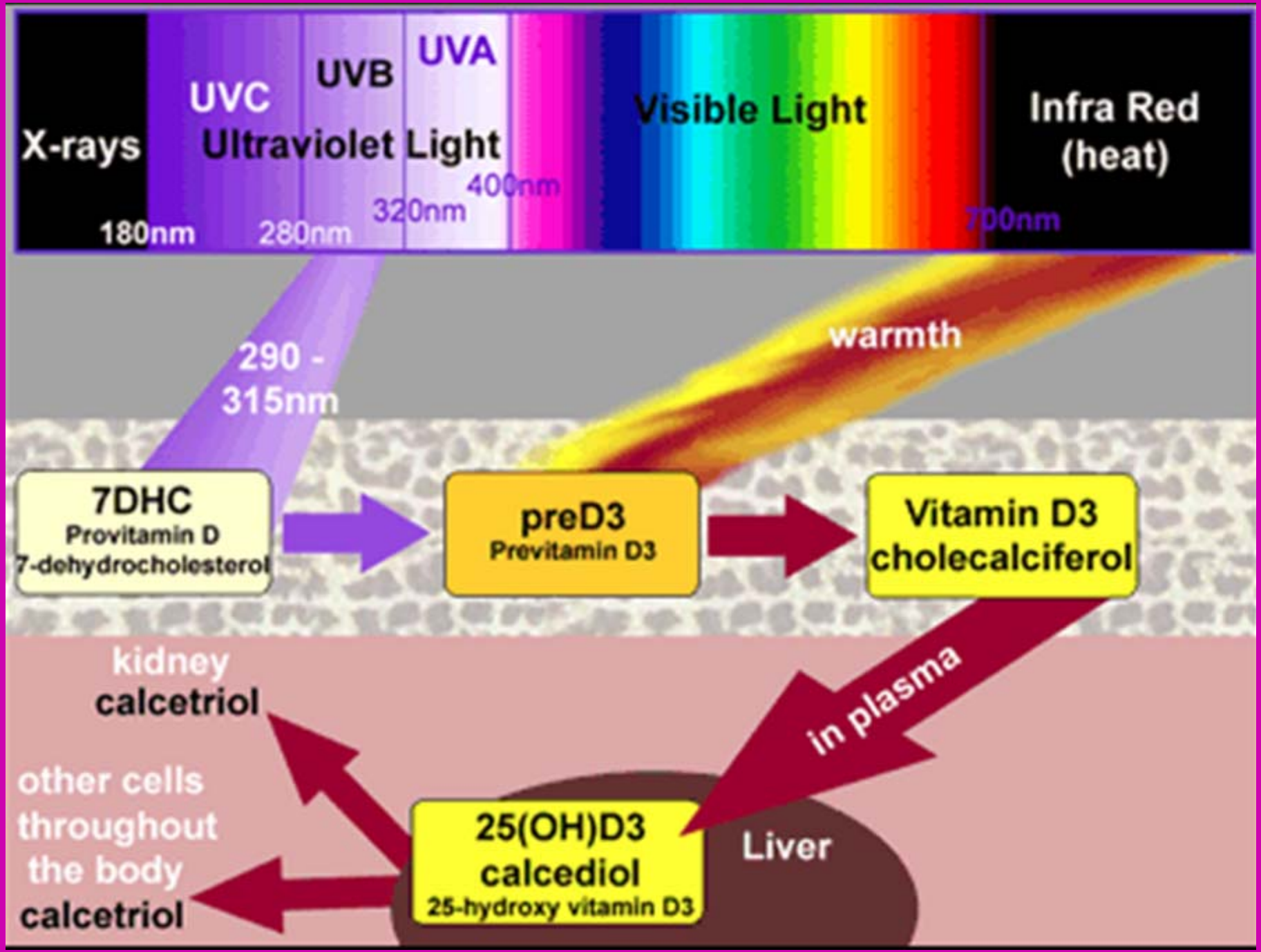
The sun is the source of UVB used to make vitamin D

Less than 1% of solar radiation is UVB

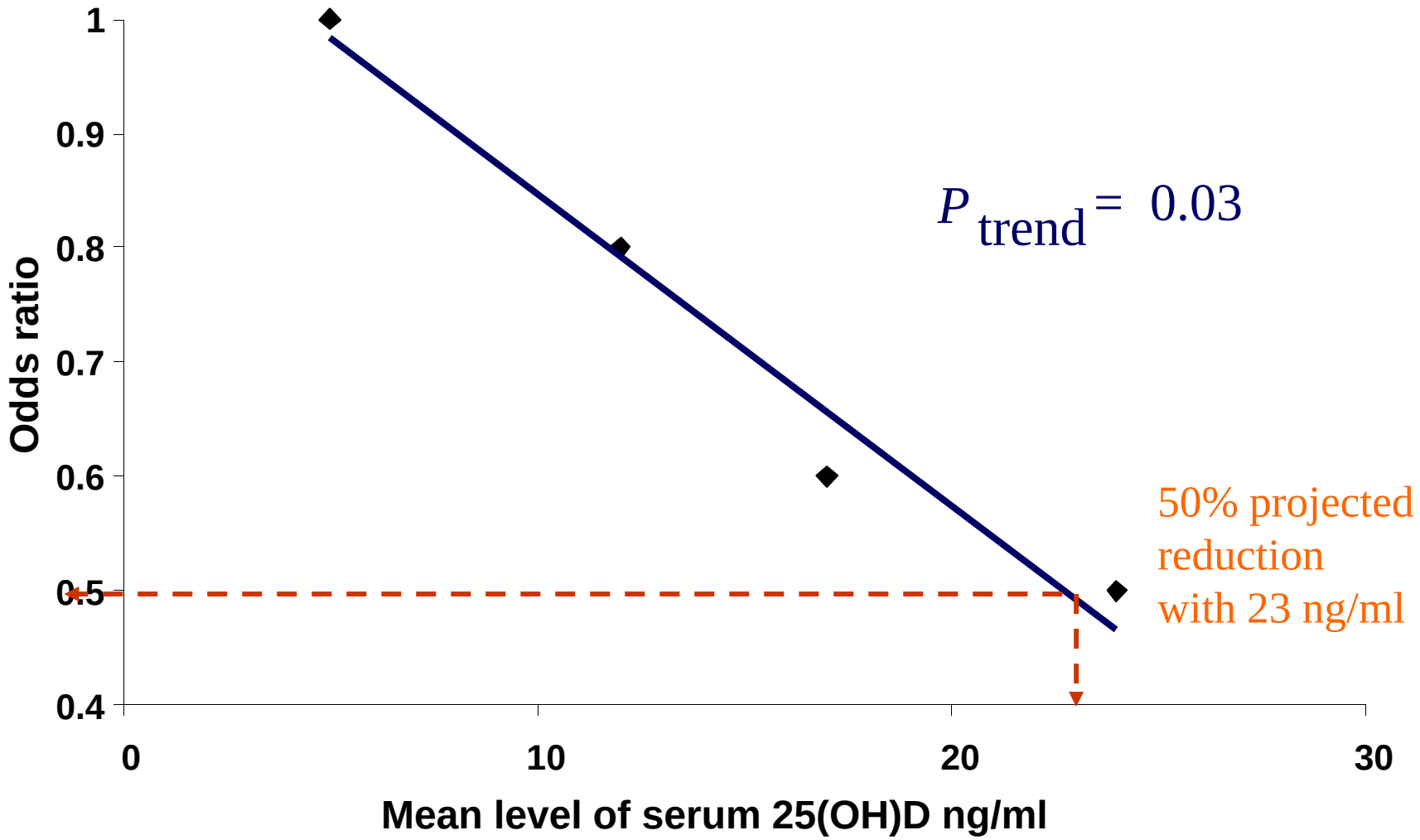
Four UVB photons combine with one molecule of cholesterol (7DHC), opening a ring to make previtamin D

There is no change in molecular weight.


Ultraviolet B Range, 295-319 nm
Ultraviolet A Range, 320-399 nm
Solar irradiance (joules per square meter per day per nm)
30000
20000
10000
0
270 280 290 300 310 320 330 340 350 360 370 380 390 400 500 600 700 800
Wavelength (nm)
Solar ultraviolet irradiance
Visible light

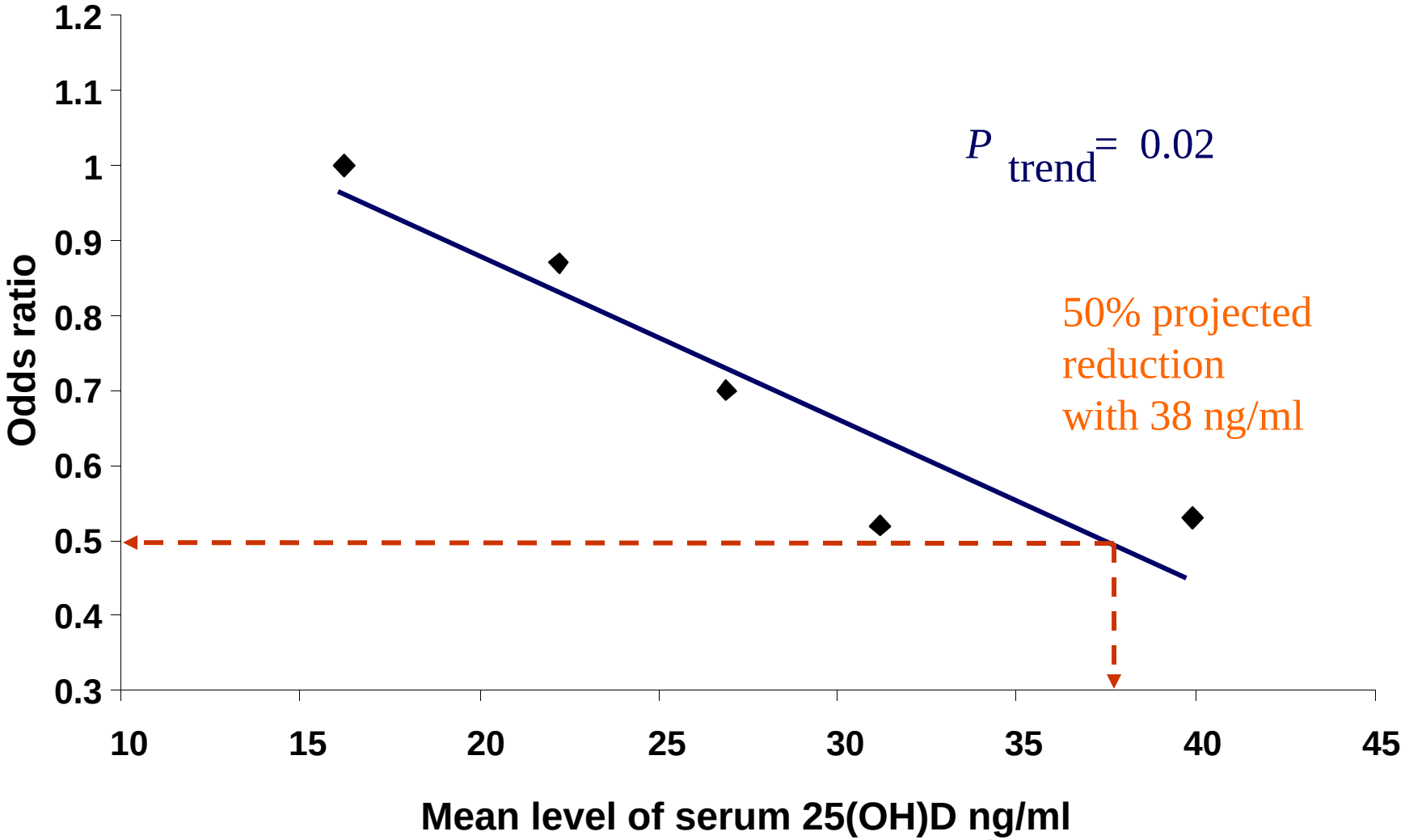

X-rays
UVC
UVB
UVA
Ultraviolet Light
Visible Light
Infra Red
(heat)
180nm
280nm
320nm
400nm
700nm
290 -
315nm
warmth
7DHC
Provitamin D
7-dehydrocholesterol
preD3
Previtamin D3
Vitamin D3
cholecalciferol
kidney
calcetriol
in plasma
other cells
throughout
the body
calcetriol
25(OH)D3
calcediol
25-hydroxy vitamin D3
Liver

Tangrea et al. 1997



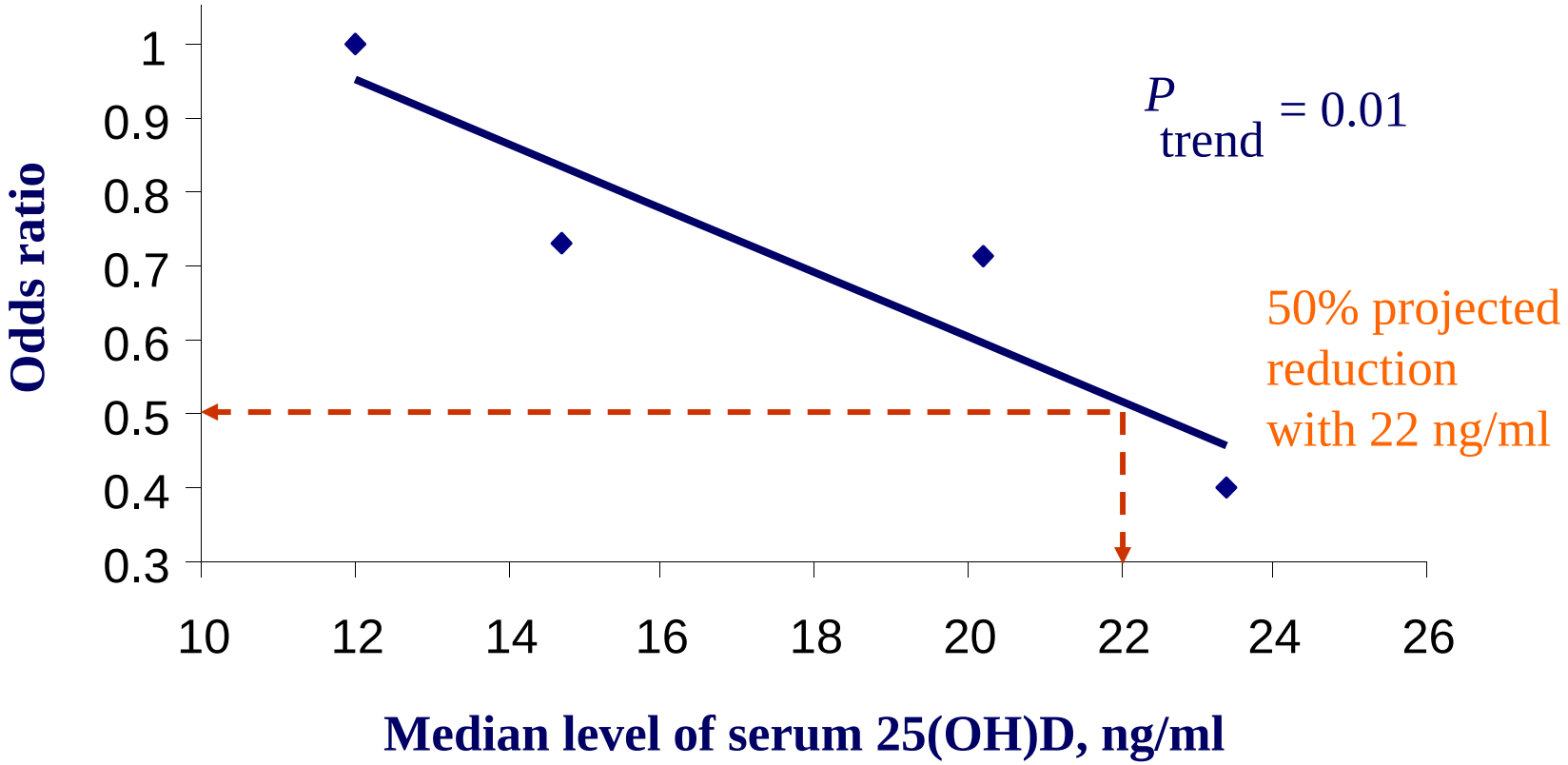
Source: Tangrea J, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control 1997;8:615–25.

Feskanich et al. 2004

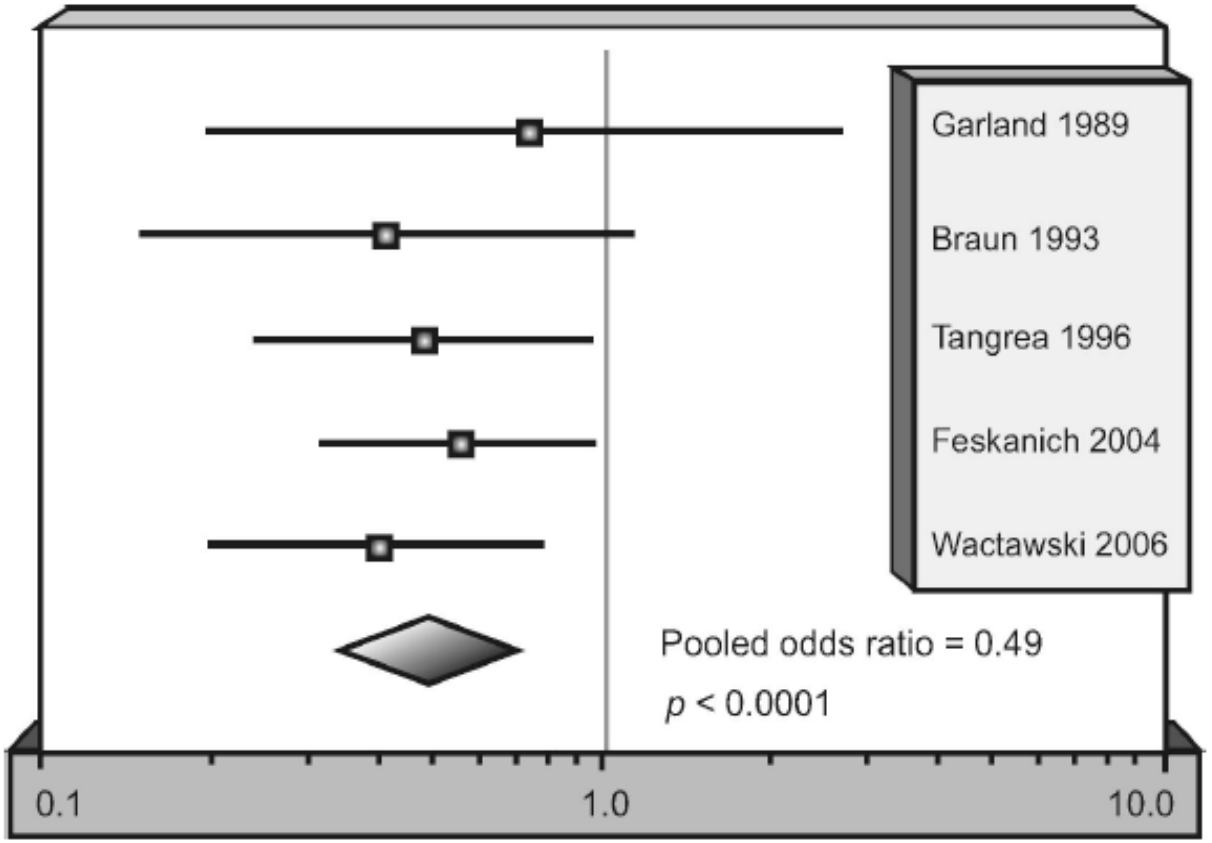


Source: Feskanich D, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004;13:1502– 8.

Women's Health Initiative Nested Study (N=295)

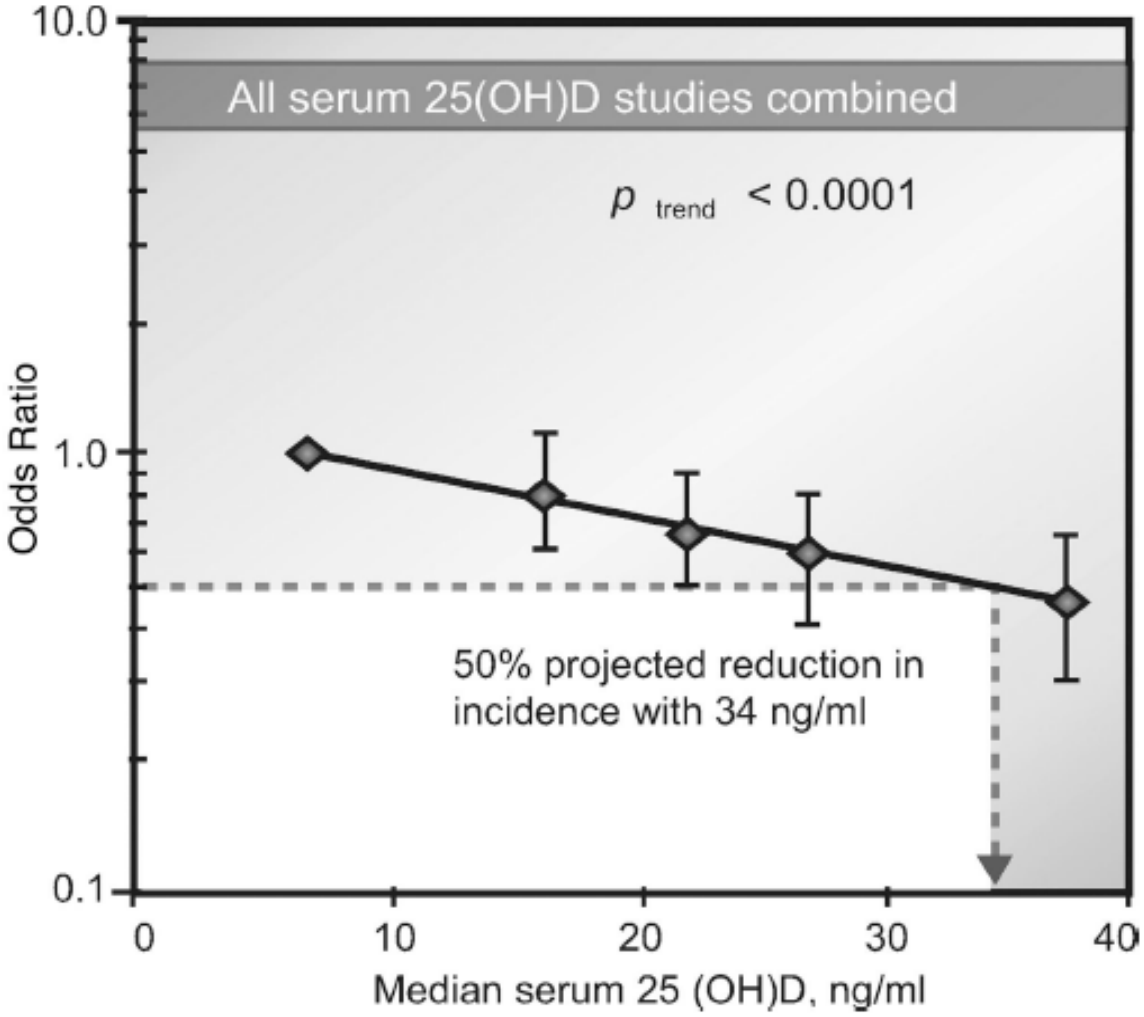


Source: Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. New Engl J Med 2006; 354:684-96.

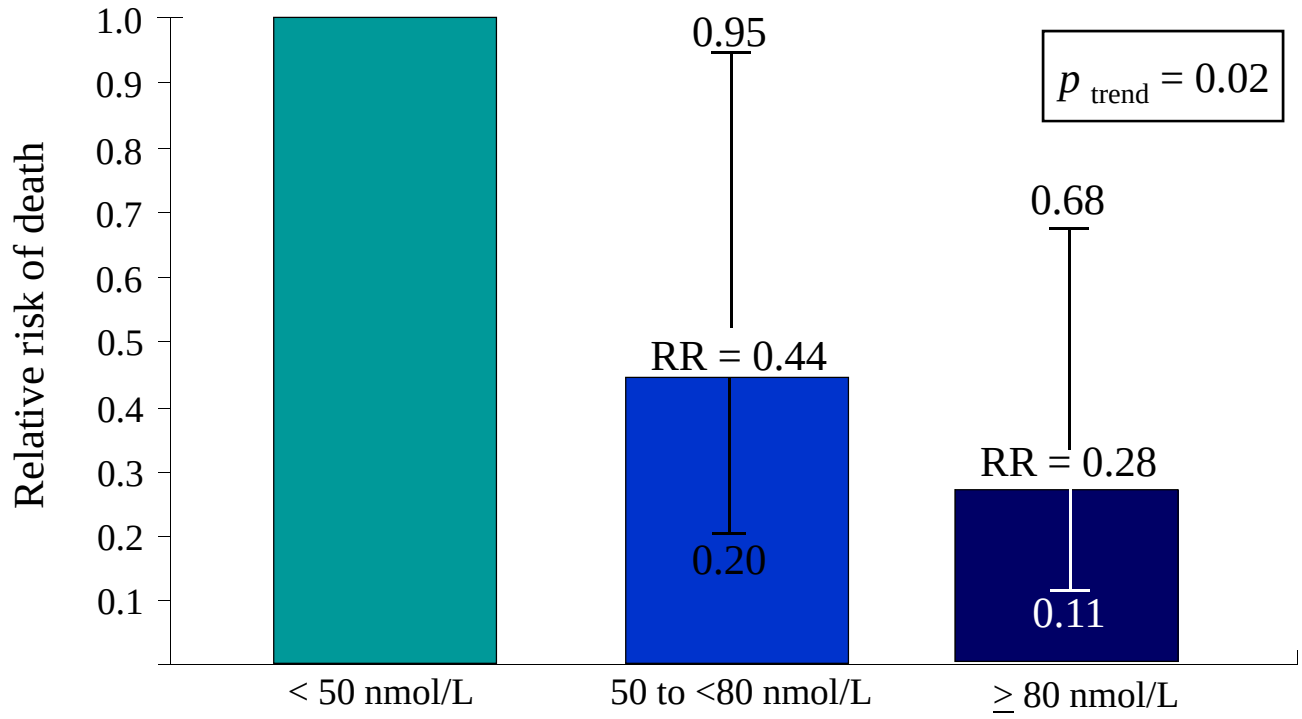


Forest plot of all studies of serum 25(OH)D and risk of colorectal cancer. The upper and lower 95% confidence limits on the odds ratio are denoted by horizontal lines for each study, and the 95% confidence limits for the combined estimate for all studies are denoted by the points of the diamond. The odds ratios compare the highest quintile to the lowest.

Source: Gorham ED, et al. Optimal vitamin D status for colorectal cancer prevention: A Quantitative Meta Analysis. Am J Prev Med March 2007; 32:210-6.

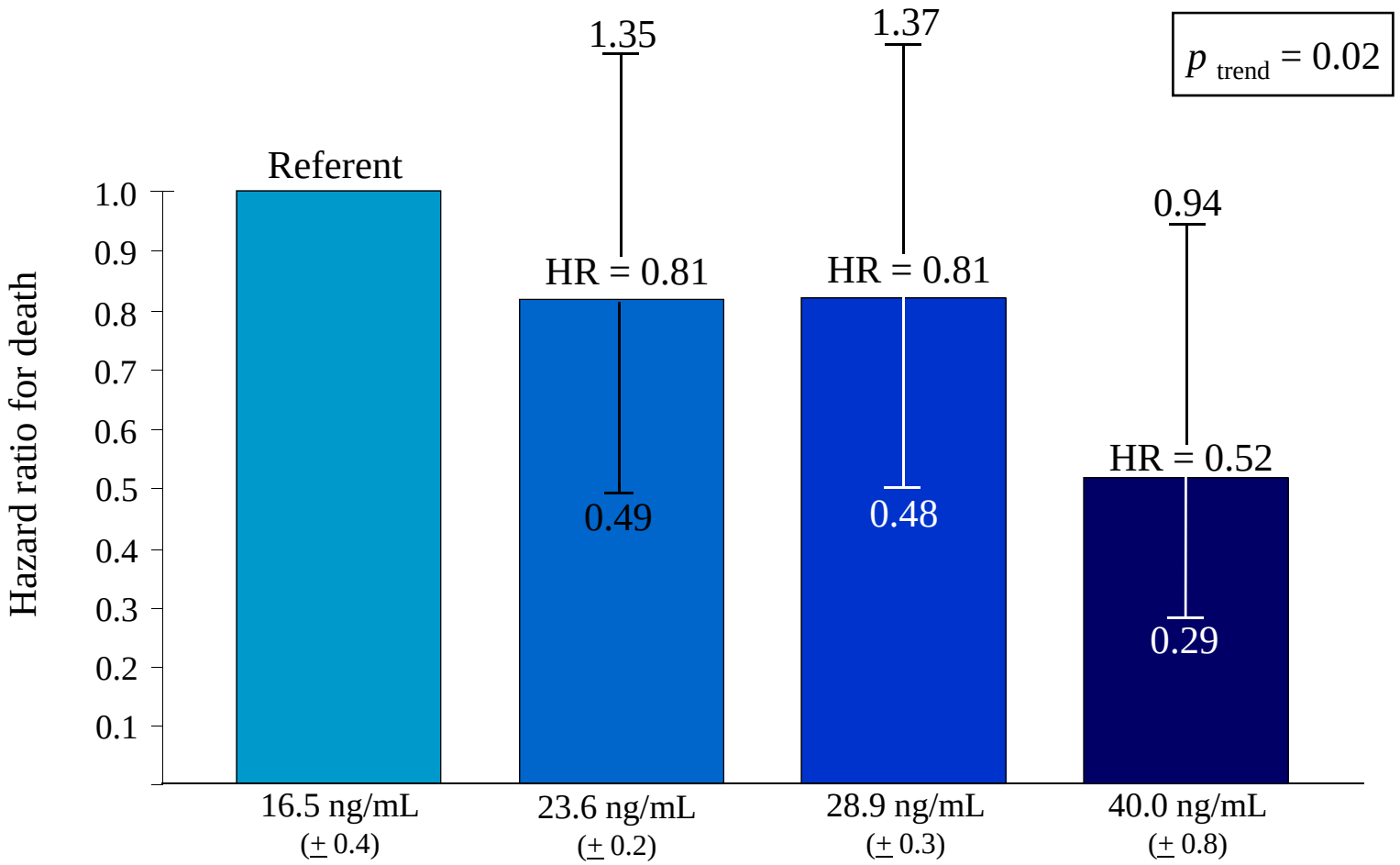


Dose–response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined. The five points are the odds ratios for each quintile of 25(OH)D based on combined data from the five studies. Source: Gorham ED, et al. Optimal vitamin D status for colorectal cancer prevention: A Quantitative Meta Analysis. Am J Prev Med March 2007; 32:210-6.



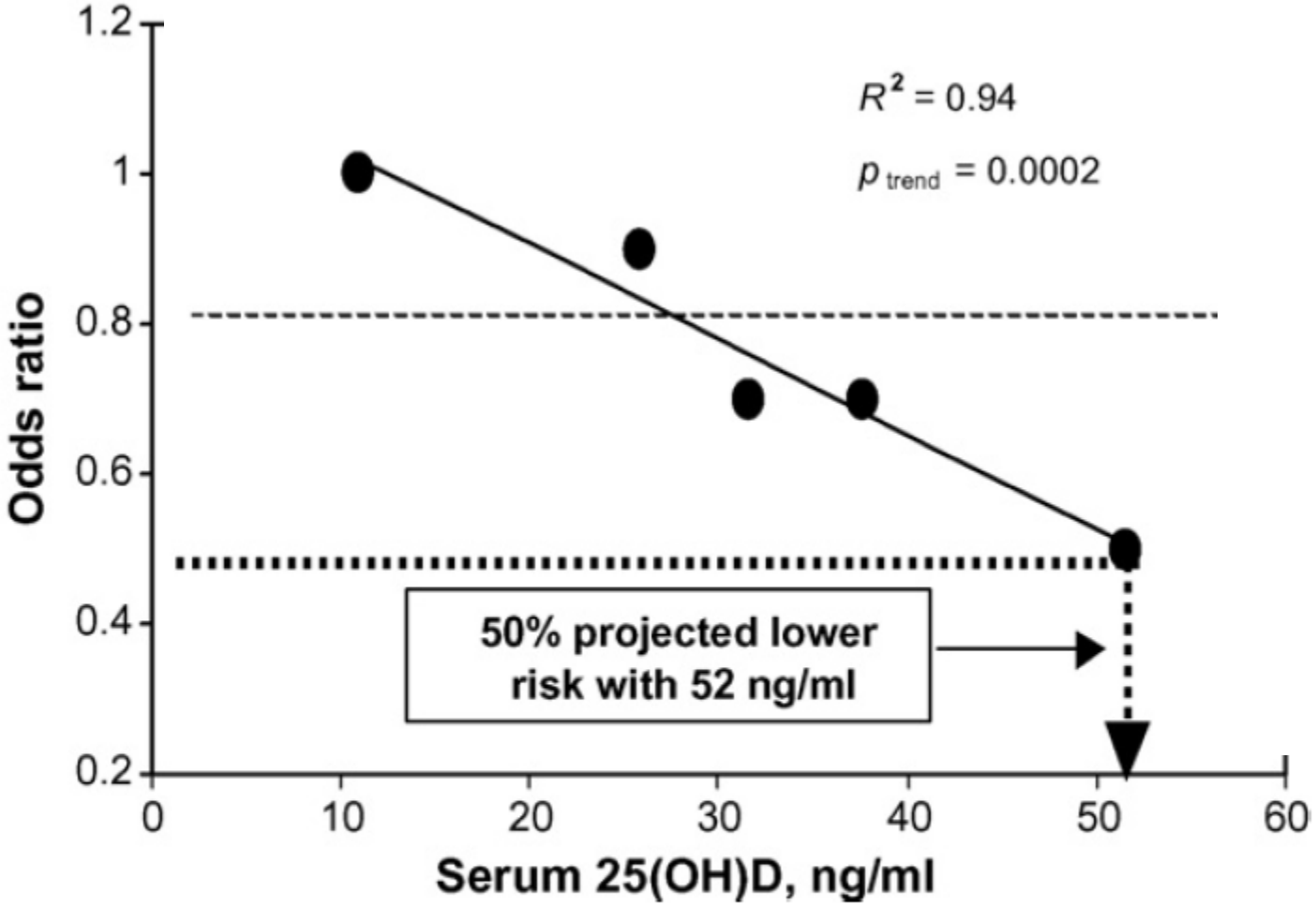
Relative risk of colon cancer mortality, by baseline serum 25-hydroxy-vitamin D concentration in tertiles, NHANES III cohort, 1988-2000
(Note: 50 nmol/L = 20 ng/ml; 80 nmol/L=32 ng/ml)

Source: Freedman DM, Looker AC, Shih-Chen C, et al. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007;99:1594-602.



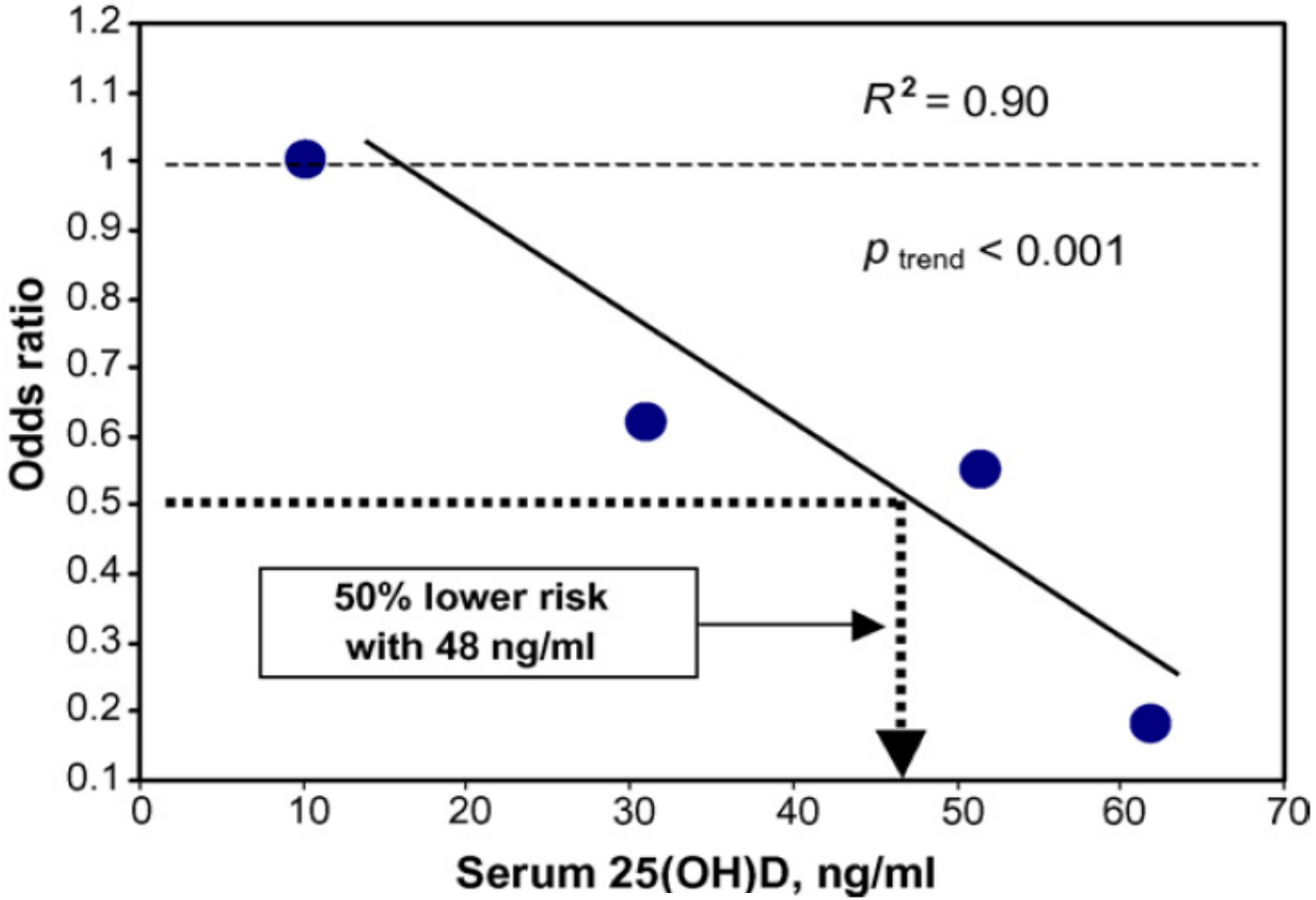
Multivariate-adjusted hazard ratios for death, 304 colorectal cancer patients, by prediagnostic mean plasma 25-hydroxyvitamin D concentration quartiles, Nurses Health and Health Professionals Study Cohorts

Source: Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, Fuchs CS. Circulating 25-hydroxyvitamin D levels and survival in patients with colorectal cancer J Clin Oncol 2008; 26: 2984-91.



Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

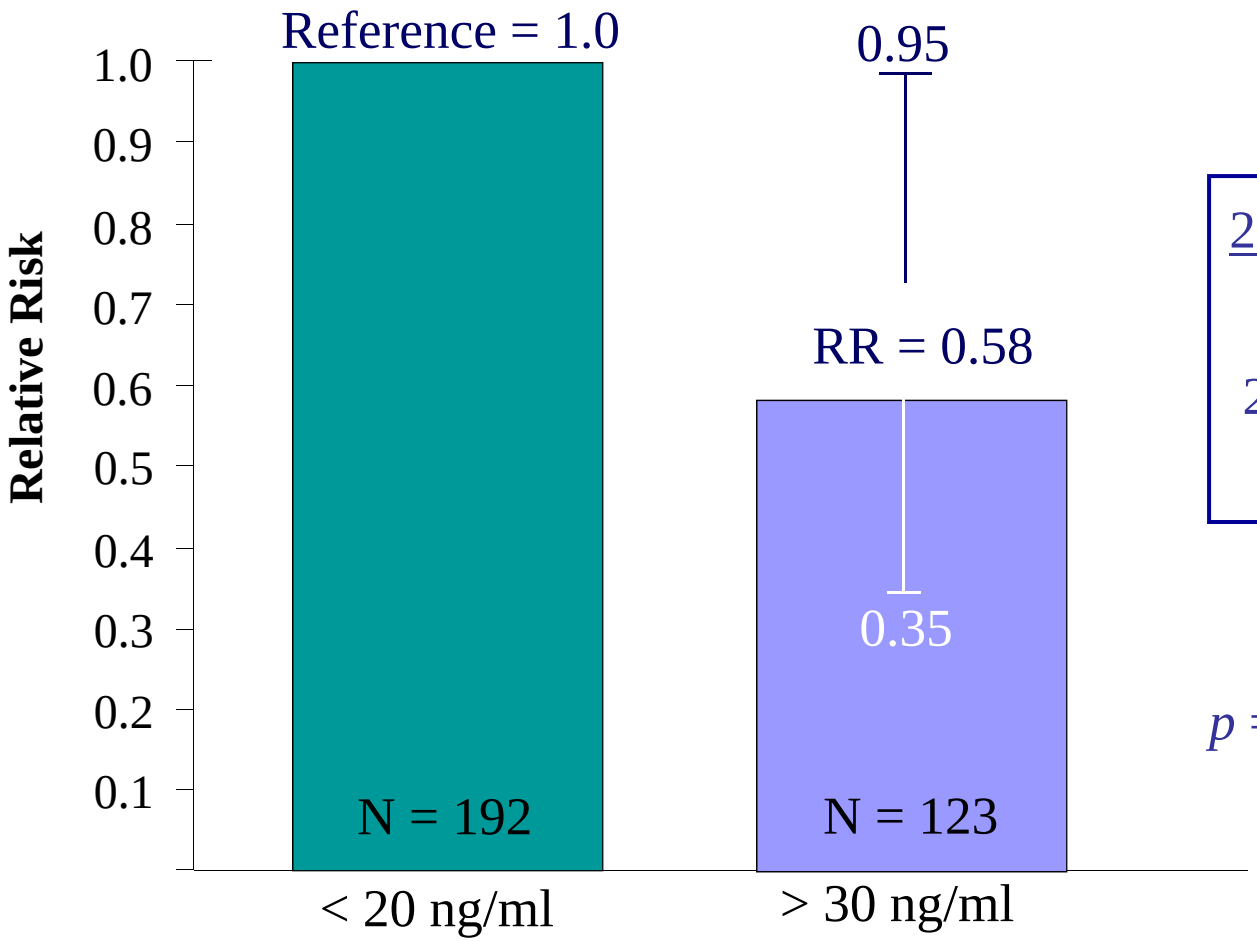
Source: Garland CF, et al. Vitamin D and prevention of breast cancer: Pooled analysis, J Steroid Biochem Mol Biol. 2007;103:708-11



Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, St. George's Hospital, London

Data from: Lowe LC, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer. 2005;41:1164-9.

Overall Survival among 512 women with early stage breast cancer by serum 25(OH)D level at diagnosis, median follow-up 11.6 years, Toronto, Canada



25 (OH)D at dx (ng/ml)	
< 20	N= 192
20 - 29.9	N= 197
> 30	N= 123

$p = 0.02$

Hazard ratio and 95% confidence intervals for overall survival by 25(OH)D serum level at diagnosis, Toronto, Canada (latitude 43^0 40')

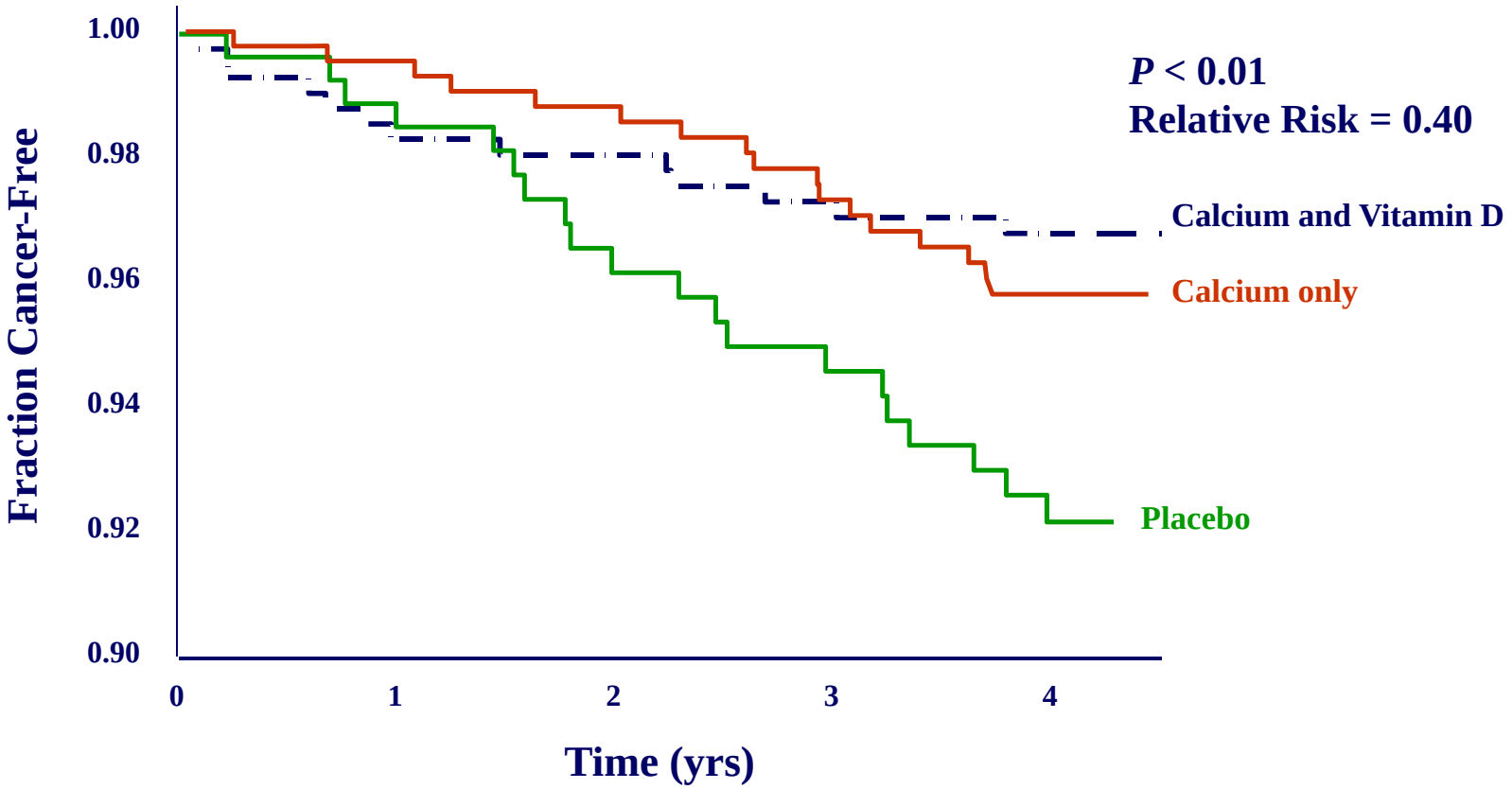
Source: P J Goodwin, et al. Vitamin D deficiency is common at breast cancer diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, May 30-June 3, 2008. Abstract number: 08-AB-31397-ASCOAM.

Randomized Controlled Trial of Vitamin D and Calcium

- Four years, N = 1,179 healthy women in Omaha NE
- Mean age 66.7 ± 7.3 years
- N = 1,032 finished trial (87.5%)
- Baseline serum 25(OH)D: 29 ± 8 ng/ml (72 ± 20 nmol/L)
- Three treatment groups:
  - Vitamin D_3 (1,100 IU/day) and calcium (1450 mg/day)
  - Calcium (1,450 mg/day)
  - Placebo
- Outcome: All cancers (mainly breast, lung and colon)

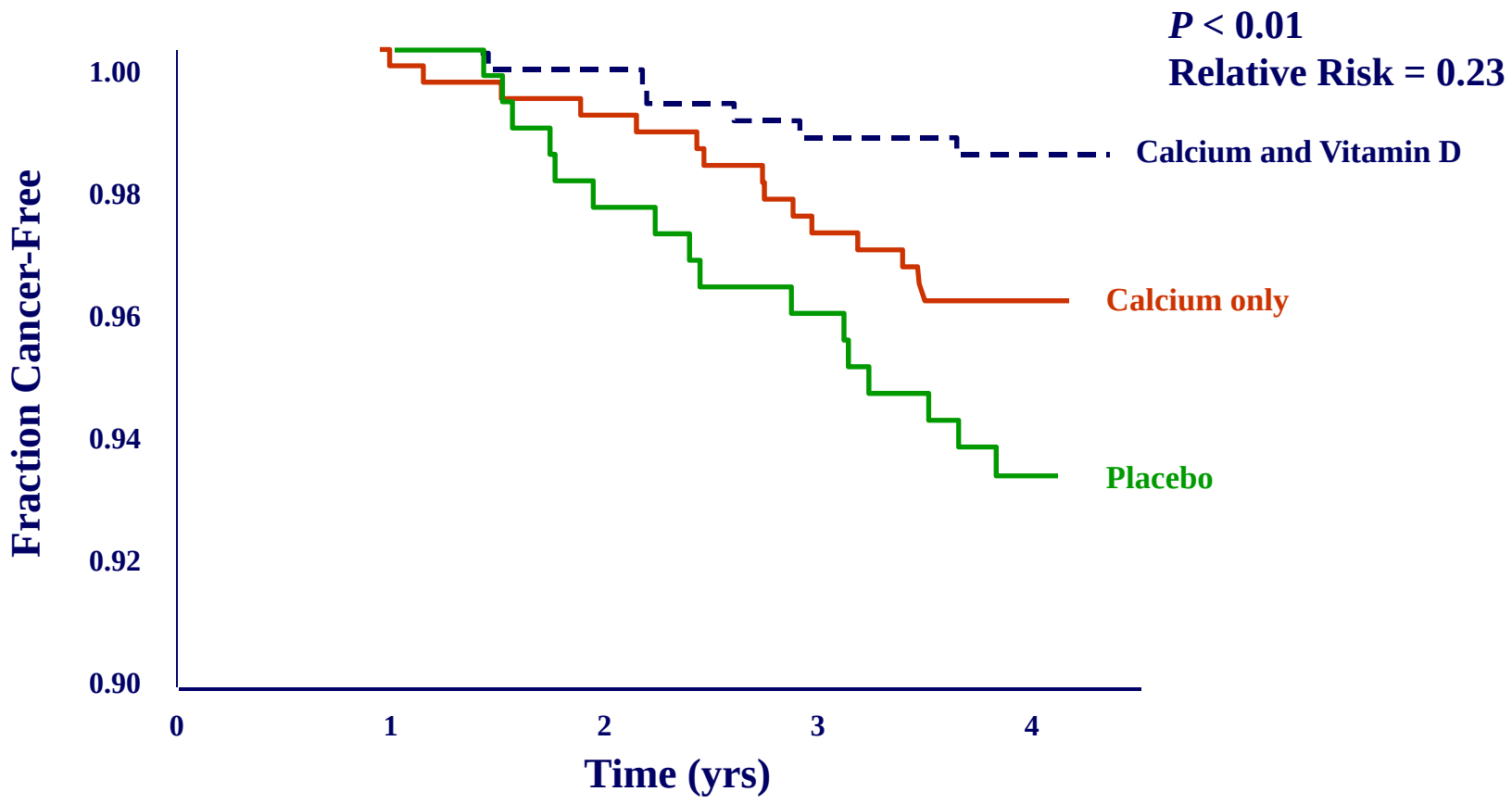
Source: Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586-91.

Randomized Controlled Trial

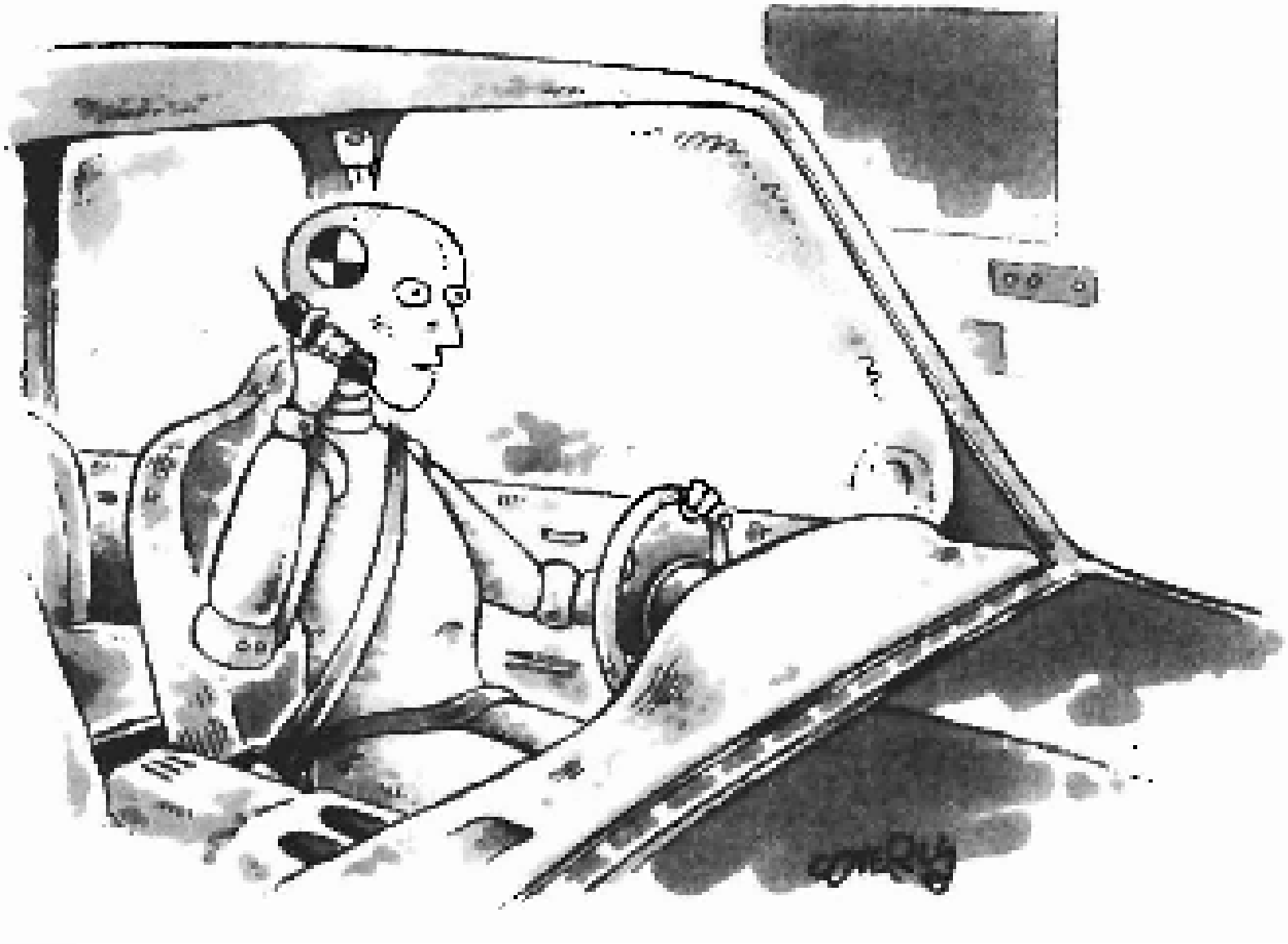


Source: Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586-91.

All Except First Year Cases



Source: Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586-91.



Well, I’d better go now. I’m almost at the wall

Epidemiological studies reporting no or adverse associations with serum 25(OH)D

Stolzenberg-Solomon RZ et al. – Finland - Pancreatic cancer in male smokers, 50-69 yrs in ATBC study, particularly in winter months (*Cancer Res 2006*;66:10213-9)(Pickled herring vs. ?)

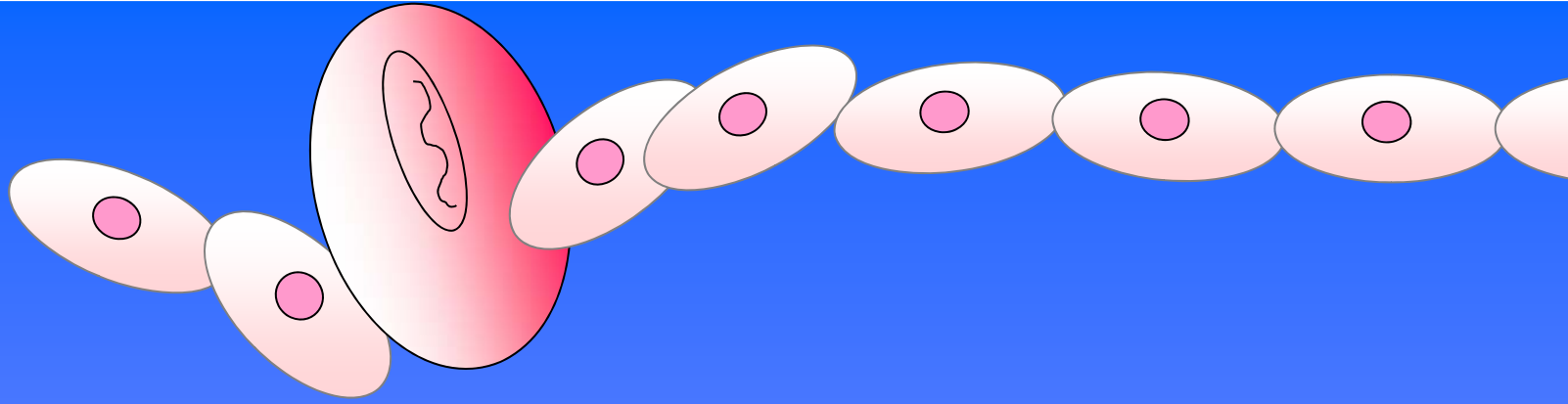
Abnet C et al.– China - Esophageal squamous cell dysplasia/cancer in poor rural Linxian men but not women (*Br J Cancer* 2007;97:123-8 (Plant/mushroom source of vitamin D vs. malnutrition vs.?)

Ahn et al. – PLCO - No association with prostate cancer incidence, but cases found in screening study were more advanced (*JNCI* 2008;100:796-804)(Possibly unmasking bias?; opposite result in Harvard HPFS.)

Freedman et al. – PLCO -No association with breast cancer in nested case-control study (*Cancer Epidemiol Biomark Prev* 2008; 17:889-94)(Matching, latency issues)

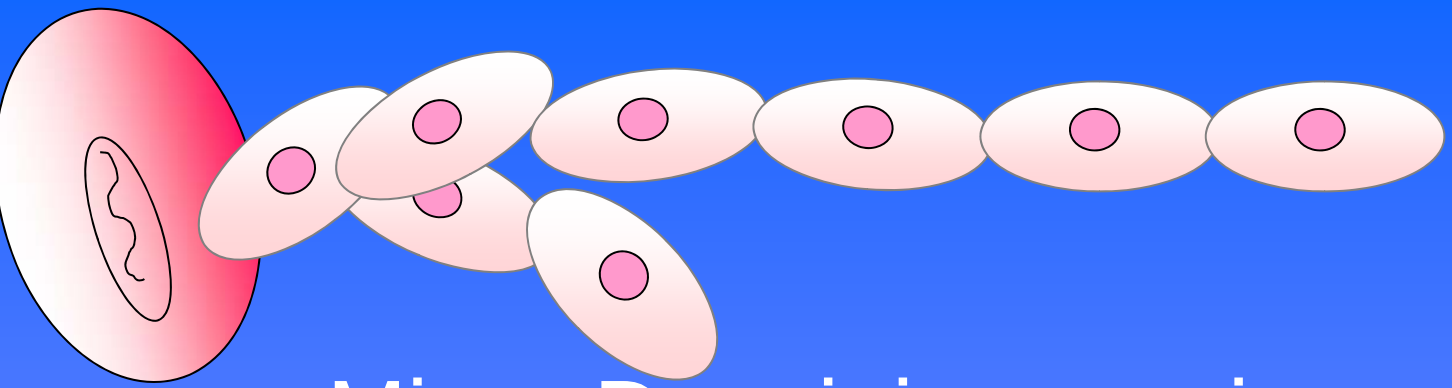
No association with breast cancer (Hiatt RA et al., JNCI 1998;90:461-3); 1,25 only with breast cancer (Janowsky et al. *Pub Health Nutr* 1999;2:283-91); Chlebowski RT et al. (*JNCI* 2008;100:1581-91) using 400 IU WHI trial, but favorable association with baseline 25(OH)D.

You raised it from a mutant seed, you whack it!



Classical theories of carcinogenesis

- Mutation theory: Boveri, 1902
- Two-hit theory: Knudson, 1980.
- “Many-hit” theory: A number of hits are needed (authors include Vogelstein et al., 1991).



Micro-Darwinian carcinogenesis and Vitamin D deficiency induced D-volution

- In vitamin D deficiency, the first lesion is harm to the intercellular junction.
- This unleashes natural selection.
- Natural selection is the engine of growth of the cancer.

DINOMIT Theory of Breast Cancer

Disjunction – Loss of tight junctions

Initiation – Genetic variation

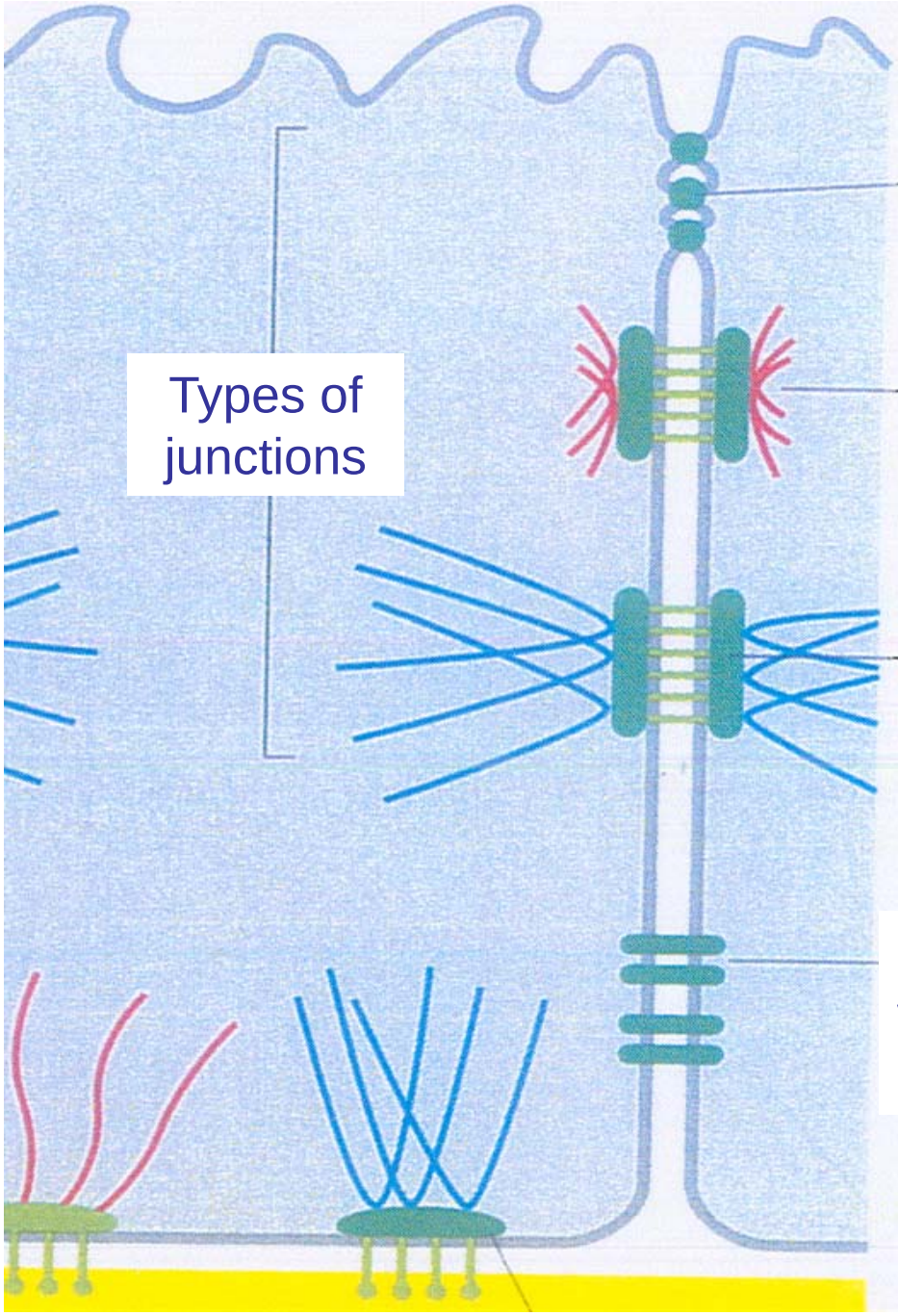
Natural selection – Competition for growth

Overgrowth – Palpable mass and invasion

Metastasis – Remote colonization

Involution – Growth inhibition

Transition – Coexistence with normal tissue



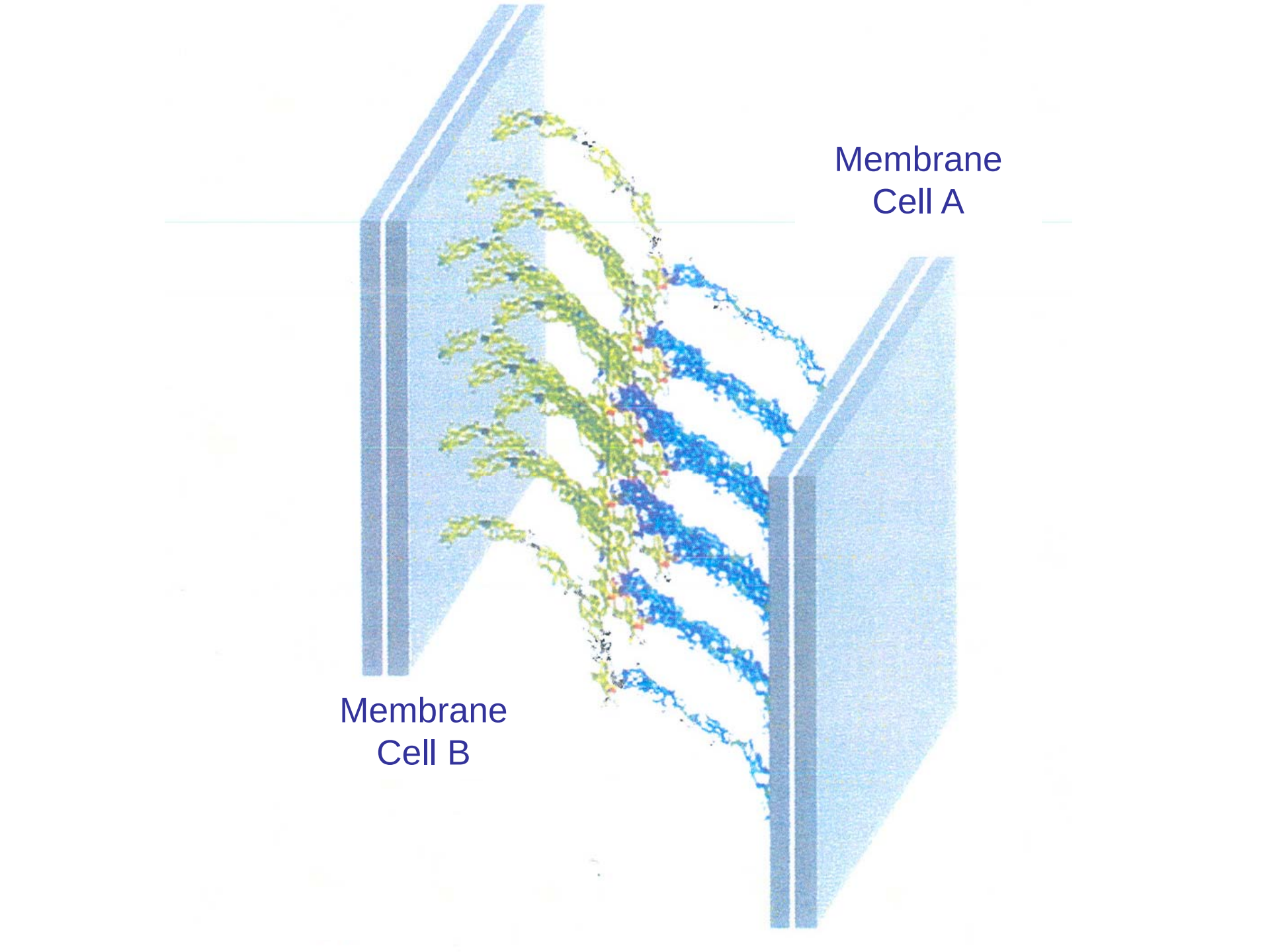
Types of junctions

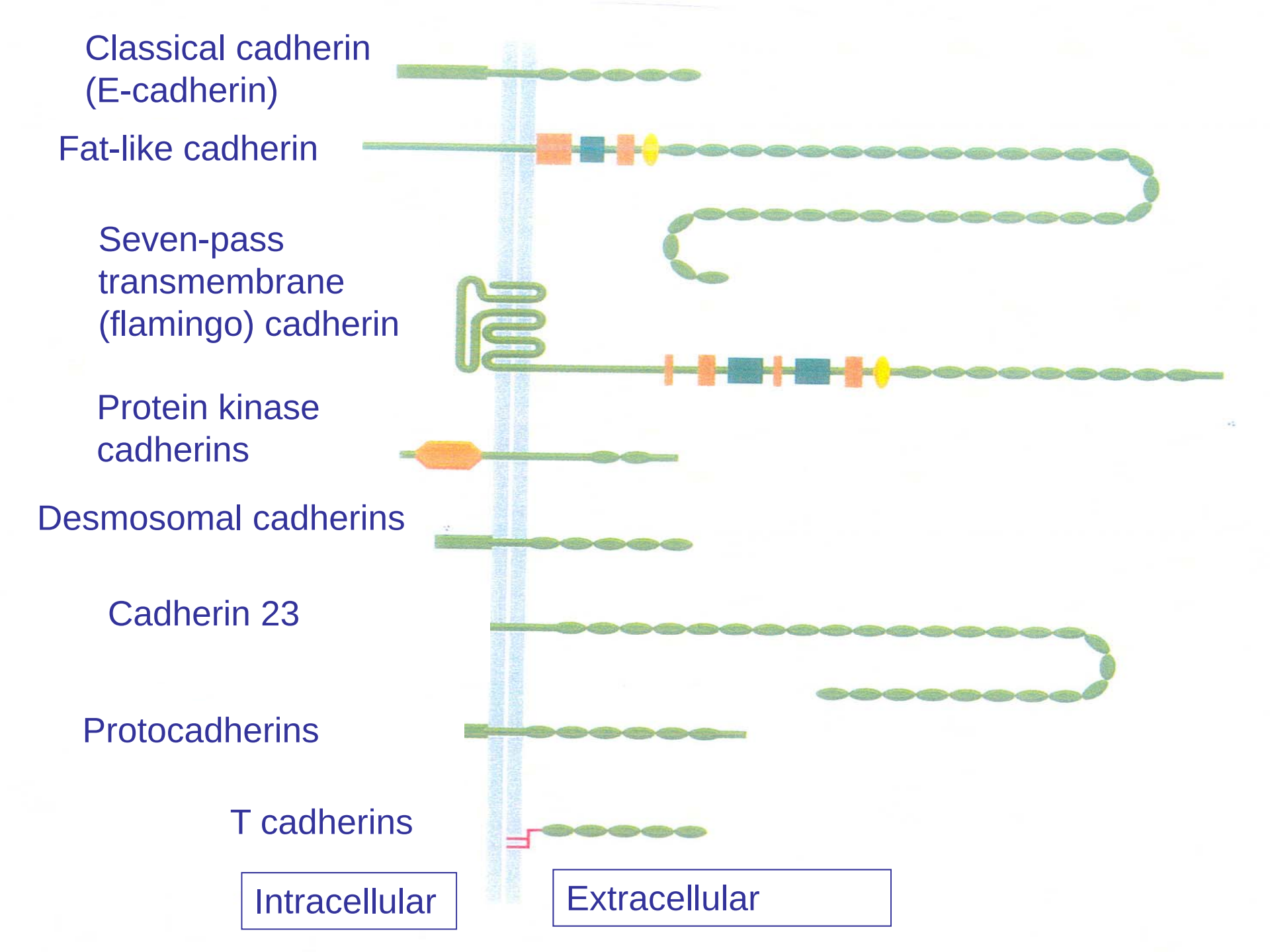
Tight junctions seal gaps between epithelial cells

Adherens junctions connect actin filament bundles between cells

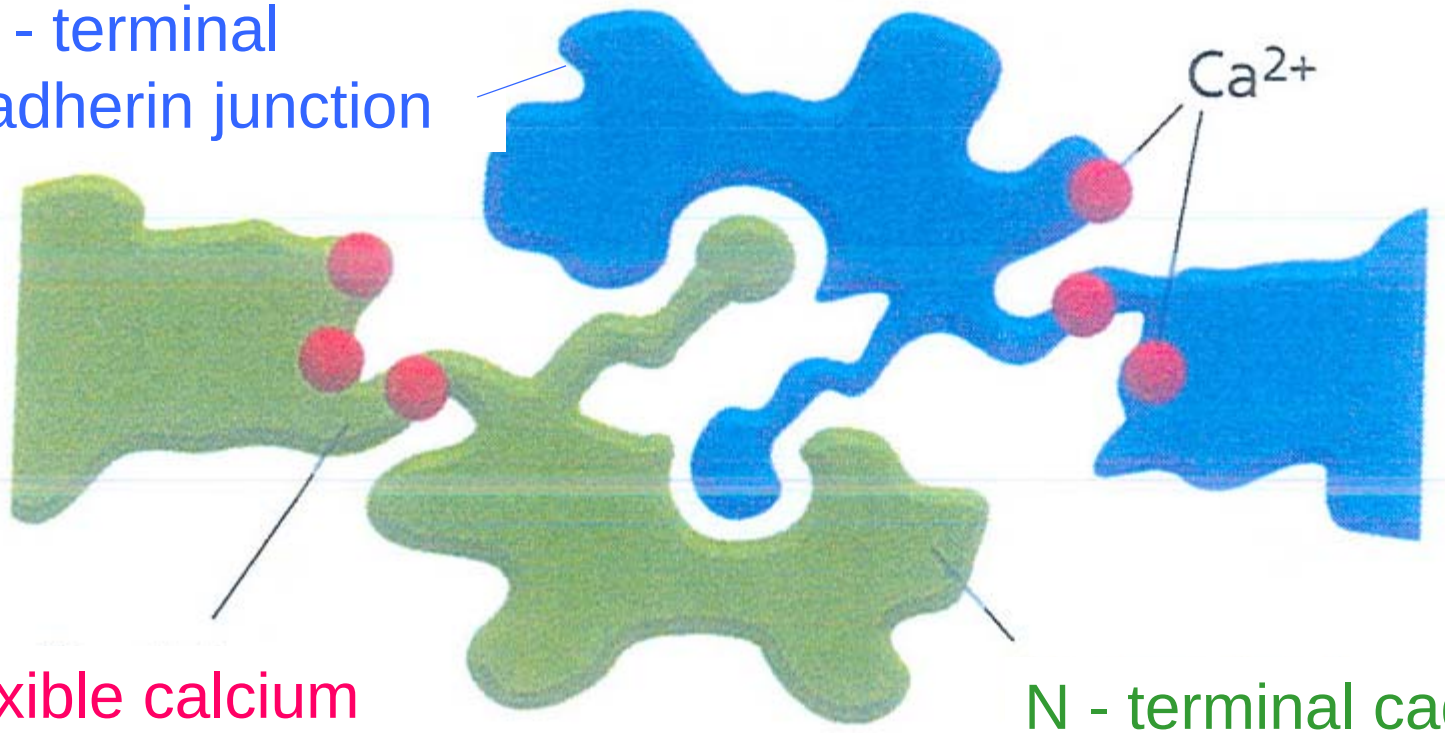
Desmosomes connect intermediate filaments in adjacent cells

Gap junctions allow passage of small water-soluble molecules between cells


Membrane
Cell A
Membrane
Cell B


Classical cadherin
(E-cadherin)
Fat-like cadherin
Seven-pass
transmembrane
(flamingo) cadherin
Protein kinase
cadherins
Desmosomal cadherins
Cadherin 23
Protocadherins
T cadherins
Intracellular
Extracellular

N - terminal cadherin junction



Flexible calcium dependent hinges

N - terminal cadherin junction

Coupling between cadherins from two cells

Gene-fold changes in a colon cancer cell line (SW480-ADH) after 48 hours exposure to 1,25 $(OH)_2$ vitamin D_3

Cytoskeleton/adhesion

+ 39 Type II keratin (hHKb1)
+ 14 Gravin
+ 12 E-cadherin
+ 7 Keratin 15
- 4 Calgizzarin

GTPases and related

+ 42 RAB2
+ 21 RA1BP1-interacting protein
+ 4 Breast cancer anti-estrogen resistance protein (BCAR3)

Channels and transporters

+30 Putative monocarboxylate transporter (MCT)
+15 3-*beta*-hydroxysteroid dehydrogenase (3-*beta*-HSD)

Apoptosis related

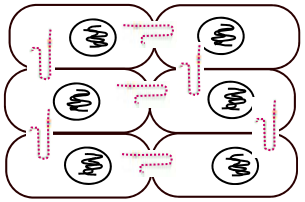
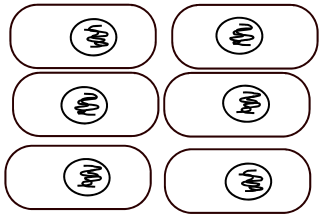
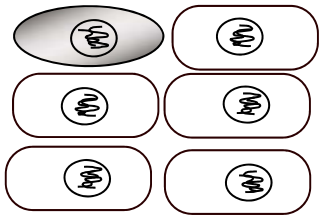
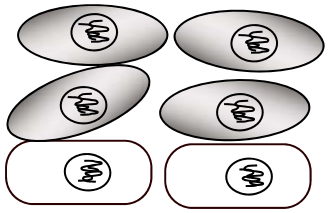
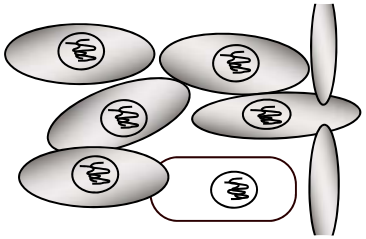
+24 Insulin-like growth factor binding protein-3 (IGFBP-3)
+11 DAP-1 *alpha*
+10 TNF-alpha converting enzyme
+7 gadd45
+6 Ceramide glucosyltransferase
+6 Prostate apoptosis response protein (par-4)
-5 CD27BP (Siva)
+74 17-*beta*- hydroxysteroid dehydrogenase (17-HSD)
+20 Cytochrome P450 III A

DNA cell cycle

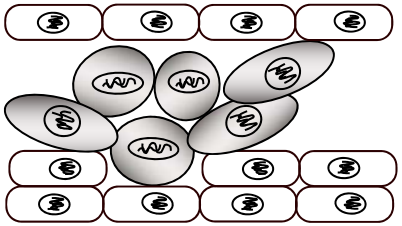
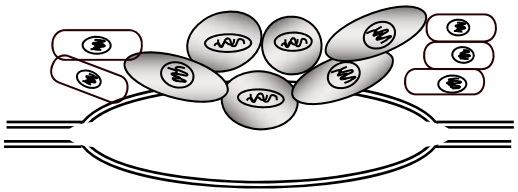
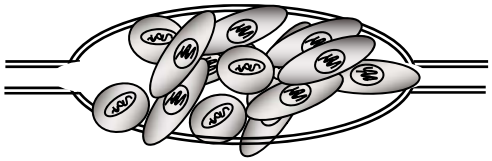
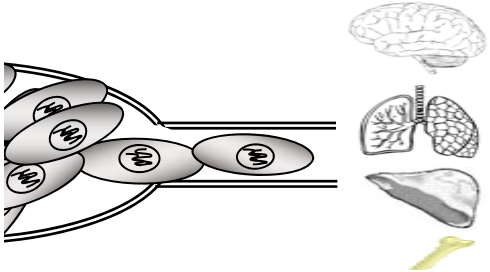
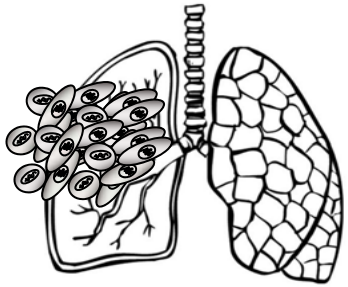
+ 24 G_0S2
- 4 Cyclin F

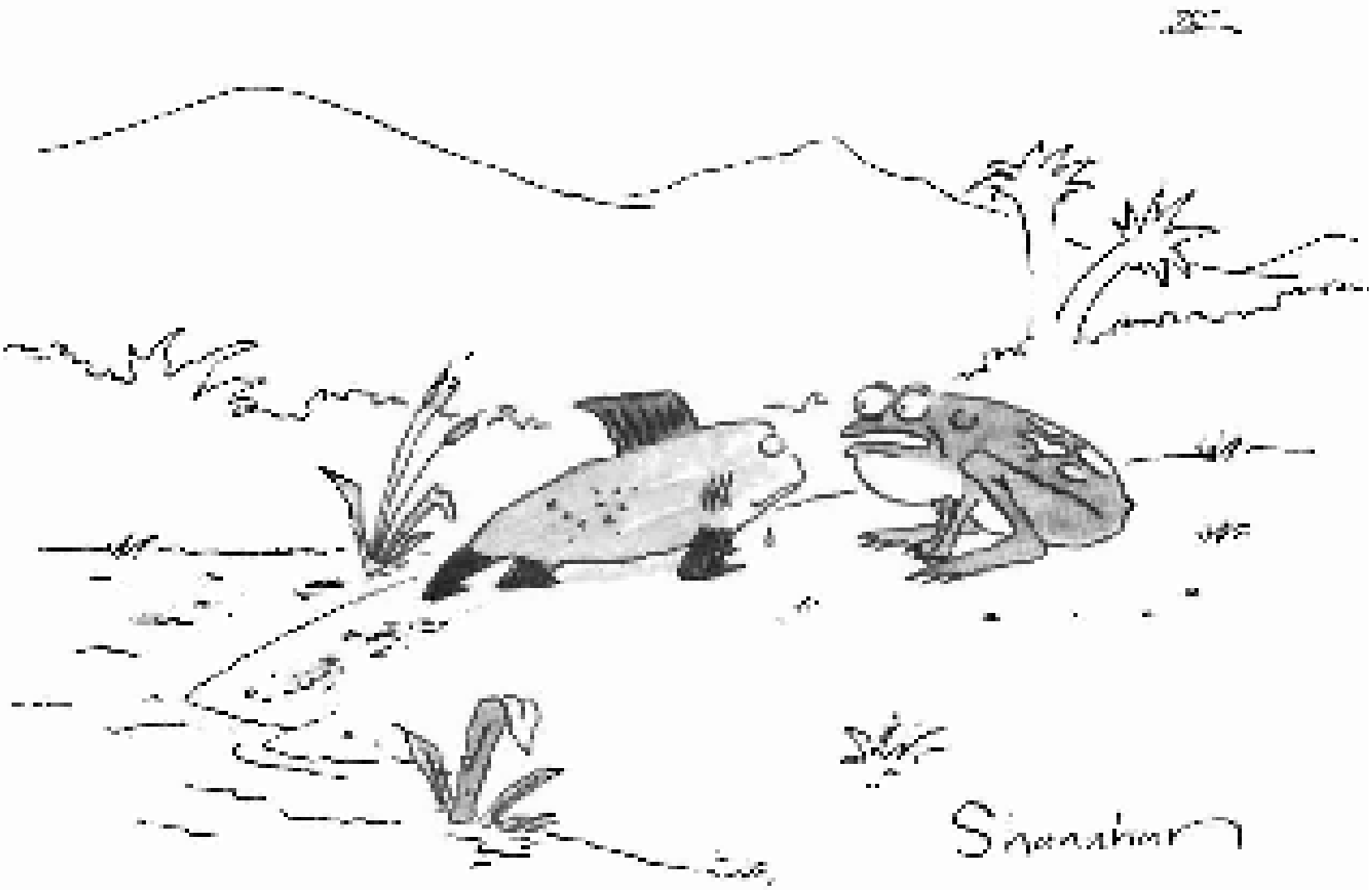
Source: Data from Palmer HG, et al. *Cancer Research* 2003;63:7799-7806.

DINOMIT Theory of Breast Cancer I

Phase	Diagram	Process	Preventive or therapeutic Action
Vitamin D Replete (Normal)		Tight junctions intact Intercellular communication, growth inhibition and cell cycle normal non-mitotic	Maintain 25(OH) D level of 40-60 ng/ml
1. Vitamin D Insufficiency Disjunction		Tight junctions weak or absent. Cells separate from each other very slightly. Cadherins lost or weak. Contact inhibition lost. Beta-catenins relocate. Natural selection begins.	Upregulation of tight junctions and cadherins by vitamin D metabolites
2. Natural Selection		Natural selection favors reproduction of rapidly mitotic, aggressive cells. These appear as new stem cells (Wicha et al., 2008)	Vitamin D maintains tight junctions, contact inhibition, and normal growth and cell cycle
3. Clonal Expansion		Rapidly mitotic, aggressive progeny predominate, a 1% advantage will fill compartment in 9000 generations	Vitamin D favors apoptosis and normal cell cycle
4. Lysis and Penetration of Basement Membrane		Most aggressive cells compete for nutrients and oxygen, and penetrate basement membrane	Vitamin D inhibits lysis of basement membrane, Promotes sharing of micronutrients; Maintains intercellular junctions and desmosomes

DINOMIT Theory II

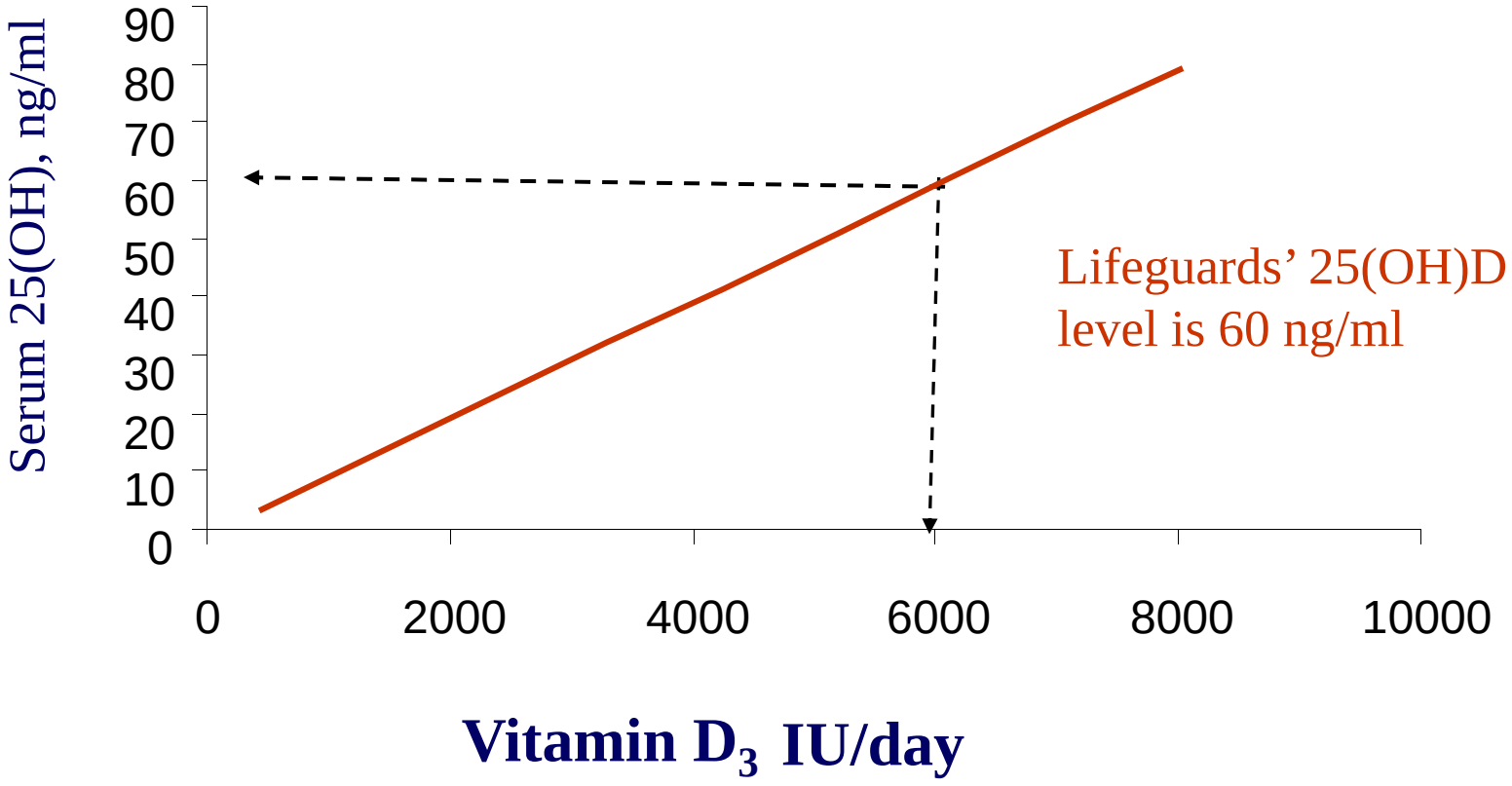
Phase	Diagram	Description	Prevention or Therapeutic Action
5. Stromal Phase		Invasion of Stroma	Re-establish tight junctions between cancer cells
6. Lymphatic Entry Phase		Lymph vessel invasion	Re-establish tight junctions Prevent lymphatic entry
7. Lymphatic Growth Phase		Lymph node colonization	Re-establish tight junctions Confine malignancy to lymph nodes
8. Lymphatic Transport Phase		Lymphatic transport to brain, lung, liver, bone	None
9. Metastasis (colonization) Phase		Malignant cells colonize remote host site	If VDR still present, re-establish tight junctions, downregulate VEGF, reduce growth rate, restore contact inhibition



The first thing you need to do is update your *CV*

Serum 25(OH)D by oral intake of vitamin D_3

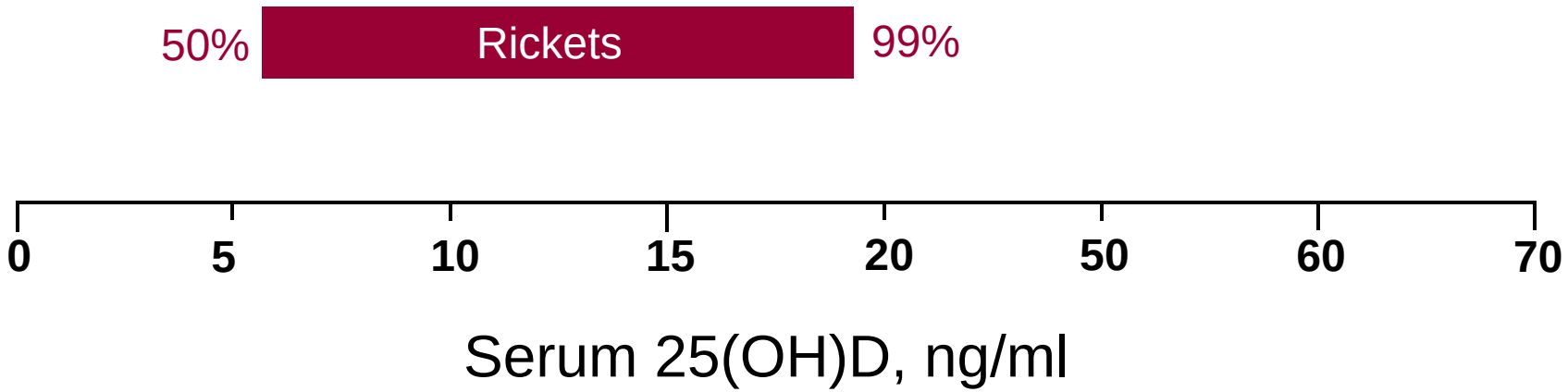
Rule of thumb: Each 1000 IU of vitamin D_3 intake increases serum 25(OH)D by approximately 10 ng/ml



Sources: 1. Barger-Lux et al. Osteoporosis Intl 1998; 8: 222-30;

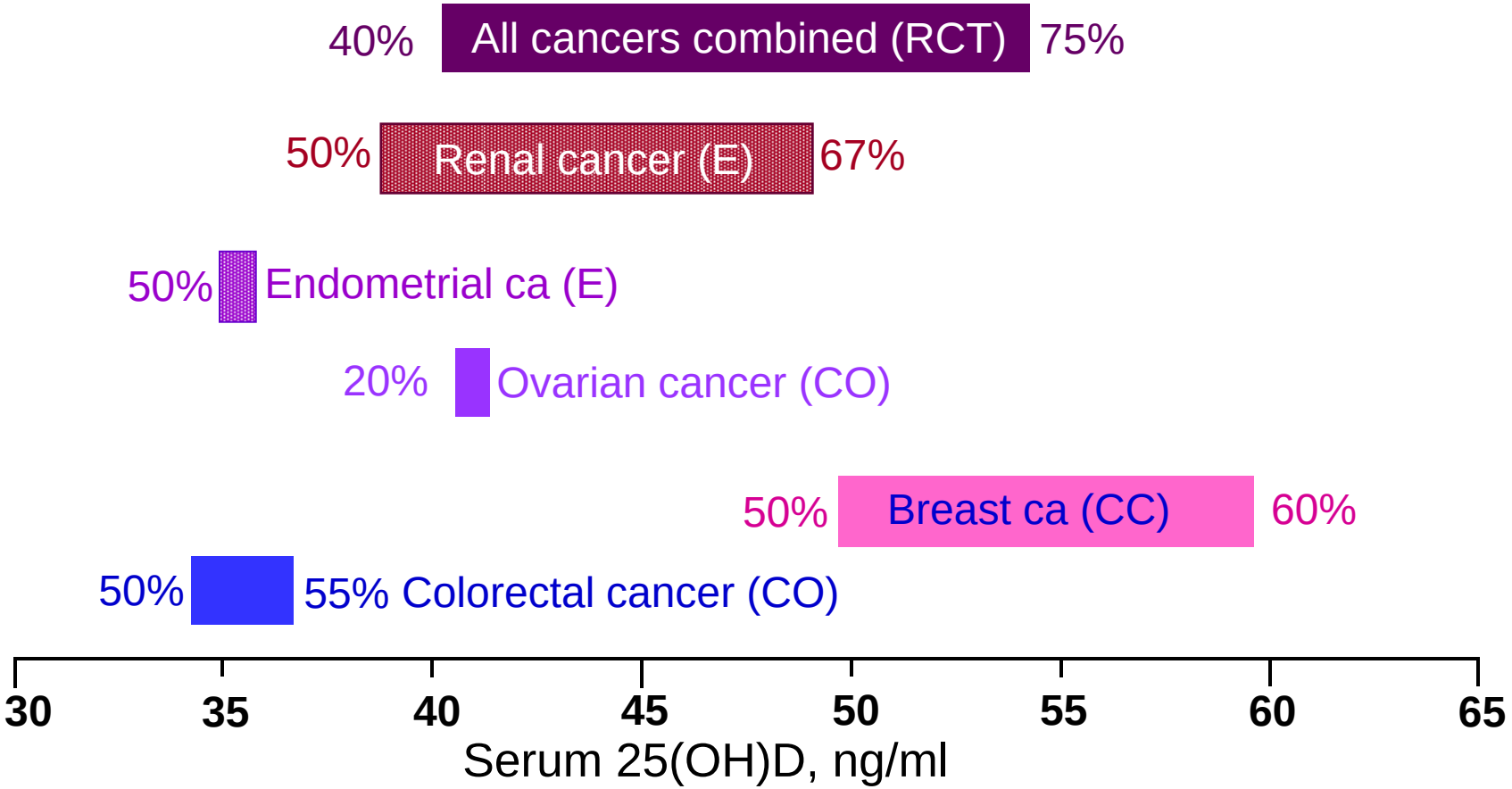
2. Haddad and Chyu. Clin Endocrinol Metab 1971; 33: 992-5.

Proportion of Rickets Prevented, by Serum 25(OH) D Level



Source: Arnaud SB et al. Serum 25-hydroxyvitamin D in infantile rickets. *Pediatrics*. 1976 Feb;57(2):221-5

Estimated Approximate Proportion of Preventable Cancers



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Tworoger SS, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:783-8.

Mohr SB, et al. Prev Med. 2007;45:323-4.

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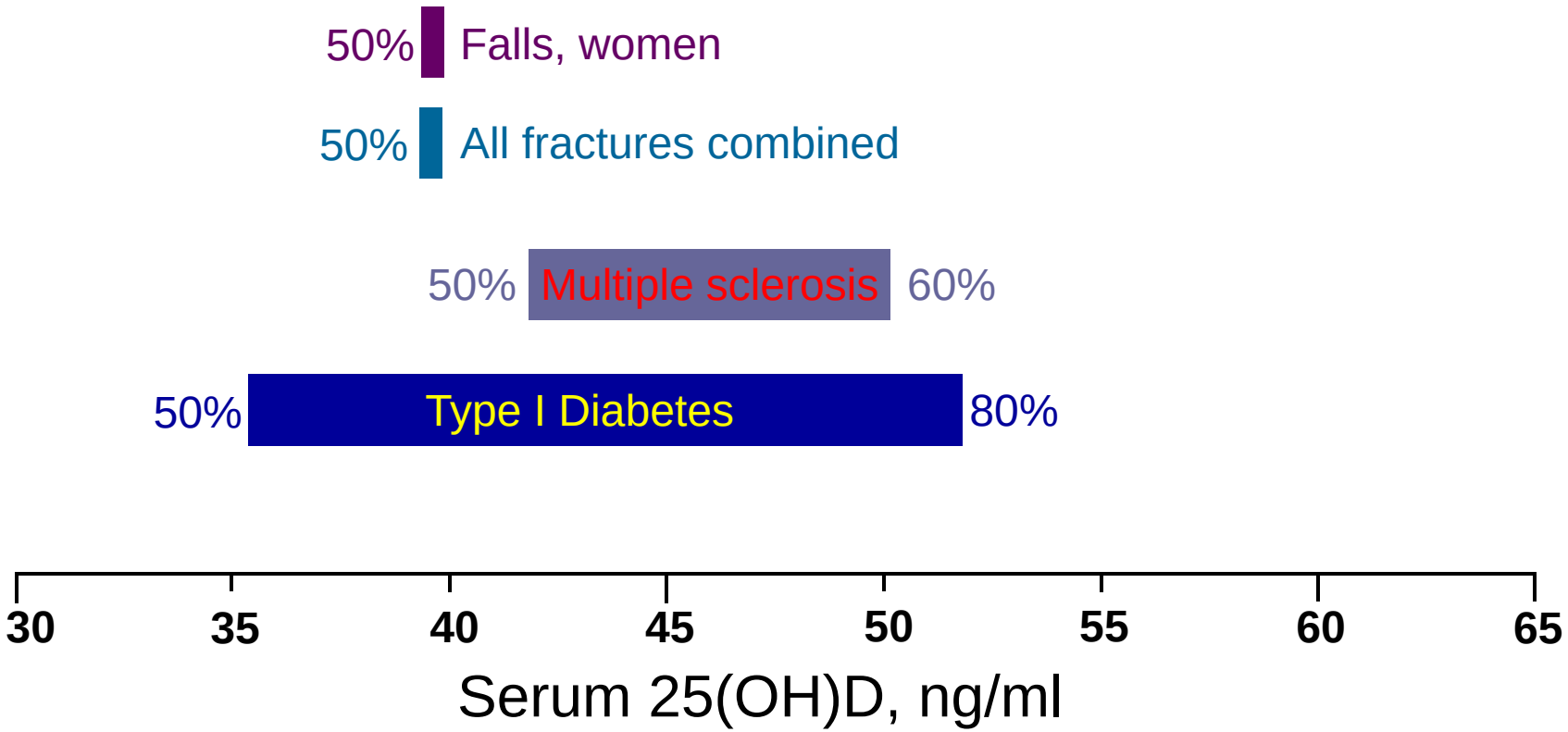
Estimated Proportion of other Conditions Preventable by Specified Range of Serum 25(OH) D Level



Hyppönen E, et al. Lancet 2001;358:1500-3.

Munger KL, et al. JAMA. 2006;296:2832-8.

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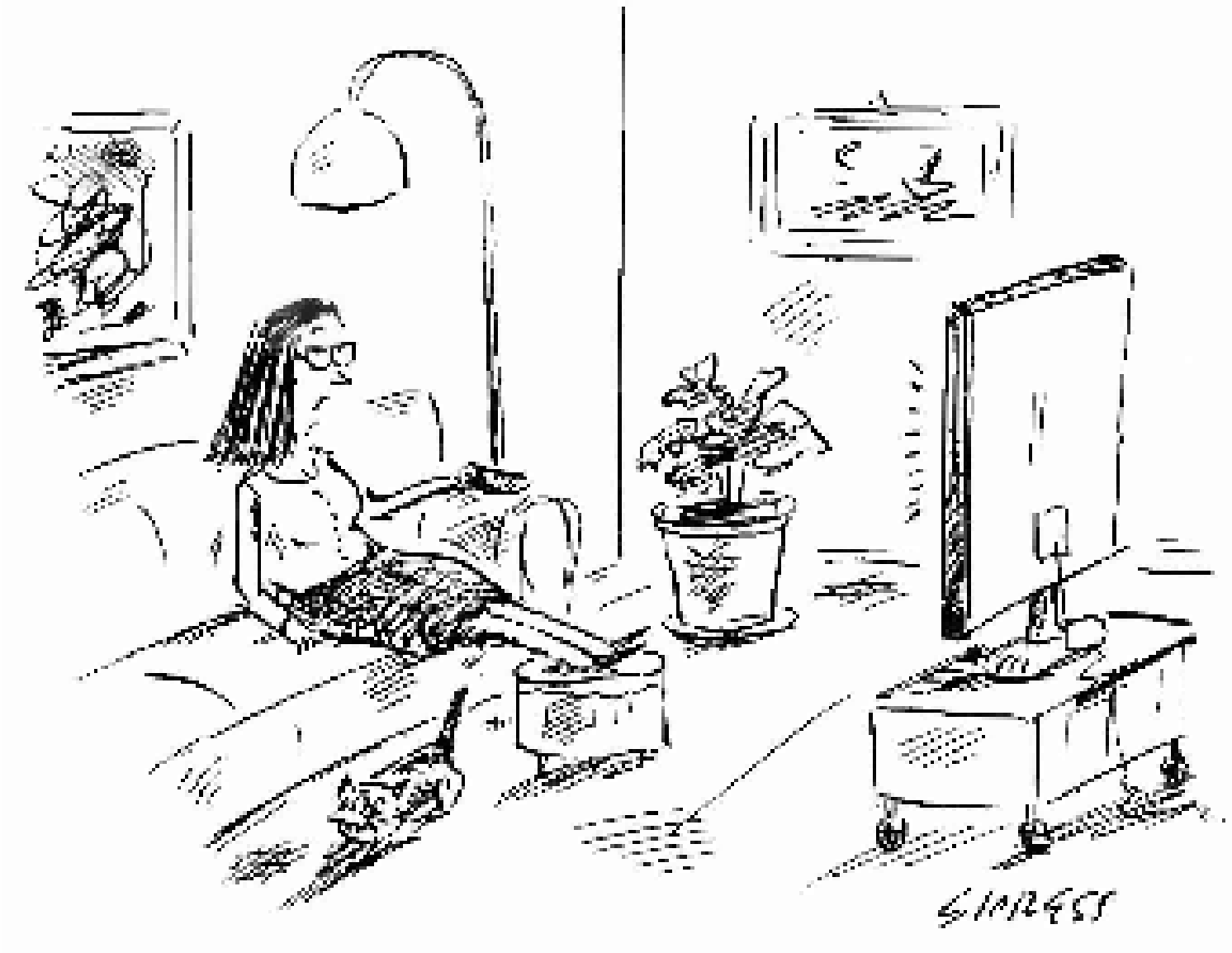


Ask your doctor if taking a pill to solve all your problems is right for you

Gauging Vitamin D Status for Breast Cancer Prevention

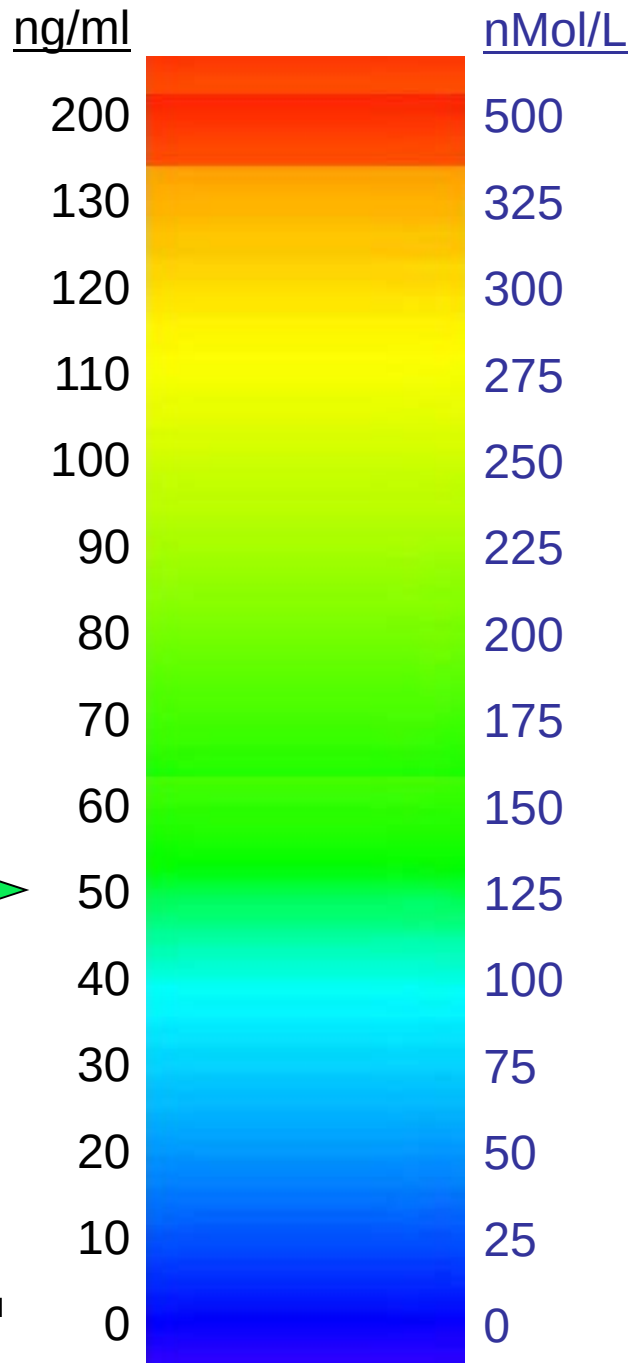
What is the optimal serum 25 (OH) Vitamin D concentration for breast cancer prevention?

People living in sunny places have serum 25(OH)D levels of 54 to 90 ng/ml (1). Adults excrete 3,000-5,000 IU/day of vitamin D metabolites (2).

A good clinical target for breast cancer prevention:

50 nanograms/ml

Rule of thumb: For every 1000 IU of vitamin D_3 you give, serum 25 (OH)D increases 10 ng/ml. If current level is 20 ng/ml you should give 4,000 IU to raise it to 50 ng/ml (2).



1. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22

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Breast Cancer
Primary Prevention Plan

Vitamin D_3:

Serum target, all ages…40-60 ng/ml

Oral intake……1,000-2,000 IU/day

or as needed for above serum level

Recommend 6 cups/day of fluids (l500 ml) and 1000 mg/day of calcium, or as needed for bone density.

Breast cancer patients

Secondary prevention plan I

_Draw blood for serum 25-hydroxyvitamin D, calcium and ionized calcium.

_Start patients with breast adenocarcinoma on 2000 IU/day of vitamin D_3 and 1000 mg/day of calcium, unless hypercalcemic, regardless of other treatment.

_Titrate vitamin D_3 intake upward to maintain 55-60 ng/ml 25-hydroxyvitamin D_3

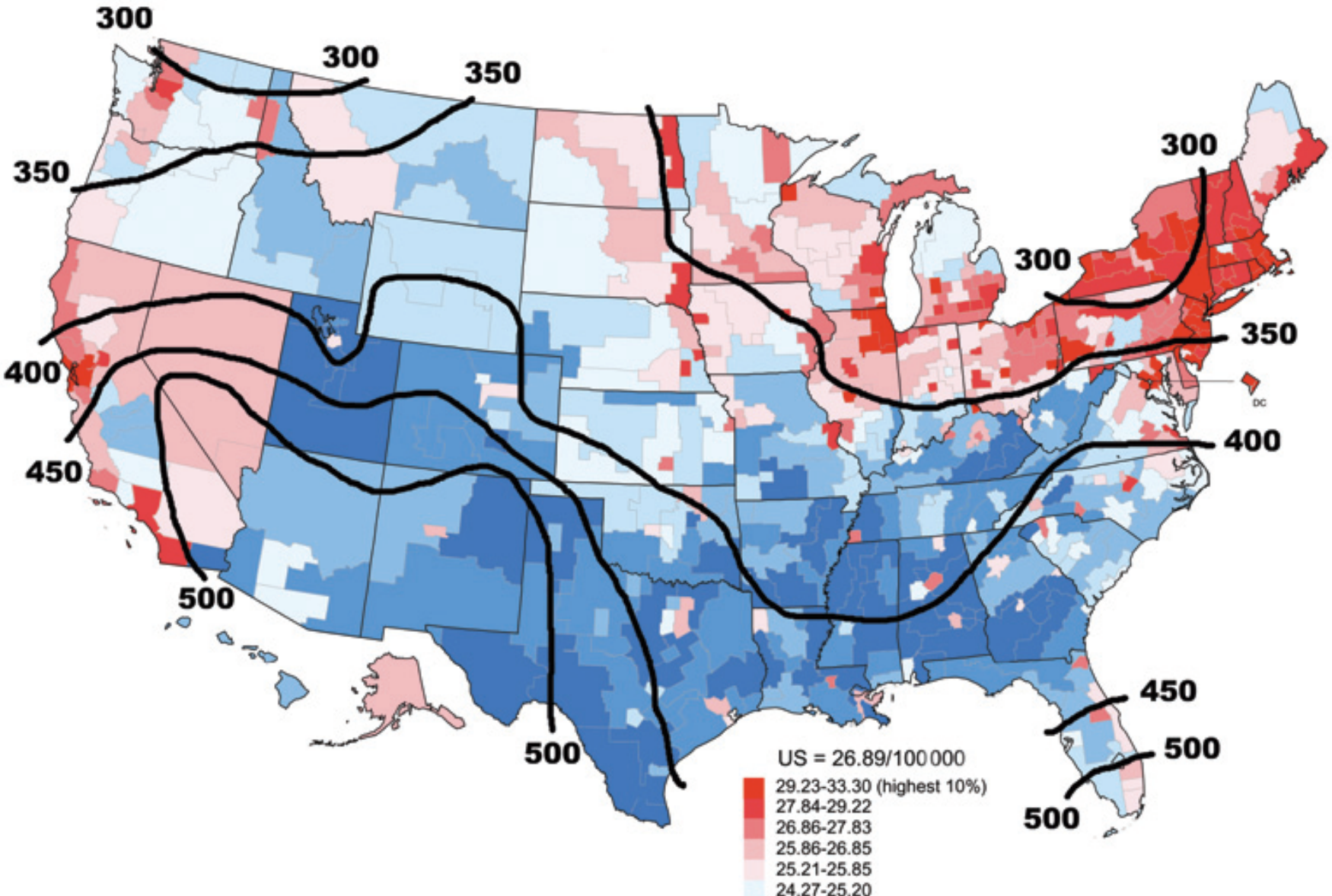
Breast cancer patients

Secondary prevention plan II

_Re-test serum 25-hydroxyvitamin D and calcium monthly.

_For selected patients, consider suggesting not more than 10 minutes/day outdoors near solar noon, weather allowing, with 40% skin exposure, unless there is a history of skin cancer or photosensitivity. No sunscreen for 10 minutes. Goal is is 0.75 minimal erythemal dose (MED)/day.

_Maintain fluid intake (≥1500 ml/day).


300
300
350
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300
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400
400
450
500
500
450
500
500
DC
US = 26.89/100 000
29.23-33.30 (highest 10%)
27.84-29.22
26.86-27.83
25.86-26.85
25.21-25.85
24.27-25.20

DINOMIT 7-Phase Theory of Breast Cancer

Disjunction – Loss of tight junctions in breast epithelium

Initiation – Genetic variation

Natural selection – Competition and selection

Overgrowth – Palpable mass and invasion

Metastasis – Remote colonization

Involution – Inhibition of growth advance

Transition – Coexistence with normal tissue