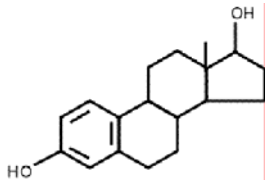


Vitamina D: más allá de la osteoporosis

José A. Riancho

Servicio de Medicina Interna

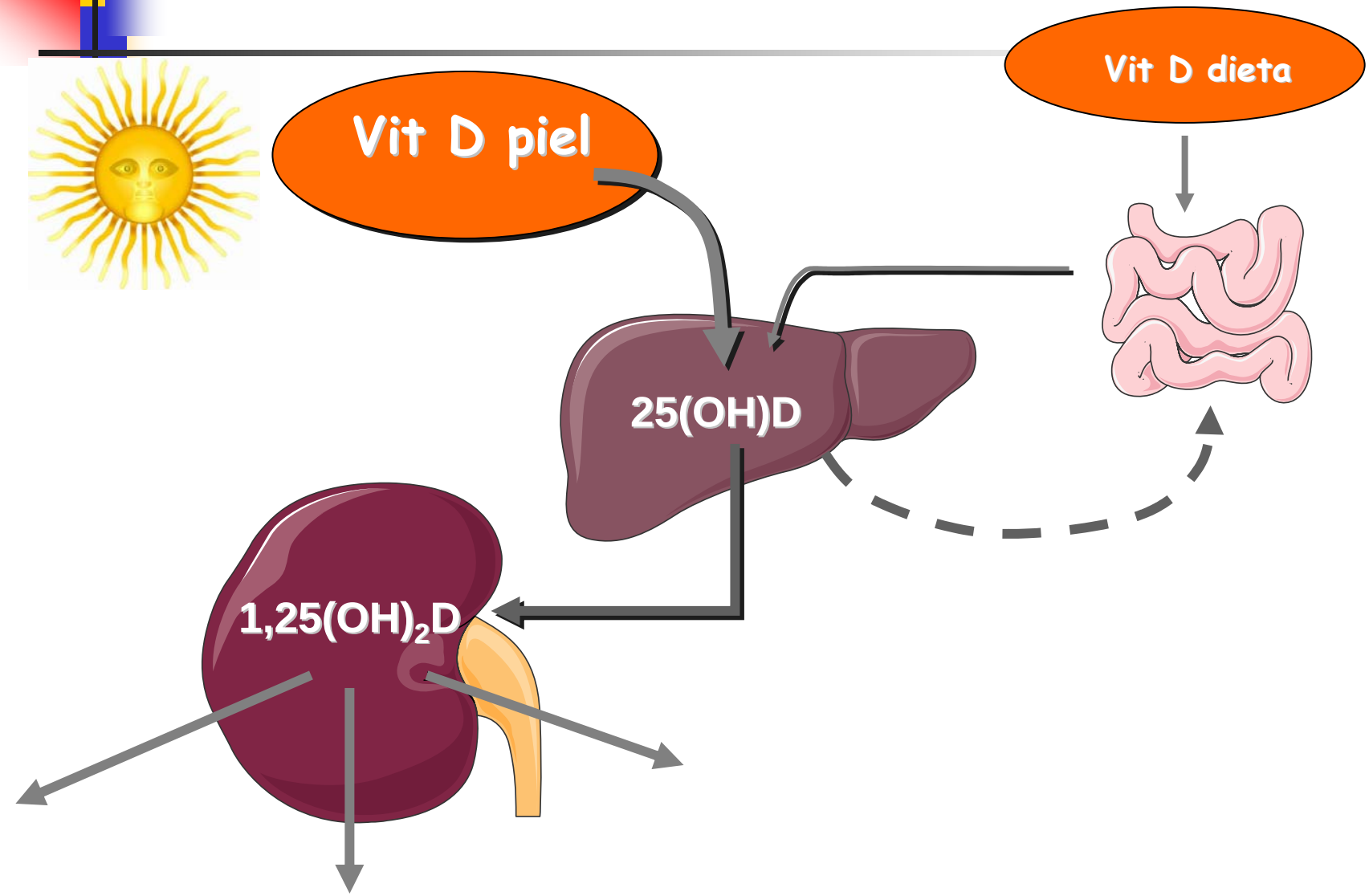
Hospital U.M. Valdecilla

Universidad de Cantabria

Santander

XXX Congreso Nacional de la SEMI. Valencia, Noviembre 2009

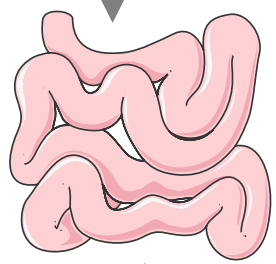
Metabolismo de la vitamina D



Metabolismo de la vitamina D

Vit D piel

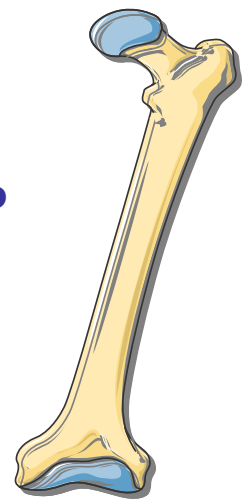
Vit D dieta



25(OH)D

$1,25(OH)_2D$

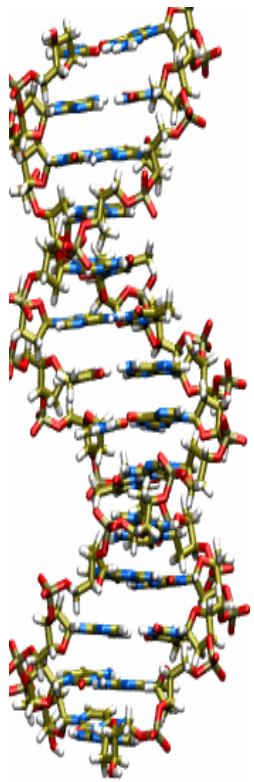
- ↑ Absorción intestinal Ca,P
- ↑ Reabsorción renal Ca
- ↓ Secreción PTH
- Diferenciación cel óseas



Receptor de vit D

$1,25(OH)_2D_3$

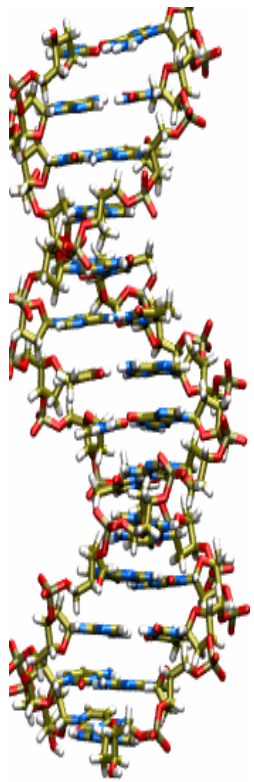
RVD



Receptor de vit D

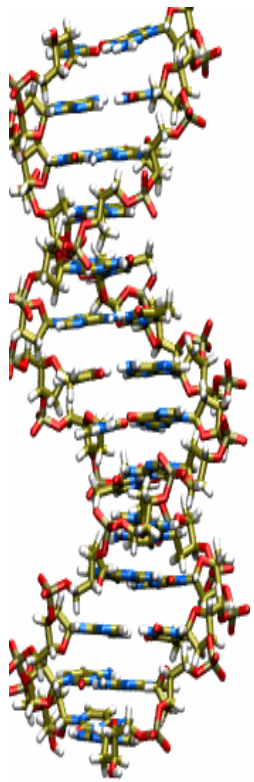
$1,25(OH)_2D_3$

RVD

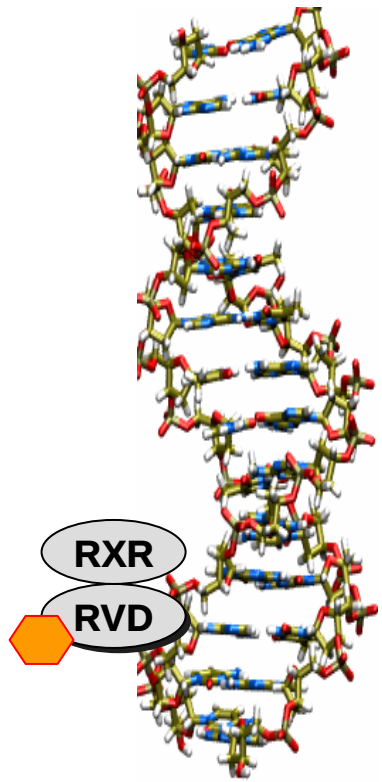


Receptor de vit D

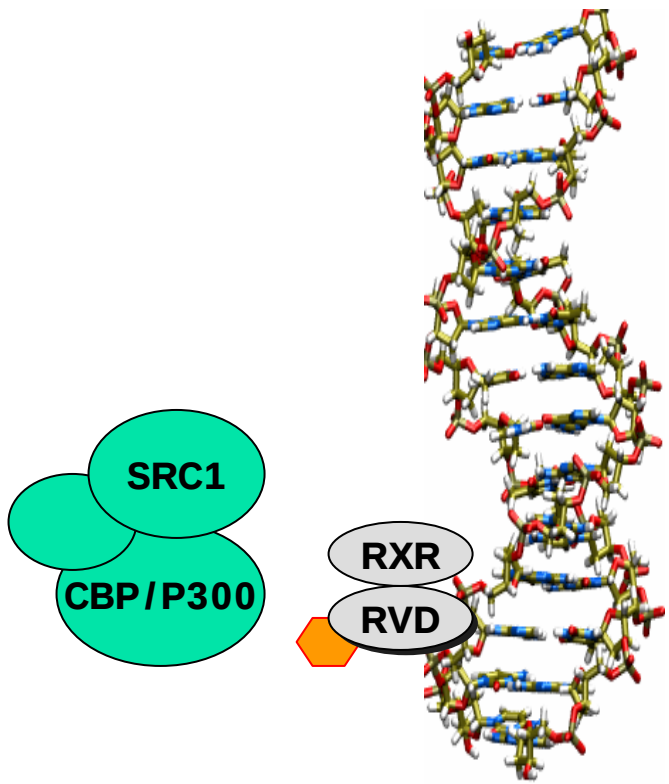
RVD



Receptor de vit D



Receptor de vit D



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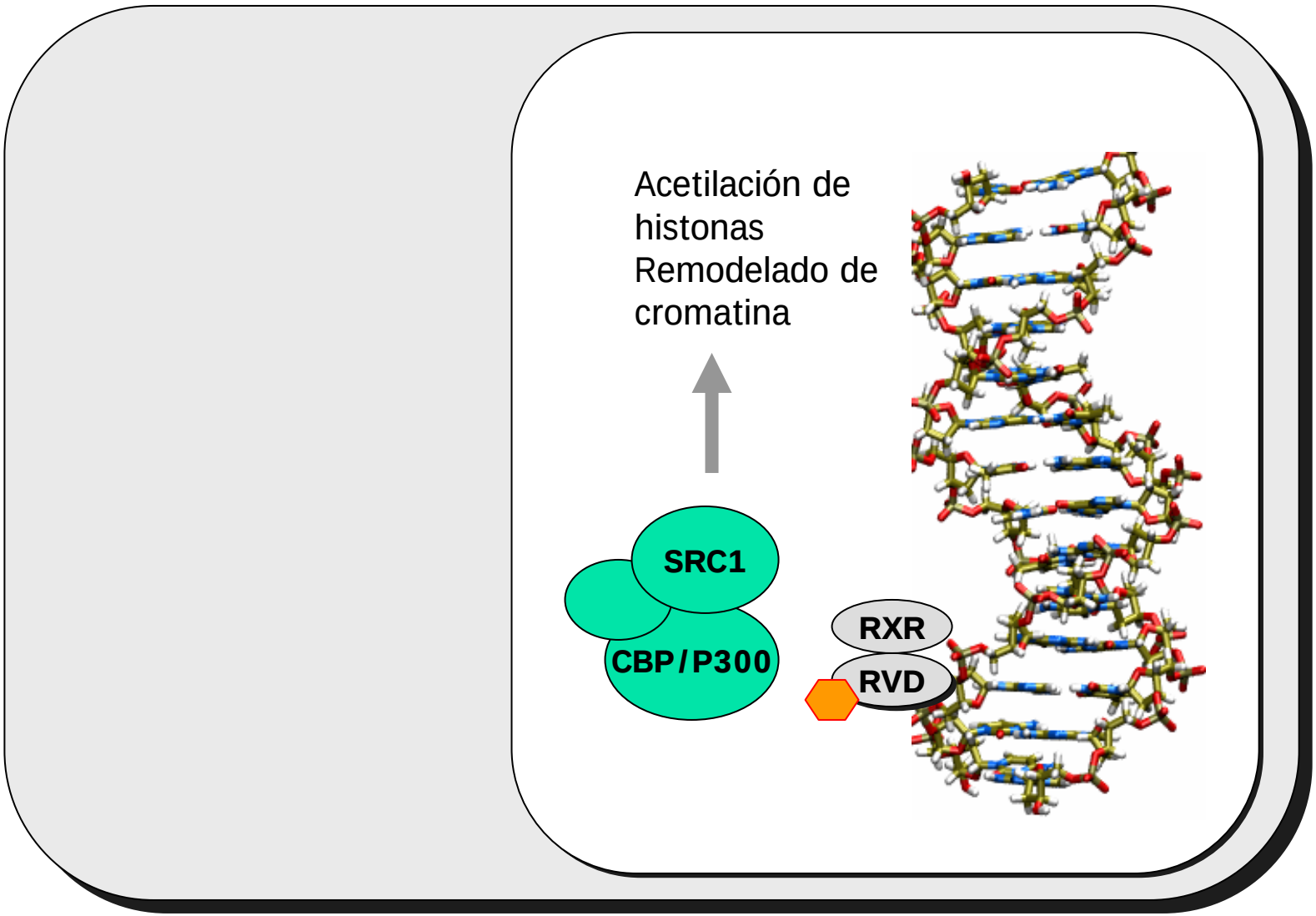
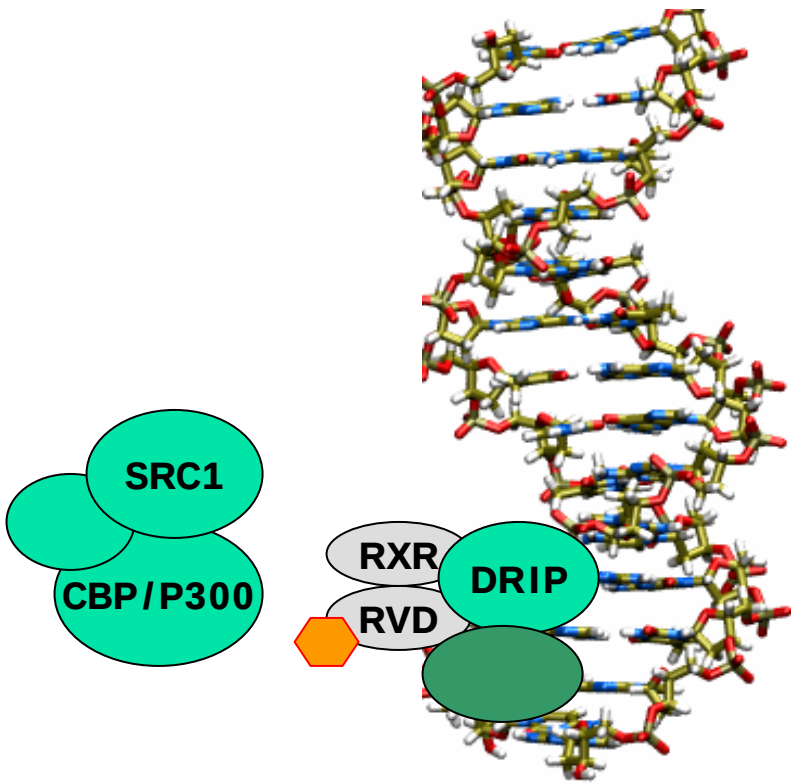
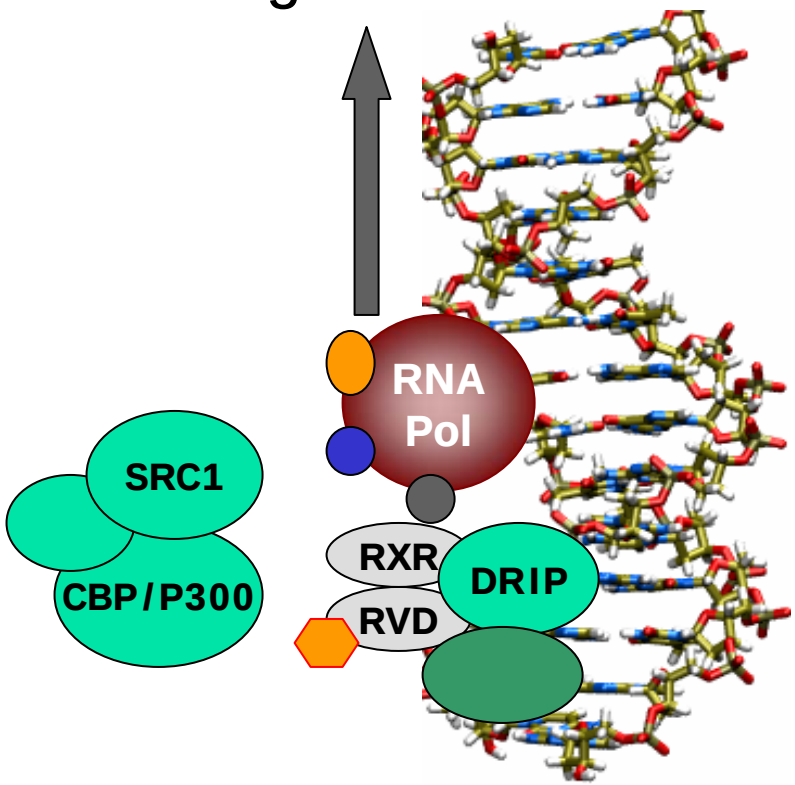


Receptor de vit D

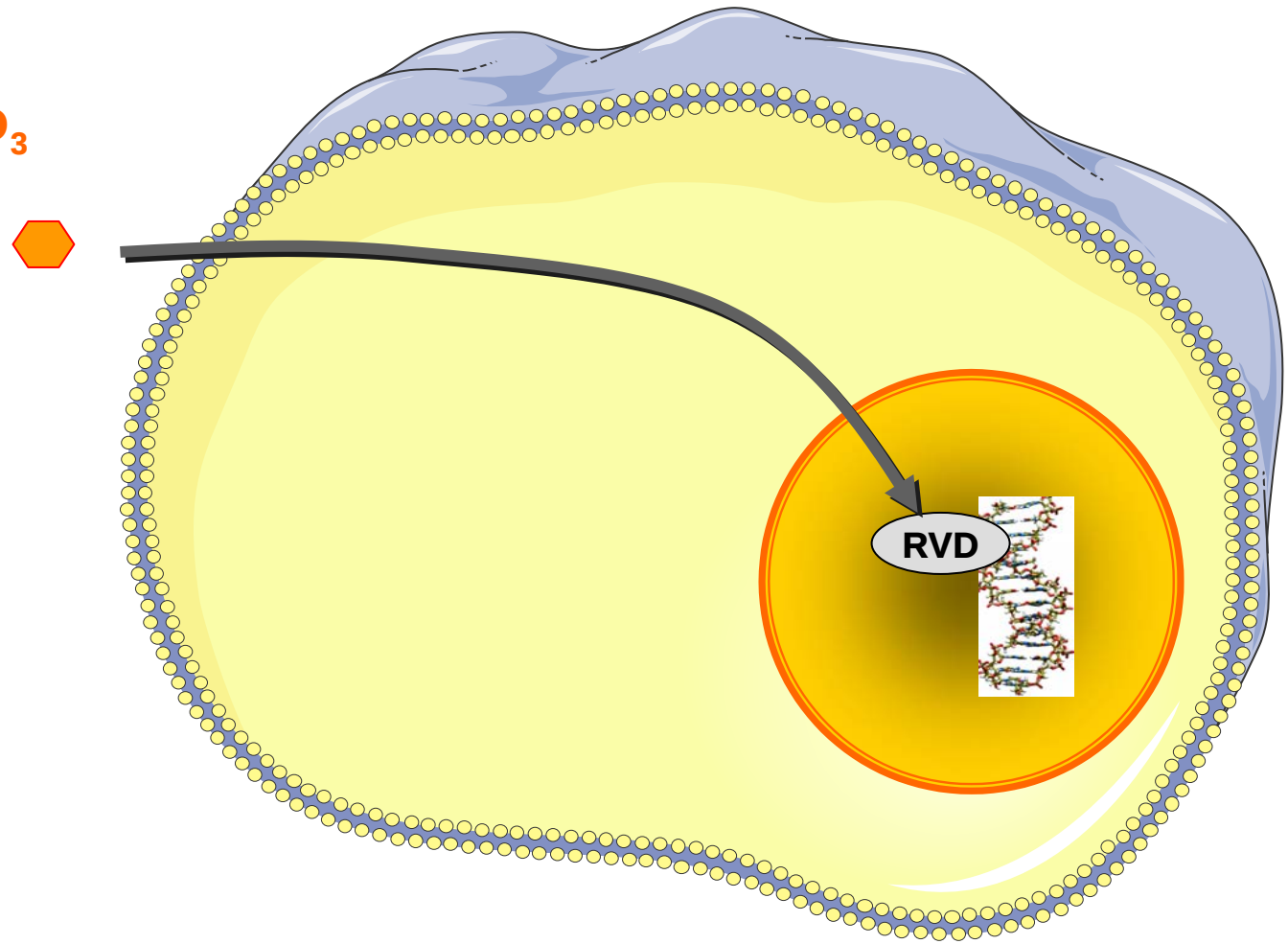


Receptor de vit D



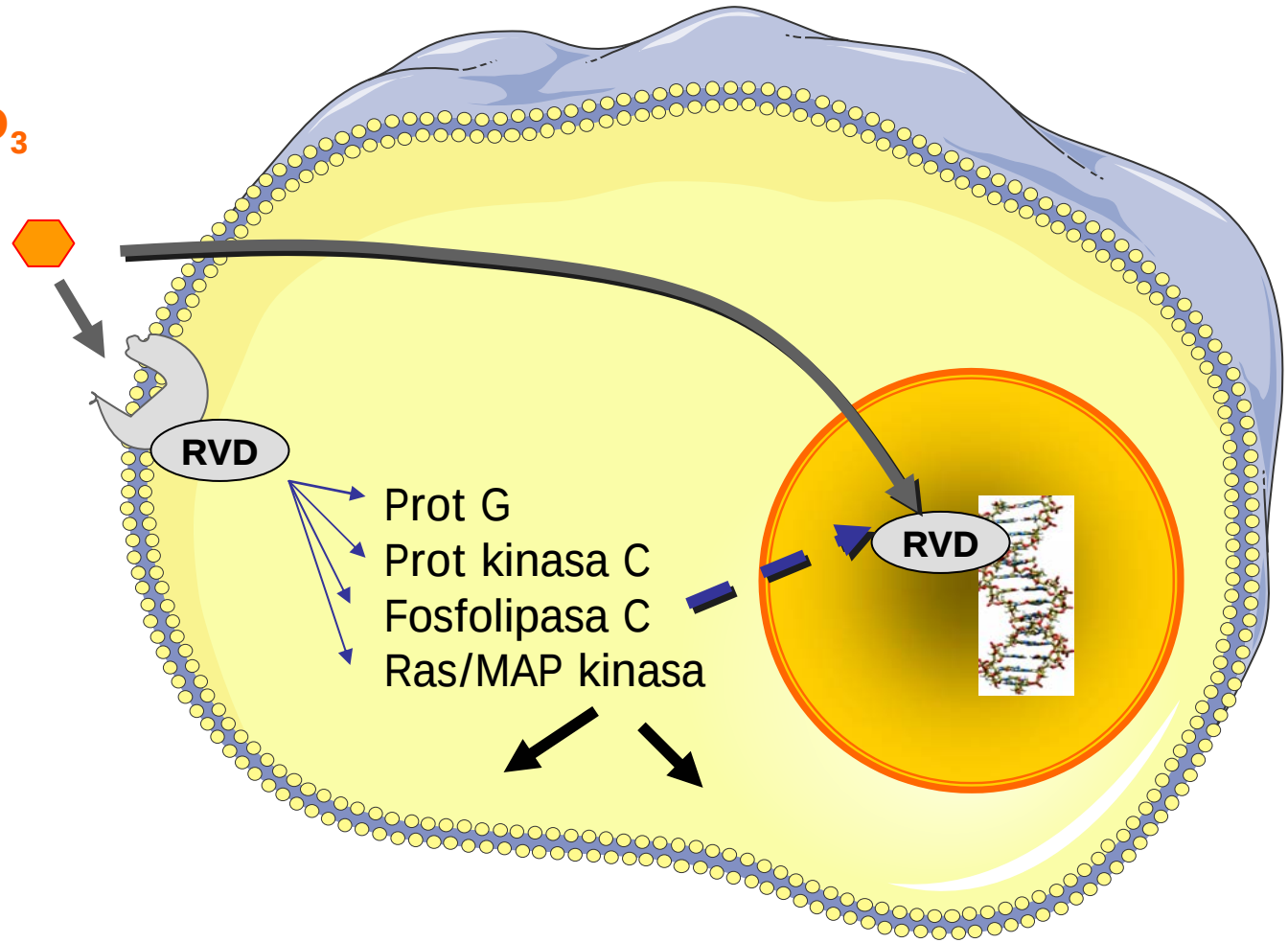
Vit D: acciones no genómicas

$1,25(OH)_2D_3$



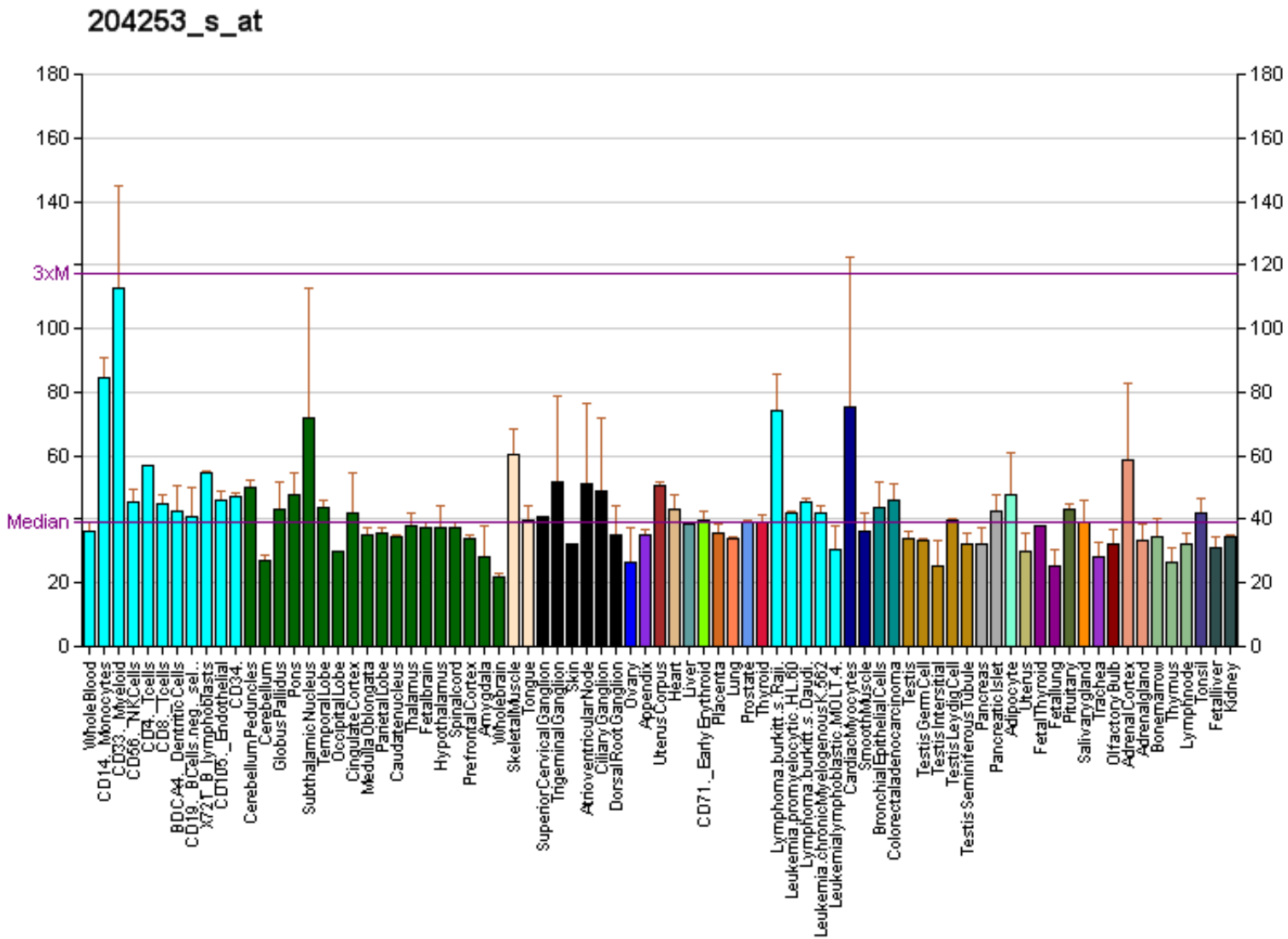
Vit D: acciones no genómicas

$1,25(OH)_2D_3$



Basado en Norman. Endocrinology 2006

Ubicuidad del Receptor de Vit D



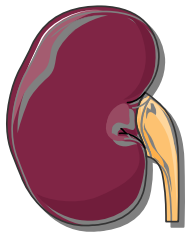
Expresión de 1-hidroxilasa (CYP27b1)

- **Riñón** (TP)

Expresión de 1-hidroxilasa (CYP27b1)

- **Riñón** (TP)
- Epitelios
  - Piel
  - Próstata
  - Colon
  - Mama
  - Endometrio
- Sist. Inmune
  - Monocitos /macrófagos
  - Cel. Dendrítica
- Hueso
  - Osteoblastos
  - Condrocitos
- Glándulas
  - Paratiroides
  - Tiroides
  - Páncreas
- Placenta
- Cerebro
- ...
- ...
- Tumores

Vitamina D: sistema endocrino y auto/paracrino

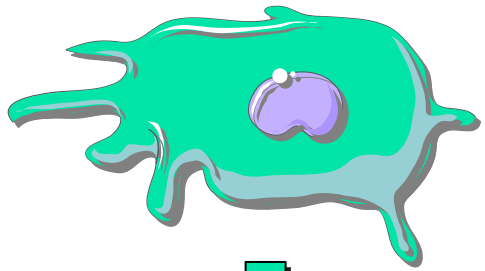


$1,25(OH)_2D_3$

Sangre

Efectos sistémicos (intestino, hueso, paratiroides)

Metabolismo mineral

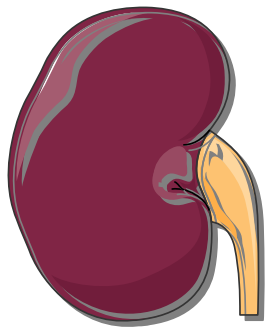


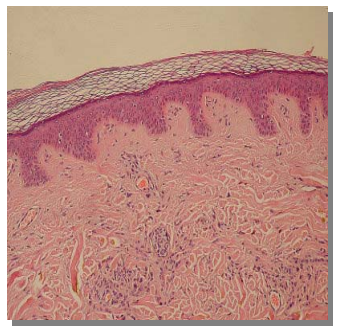
$1,25(OH)_2D_3$

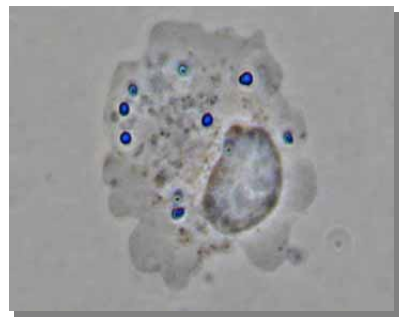
Efectos locales

Diferenciación y actividad celulares

Regulación de 1-hidroxilasa (CYP27b1)

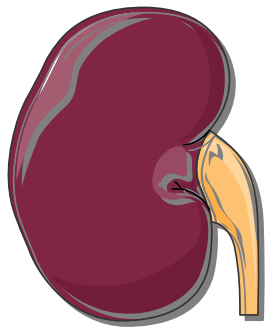


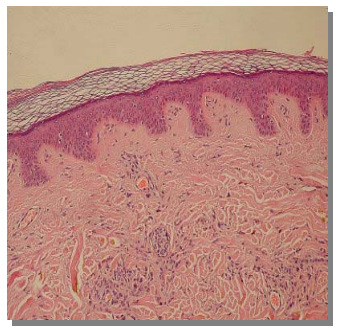


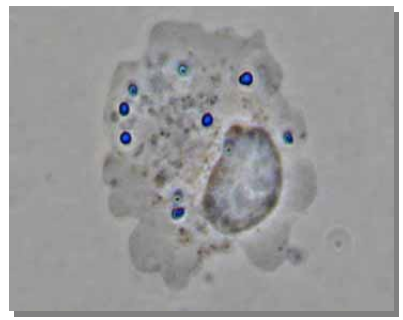


PTH	+
FGF-23	-
$1,25(OH)_2D_3$	-
(↓Ca, ↓ P)	+

Regulación de 1-hidroxilasa (CYP27b1)



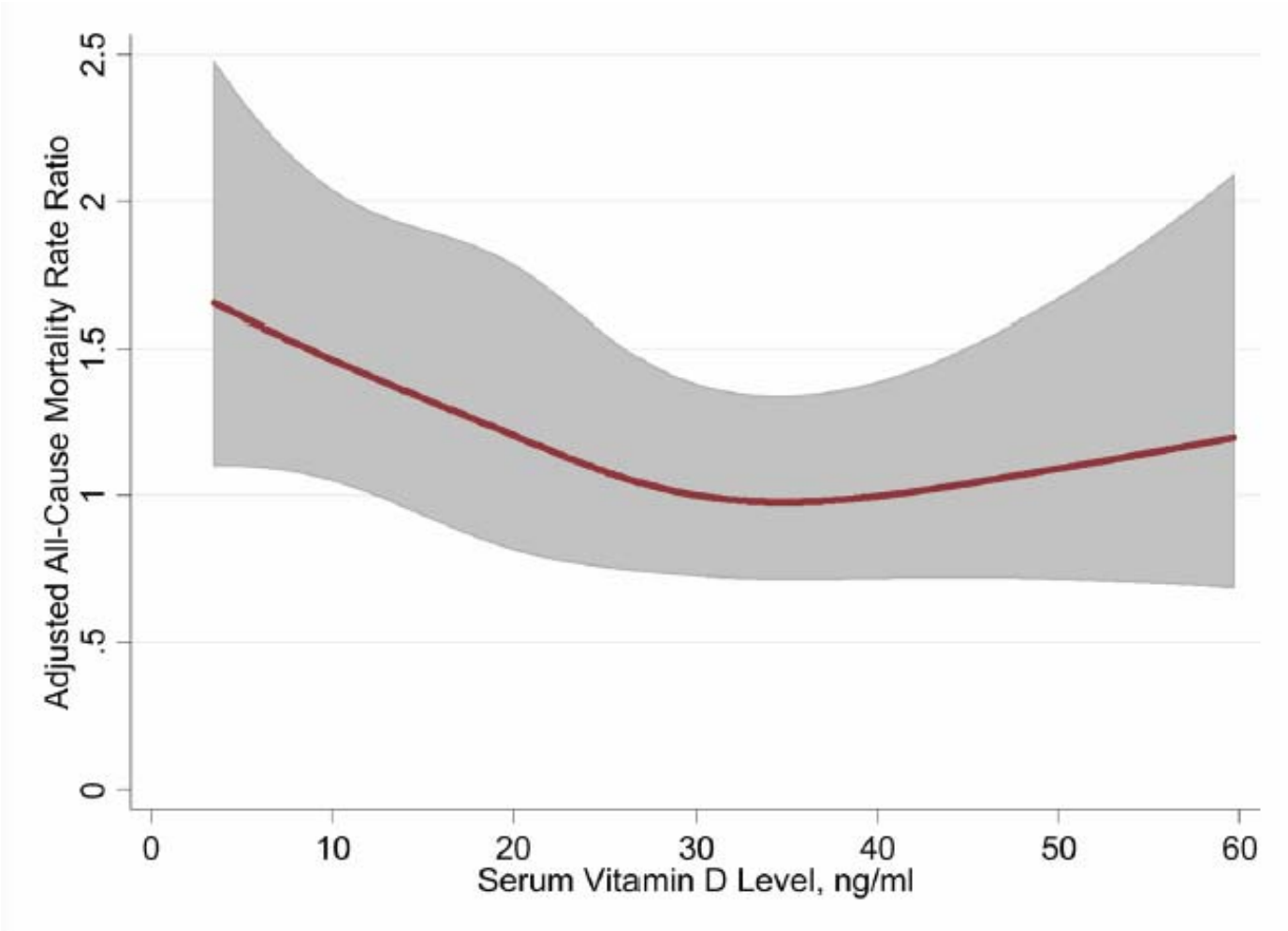




PTH	+	+	No efecto
FGF-23	-		
$1,25(OH)_2D_3$	-		
(↓Ca, ↓ P)	+		
TNFα		+	+
IFNγ		+	+
LPS			+

¿ **Q**ué importancia tienen los efectos extra-esqueléticos de la vitamina D ?

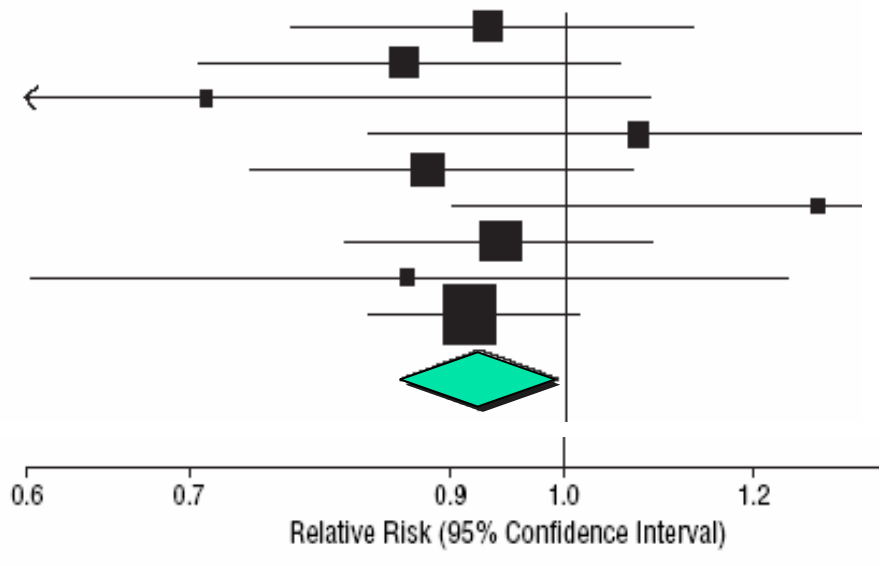
Niveles de Vit D y mortalidad global (NHANES III)



Melamed Arch Intern Med 2008

Suplementos de Vit D y mortalidad global

Trials With Decent Statistical Power	No. of Deaths/No. of Participants	
	Intervention Group	Control Group
Chapuy et al,[29] 1992	258/1634	274/1636
Lips et al,[30] 1996	223/1291	251/1287
Chapuy et al,[33] 2002	71/393	45/190
Meyer et al,[34] 2002	169/569	163/575
Trivedi et al,[16] 2003	224/1345	247/1341
Porthouse et al,[39] 2005	57/1321	68/1993
RECORD Trial,[28] 2005	438/2649	460/2643
Flicker et al,[40] 2004	76/312	85/313
Jackson et al,[42] 2006	744/18 176	807/18 106
Subtotal SRR (95% CI)		**0.92 (0.86-0.99)**

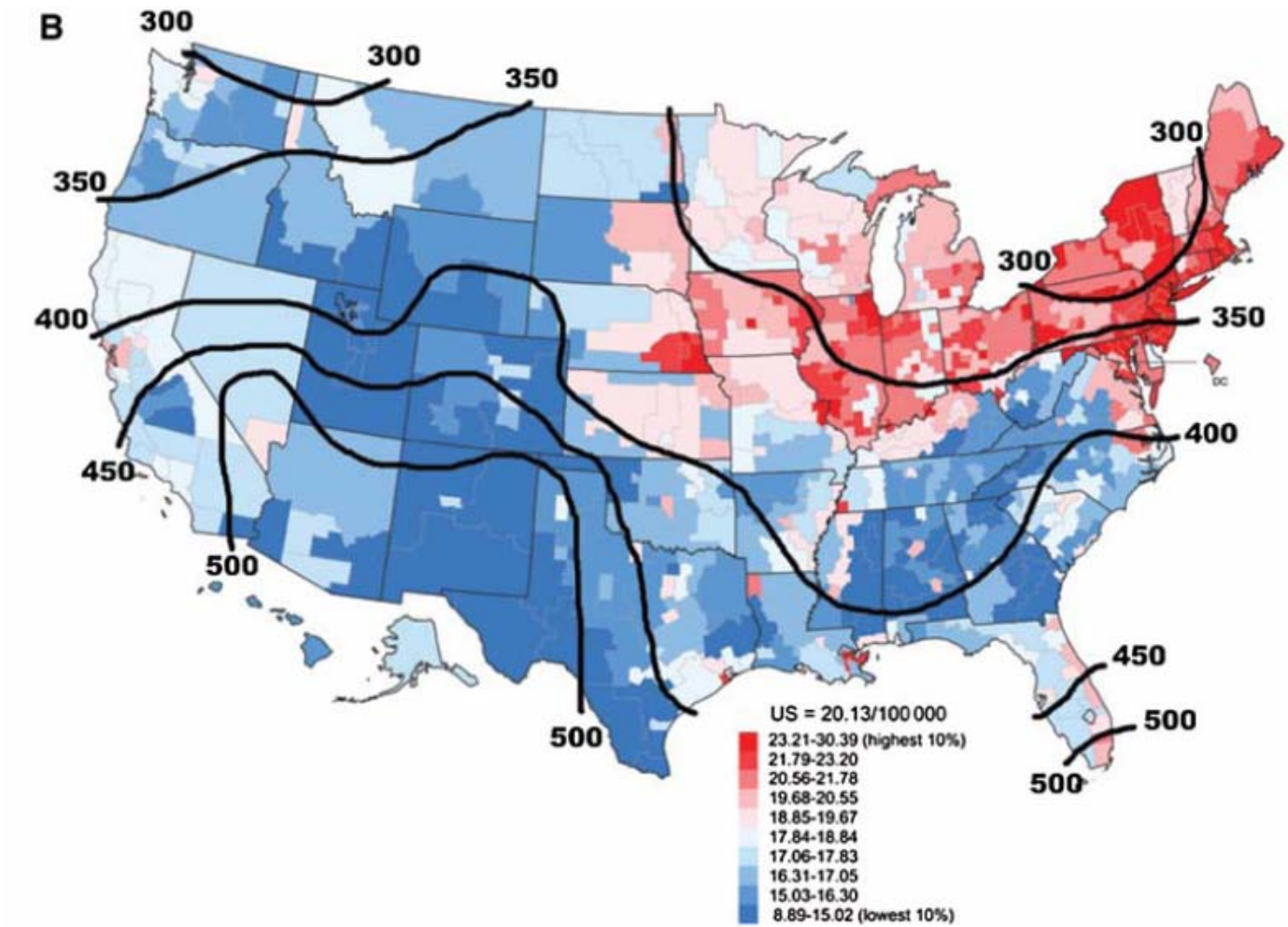


Autier Arch Intern Med 2007

Vit D: algunas acciones extraesqueléticas

- Cáncer
- Infecciones
- Autoinmunidad
- Diabetes
- Cardiovascular
- Músculo
- (Piel)

Radiación solar y mortalidad por cáncer colon



(Gorham et al Crit Rev Bone Miner Metab 2009)

Niveles de 25(OH)D y cáncer colon

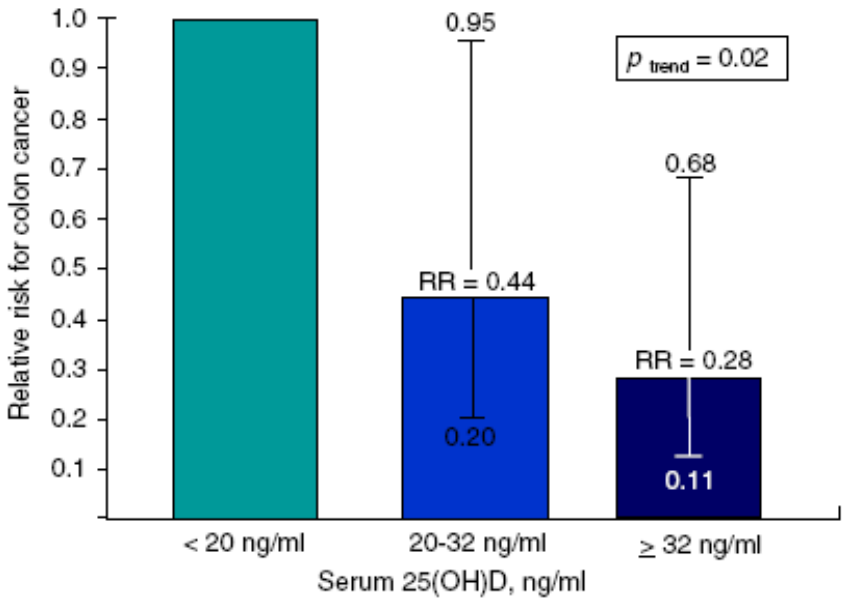


Fig. 10 Relative risk of colon cancer mortality, by baseline serum 25(OH)D concentration in tertiles, NHANES III cohort, 1988–2000.

(Gorham et al Crit Rev Bone Miner Metab 2009)

Niveles de 25(OH)D y cáncer colon

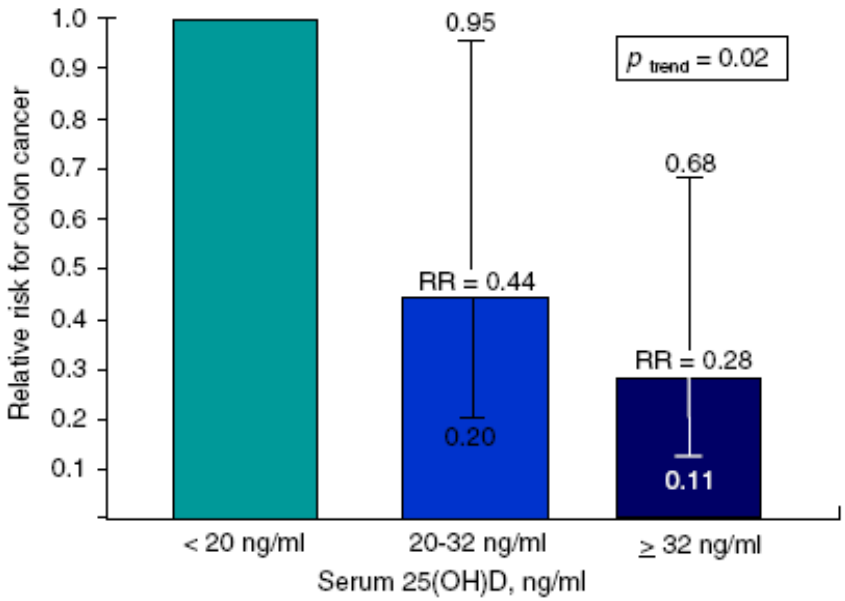
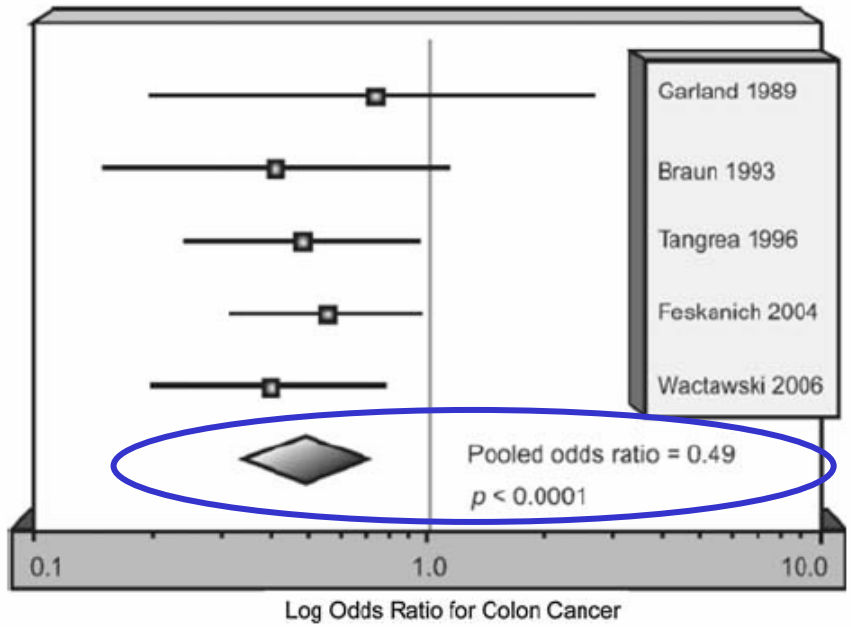


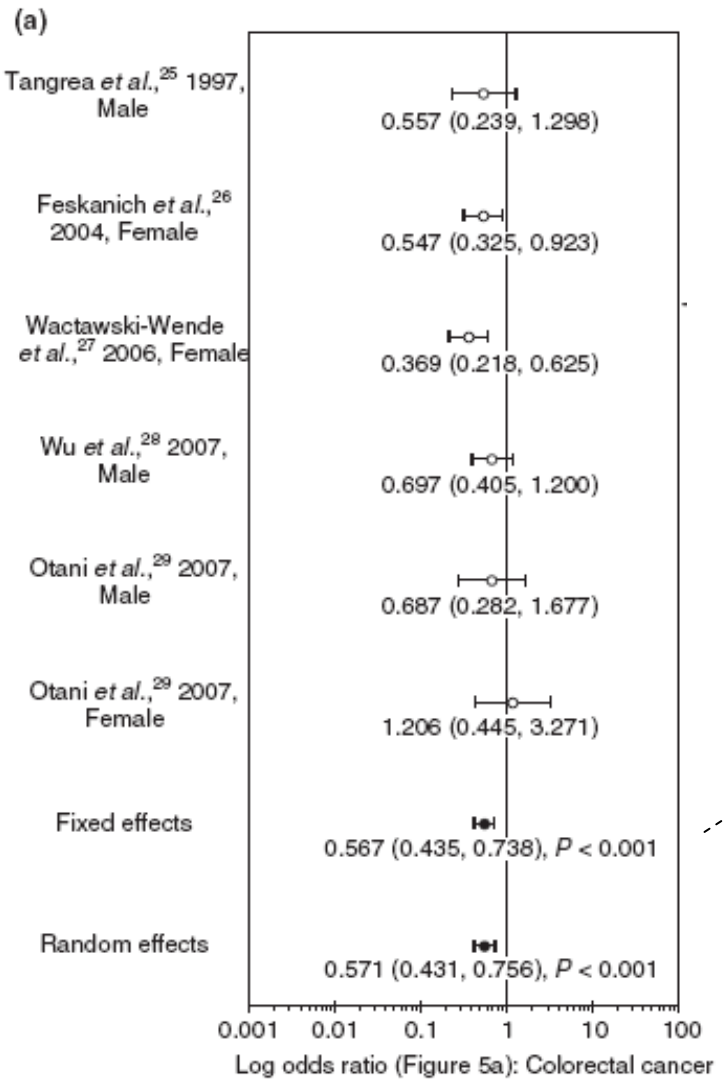
Fig. 10 Relative risk of colon cancer mortality, by baseline serum 25(OH)D concentration in tertiles, NHANES III cohort, 1988–2000.



Odds ratio según niveles séricos de 25(OH)D: Quintil 5 frente a quintil 1

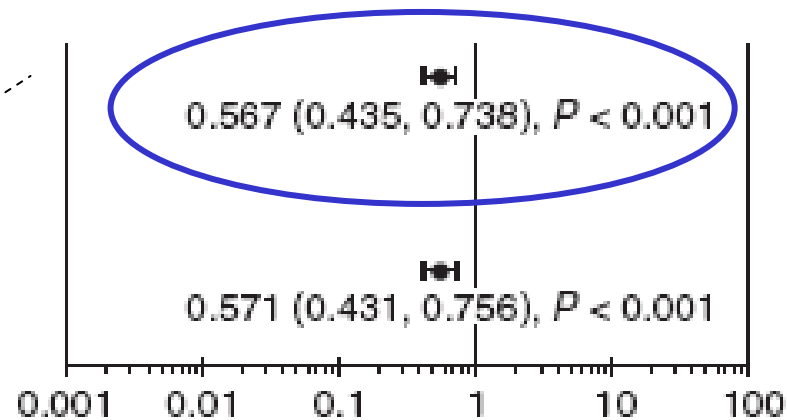
(Gorham et al Crit Rev Bone Miner Metab 2009)

Niveles de 25(OH)D y cáncer colon



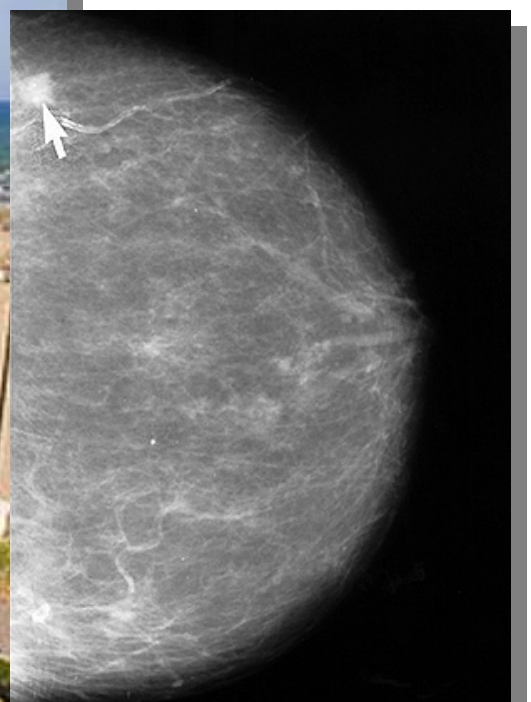
Incidencia de cáncer colo-rectal:

Odds-ratio asociada a un aumento de 25(OH)D sérico de 20 ng/ml



(Yin et al Alim Pharmacol Therap 2009)

Niveles de 25(OH)D y cáncer de mama



Niveles de 25(OH)D y cáncer de mama

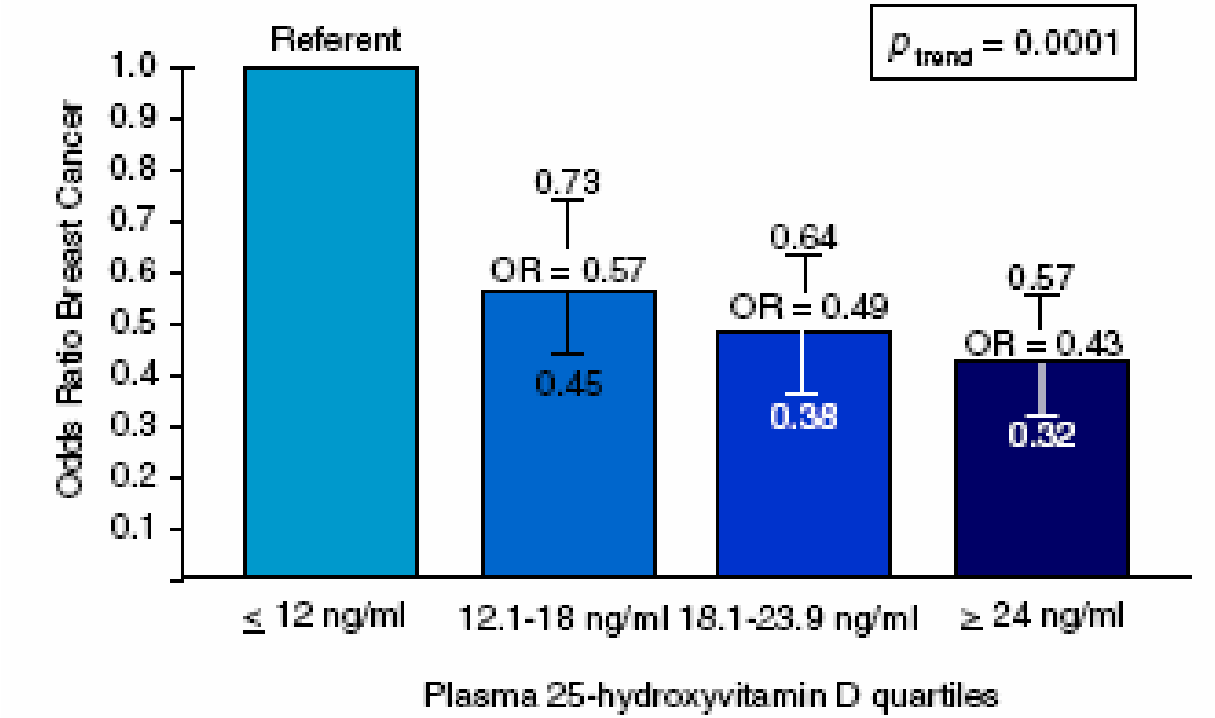
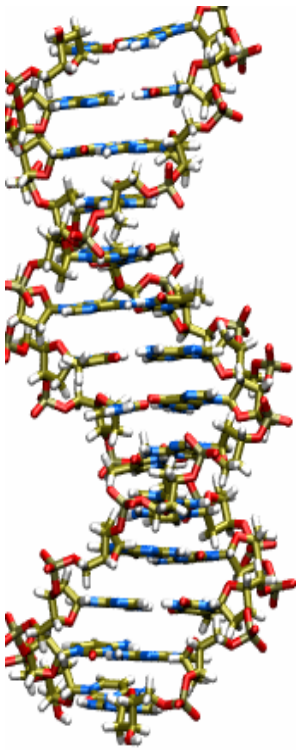


Fig. 4 Multivariate-adjusted odds ratios for post-menopausal breast cancer by plasma 25(OH)D concentration by quartiles, 1,394 cases, 1,365 matched controls, Heidelberg, Germany. *Source*: Abbas et al.

(Gorham et al Crit Rev Bone Miner Metab 2009)

Polimorfismos RVD y Cáncer

Cáncer de próstata



Polimorfismos RVD y Cáncer

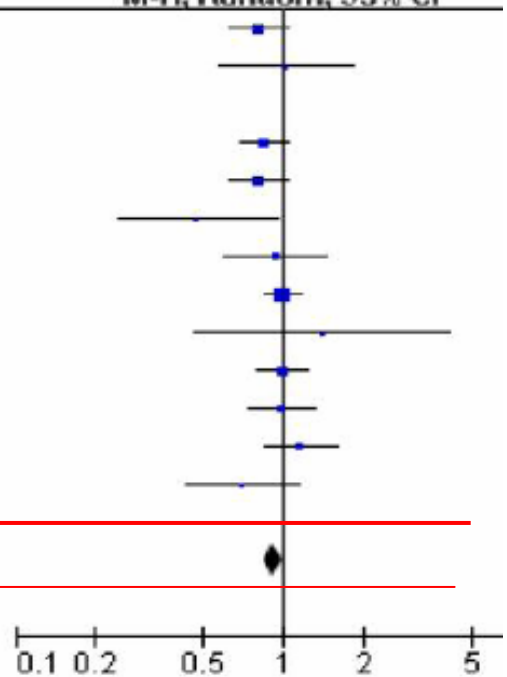
Cáncer de próstata

C. *Bsml*

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Cheteri, 2004	336	543	340	510	10.6%	0.81 [0.63, 1.04]
Chokkalingam, 2001	21	161	38	297	2.2%	1.02 [0.58, 1.81]
Habuchi, 2000	50	222	128	337	0.0%	0.47 [0.32, 0.70]
Hayes, 2005	517	812	481	713	14.8%	0.85 [0.68, 1.05]
Holick, 2007	369	590	364	541	11.3%	0.81 [0.64, 1.04]
Huang 2004	13	160	32	205	1.5%	0.48 [0.24, 0.94]
Ingles, 1998	86	151	102	174	3.6%	0.93 [0.60, 1.45]
Li, 2007	652	1034	991	1566	24.1%	0.99 [0.84, 1.17]
Liu, 2003	8	103	6	106	0.6%	1.40 [0.47, 4.20]
Mikhak, 2007	404	646	420	669	13.4%	0.99 [0.79, 1.24]
Nam, 2003	365	478	411	536	8.1%	0.98 [0.73, 1.31]
Oakley-Girvan 2004	219	345	175	292	6.7%	1.16 [0.84, 1.60]
Onen, 2008	80	133	107	157	3.0%	0.71 [0.44, 1.14]
Total (95% CI)		**5378**		**6103**	**100.0%**	**0.92 [0.84, 1.00]**
Total events	3120		3595			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.40$, df = 11 (P = 0.41); $I^2 = 4\%$

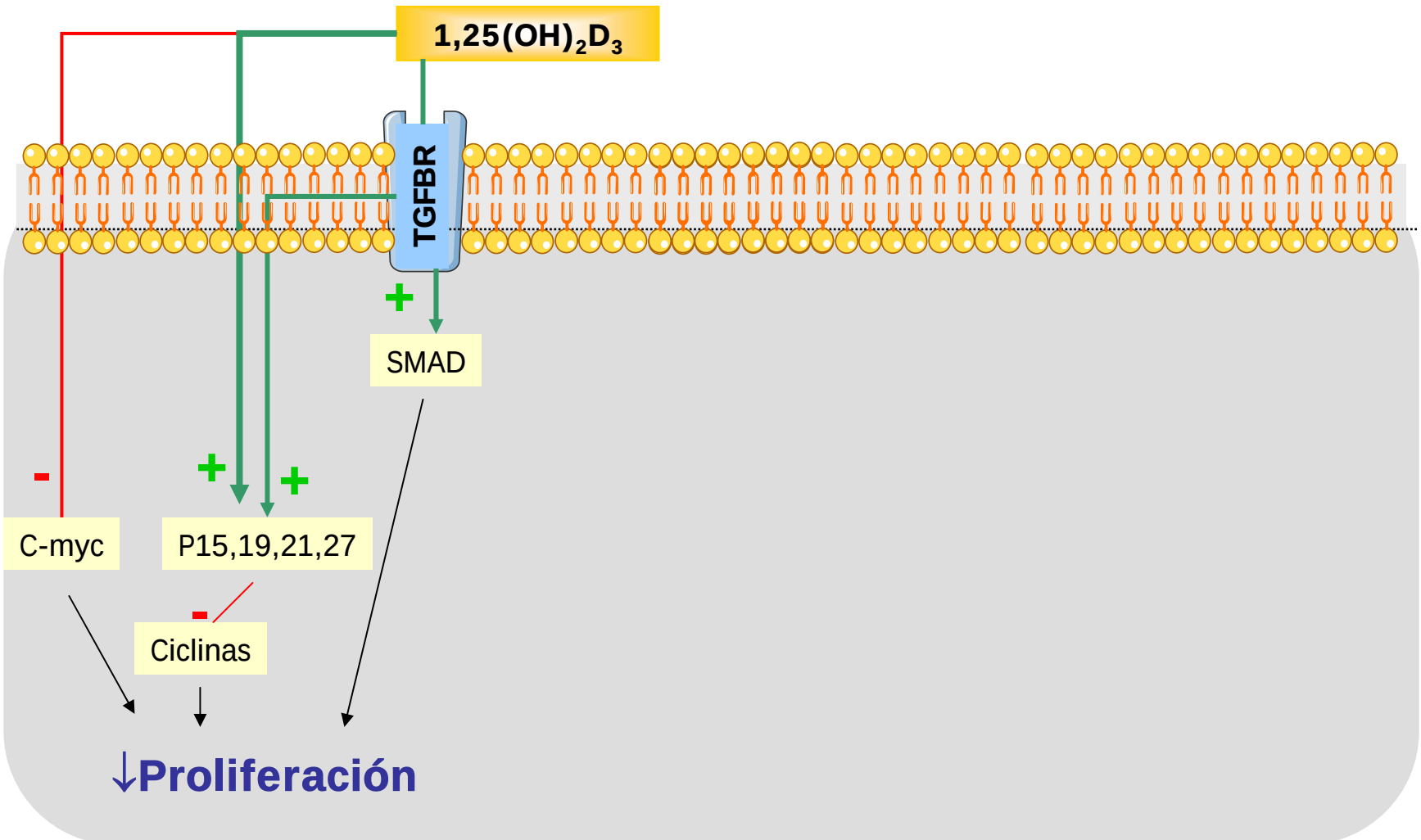
Test for overall effect: Z = 2.03 (P = 0.04)



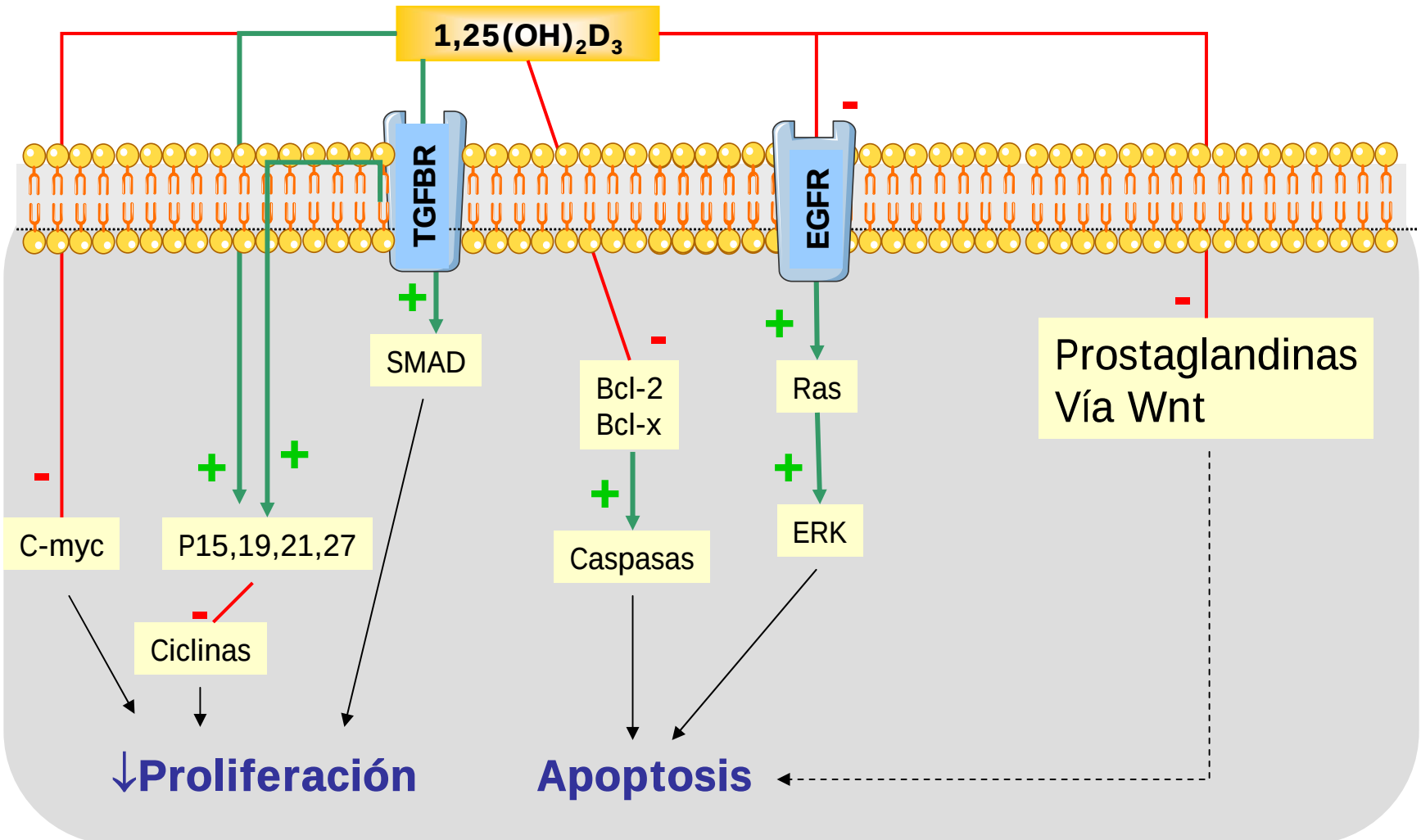
(Yin et al, Int J Clin Exp Med 2009)

Vit D: Efectos anti-proliferativos

Vit D: Efectos anti-proliferativos

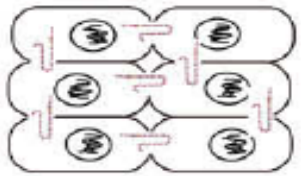


Vit D: Efectos anti-proliferativos



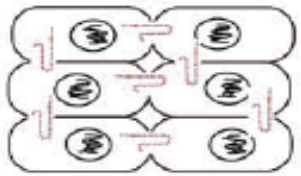
Modelo DINO

Epitelio normal



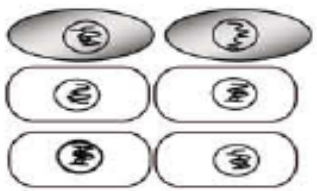
Modelo DINO

Epitelio normal

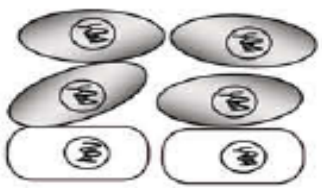


Disyunción

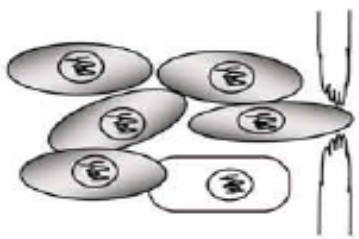
Inicio



Selección **n**atural

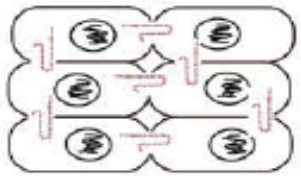


Crecimiento incontrolado (**o**vergrowth)



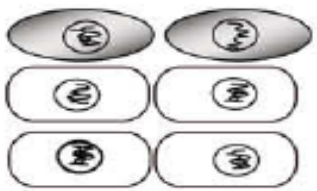
Modelo DINO

Epitelio normal



Disyunción

Inicio



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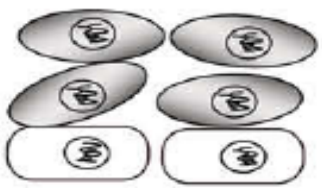

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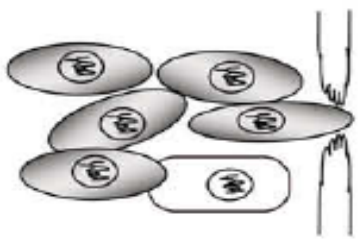


1,25(OH)$_2$D

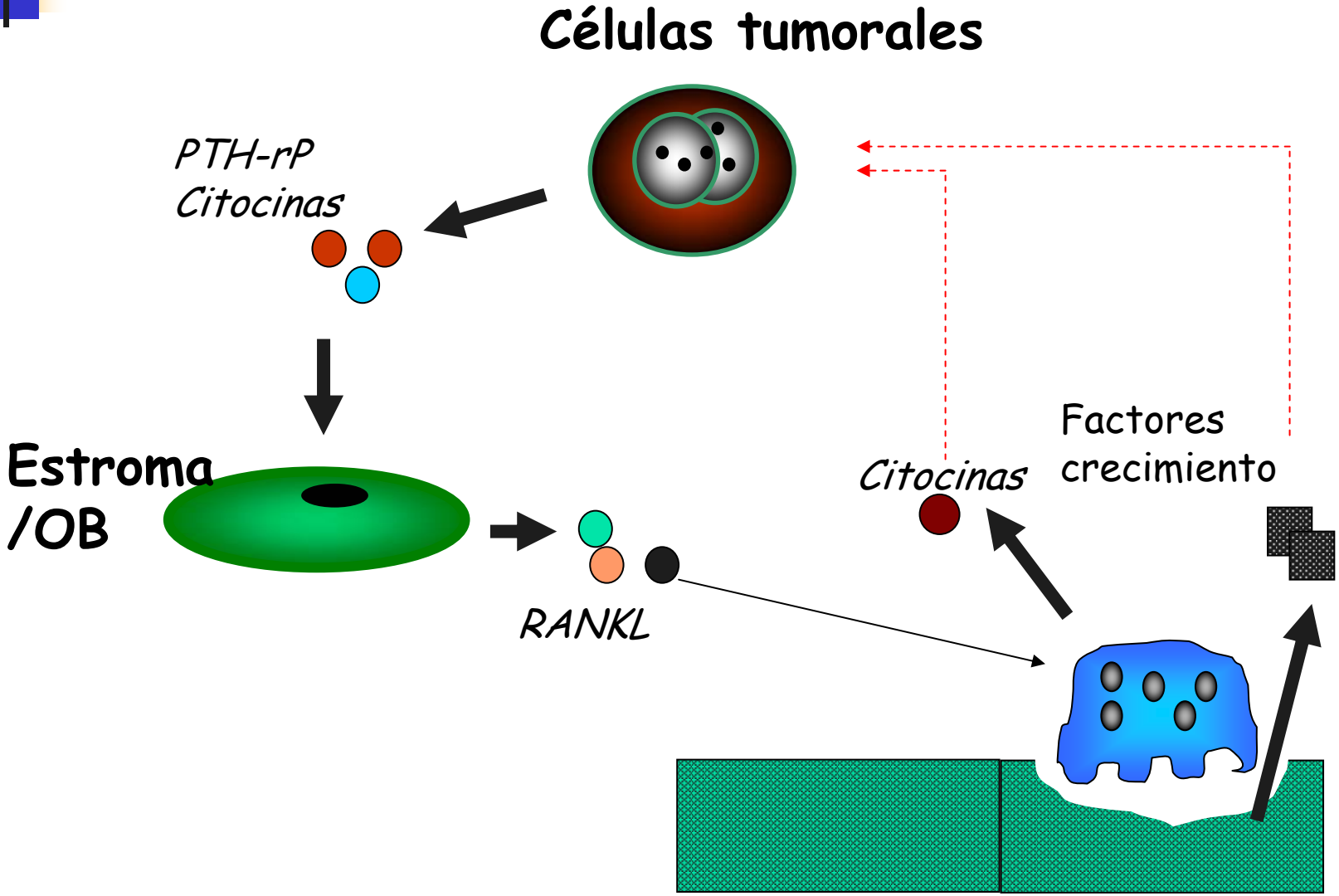
↑ Cadherinas

↑ Uniones intercelulares

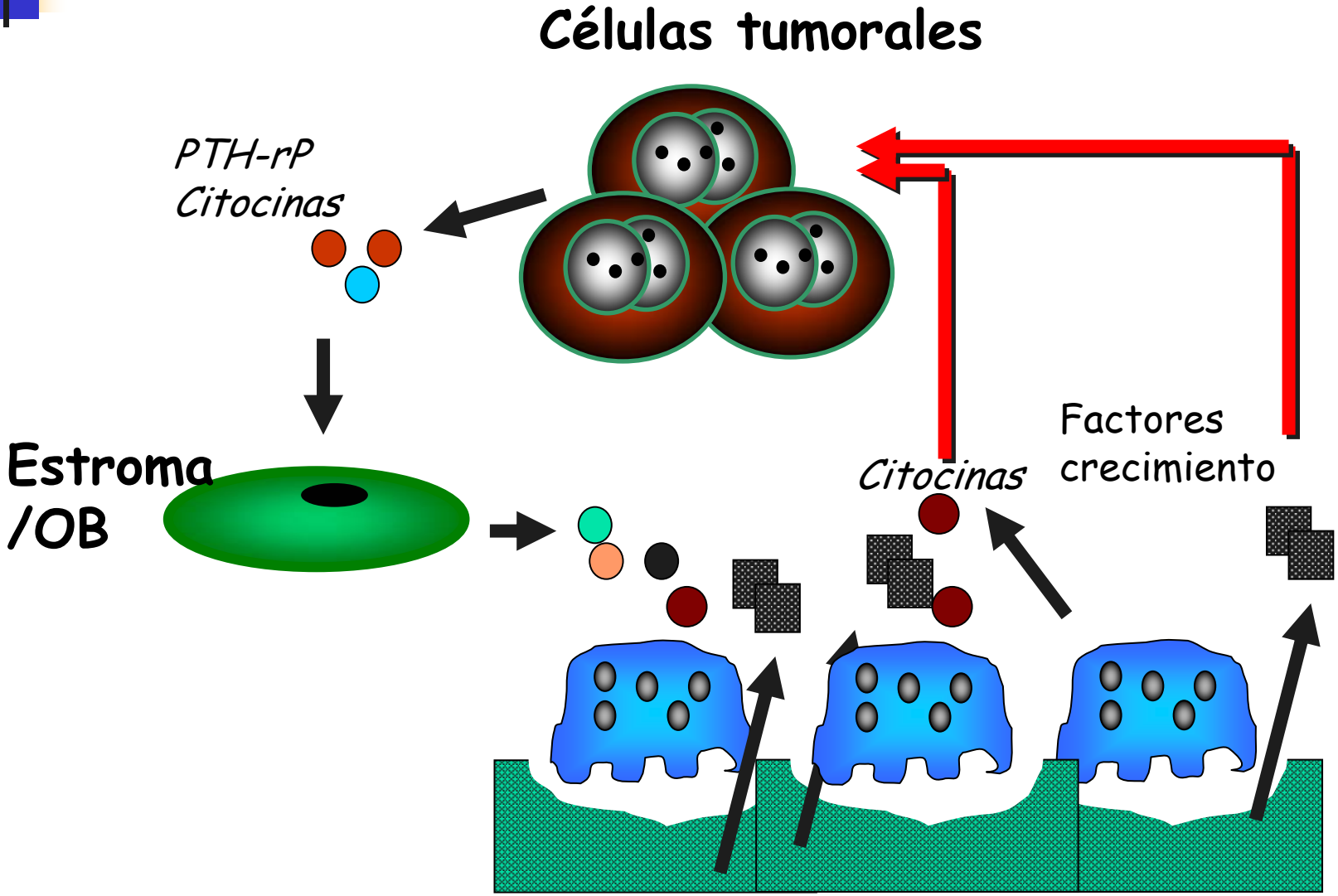
↑ Apoptosis

↓ Proliferación

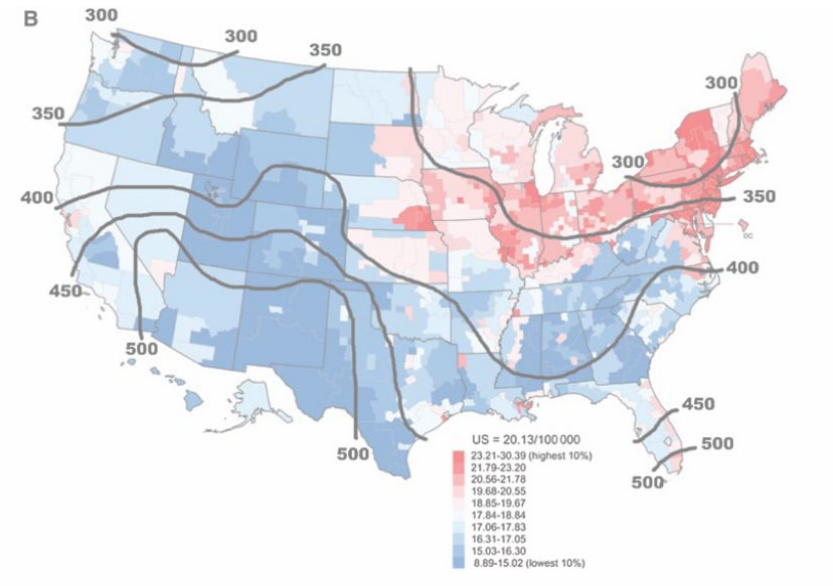
Remodelado óseo y metástasis



Remodelado óseo y metástasis



Ensayos de intervención

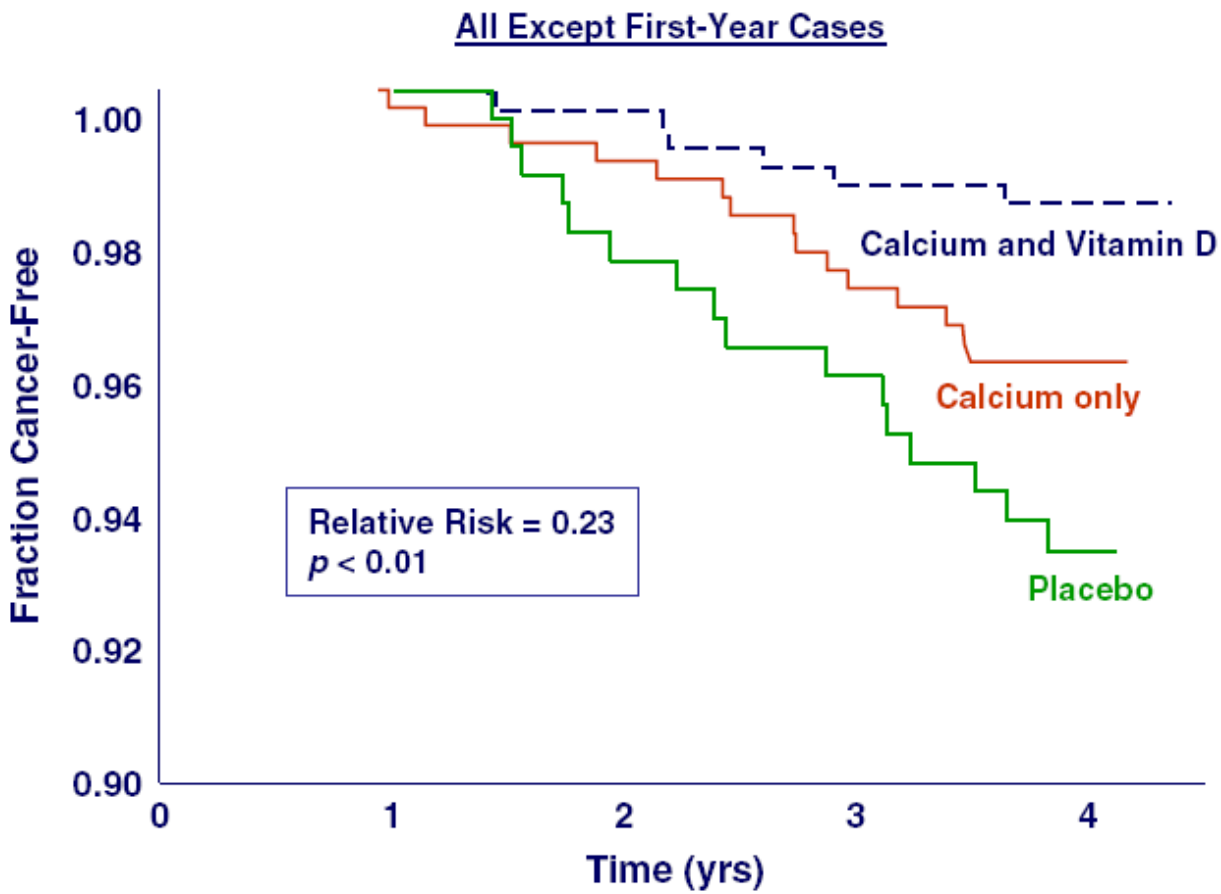


Suplementos de Ca-D y cáncer

- **Mujeres postmenopáusicas (n=1179)**
- **Ca 1500 mg +/- Vit D3 1100 U**
- **Nuevo cáncer:**
  - **13 en primer año**
  - **37 en años 2-4.**

Lappe, Am J Clin Nutr 2007

Suplementos de Ca-D y cáncer



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  - **13 en primer año**
  - **37 en años 2-4.**

Lappe, Am J Clin Nutr 2007

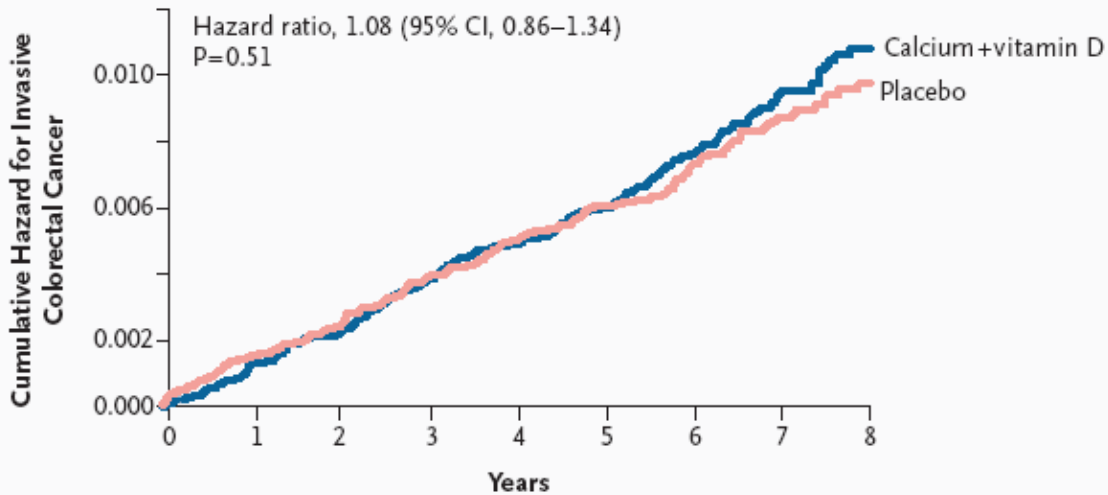
Suplementos de Ca-D y cáncer de colon

WHI (Women's Health Initiative)

- Mujeres postmenopáusicas (n=36.282)
- Ca 1000 mg + D3 400 U
- Aparición de cáncer de colon invasivo durante seguimiento de 7 años

Wactawski-Wende et al NEJM 2006

Suplementos de Ca-D y cáncer de colon



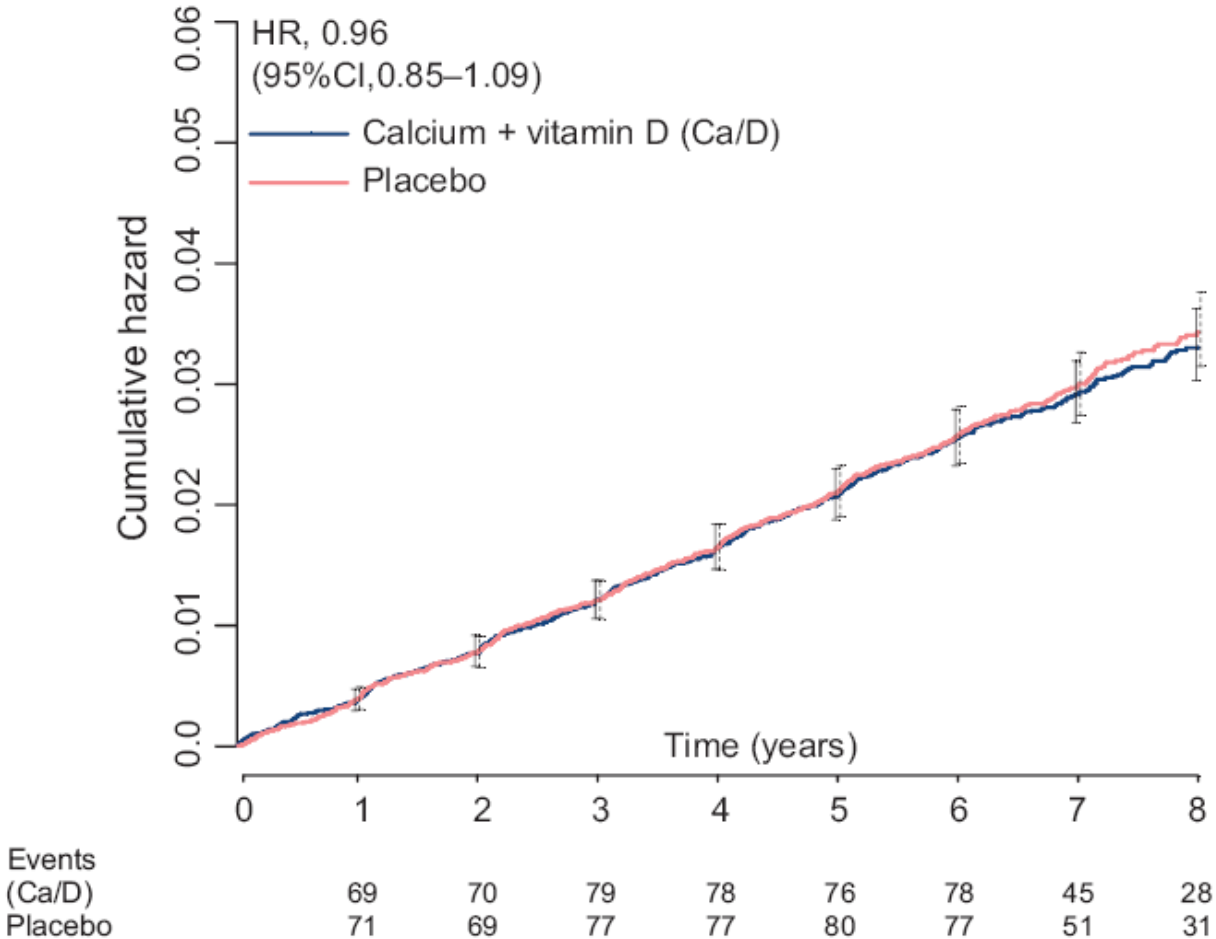
Calcium+vitamin D									
No. of events	0	23	17	28	20	19	27	23	9
No. at risk	18,176	18,048	17,936	17,780	17,605	17,248	14,680	9138	4403
Placebo									
No. of events	0	27	16	27	20	18	20	17	7
No. at risk	18,106	17,967	17,832	17,663	17,471	17,093	14,530	9041	4351

Figure 3. Kaplan–Meier Estimates of the Cumulative Hazard for Invasive Colorectal Cancer with Supplemental Calcium plus Vitamin D, as Compared with Placebo.

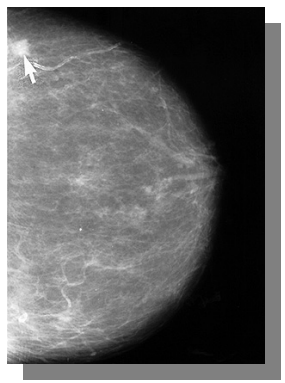
CI denotes confidence interval. Two events in each group that occurred after year 8 are not shown.

Wactawski-Wende et al NEJM 2006

Suplementos de Ca-D y Cáncer de mama



WHI



Chlebowski et al, J Natl Cancer Inst 2007

Suplementos vit D y cáncer

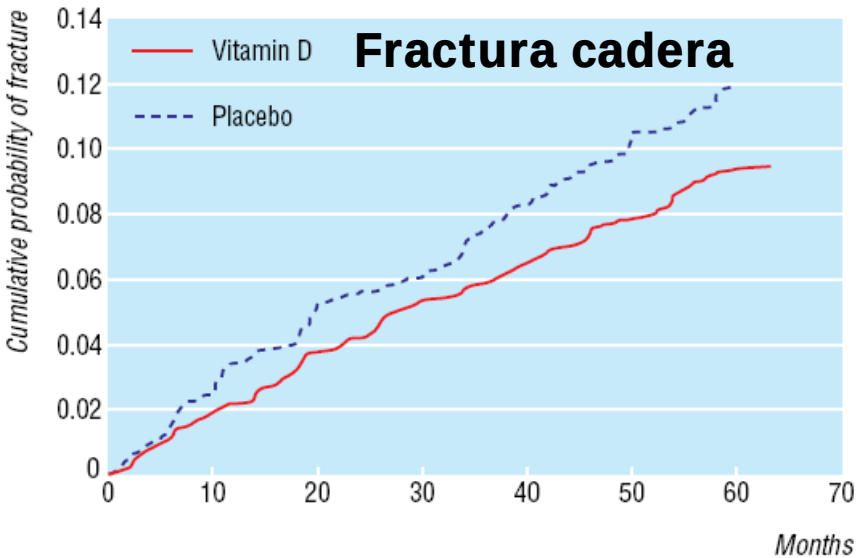


Fig 1 Cumulative probability of any first fracture according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; difference between two groups, P=0.04

- Hombres (n=2.037) y mujeres (n=649)
- 65-85 años
- Vit D 100.000 u/c 4 meses
- Seguimiento 5 años

(Trivedi et al, BMJ 2003)

Suplementos vit D y cáncer

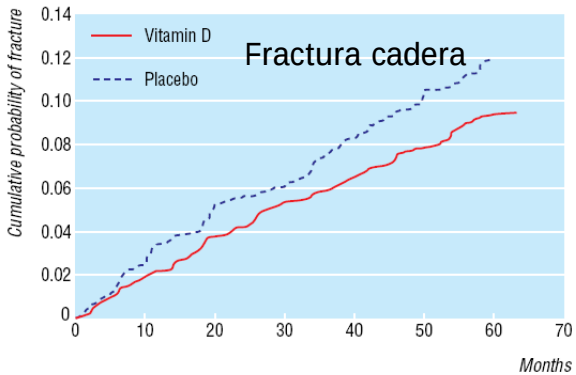
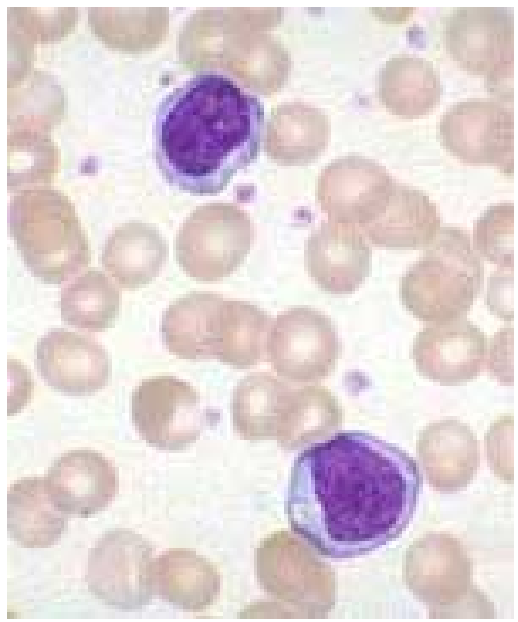


Fig 1 Cumulative probability of any first fracture according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; difference between two groups, P=0.04

	Vit D	Placebo	Relative risk	p
Cancer	63 (4.7)	72 (5.4)	0.86 (0.61 to 1.20)	0.37
Colon	7 (0.5)	11 (0.8)	0.62 (0.24 to 1.60)	0.33
Respiratory	10 (0.7)	11 (0.8)	0.89 (0.38 to 2.09)	0.78

(Trivedi et al, BMJ 2003)

Vitamina D como inmunomodulador



Vitamina D como inmunomodulador

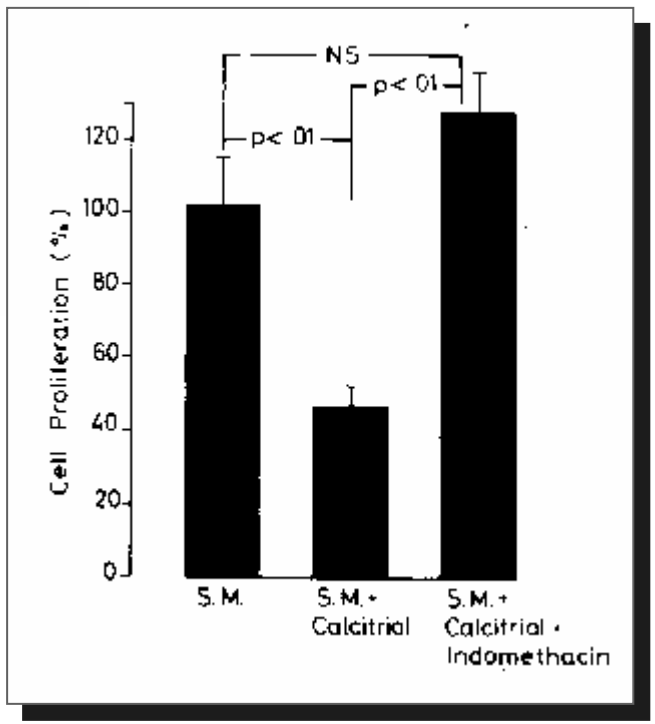
Blut (1987) 54: 343–349

Blut

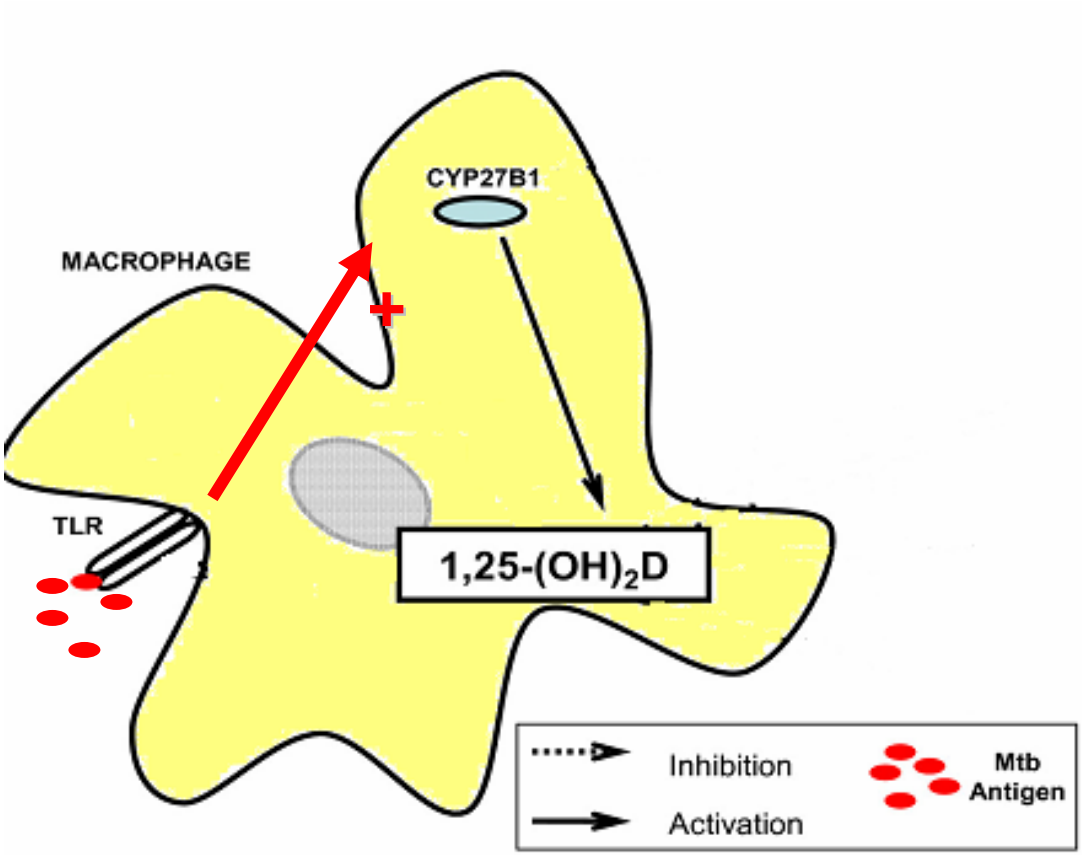
Role of Monocytes in the Inhibitory Effect of Calcitriol on PHA-Stimulated Lymphocytes*

M. T. Zarrabeitia[2], J. A. Riancho[1], V. Rodriguez-Valverde[2], M. C. Farinas[1], and J. Gonzalez-Macias[1]

La $1,25(OH)_2D_3$ inhibe la proliferación linfocitaria
Los monocitos intervienen en ese efecto



Vitamina D como inmunomodulador



Modificado de Conesa et al, AIDS Res Ther 2009

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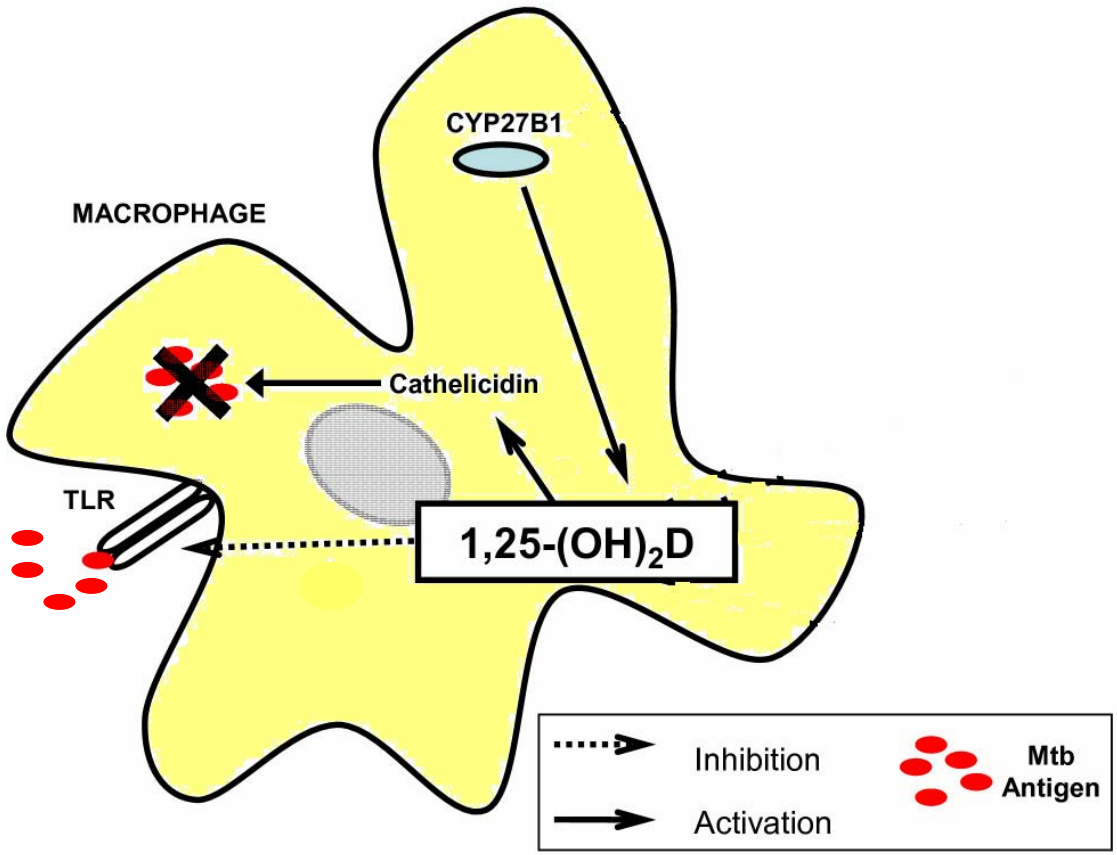
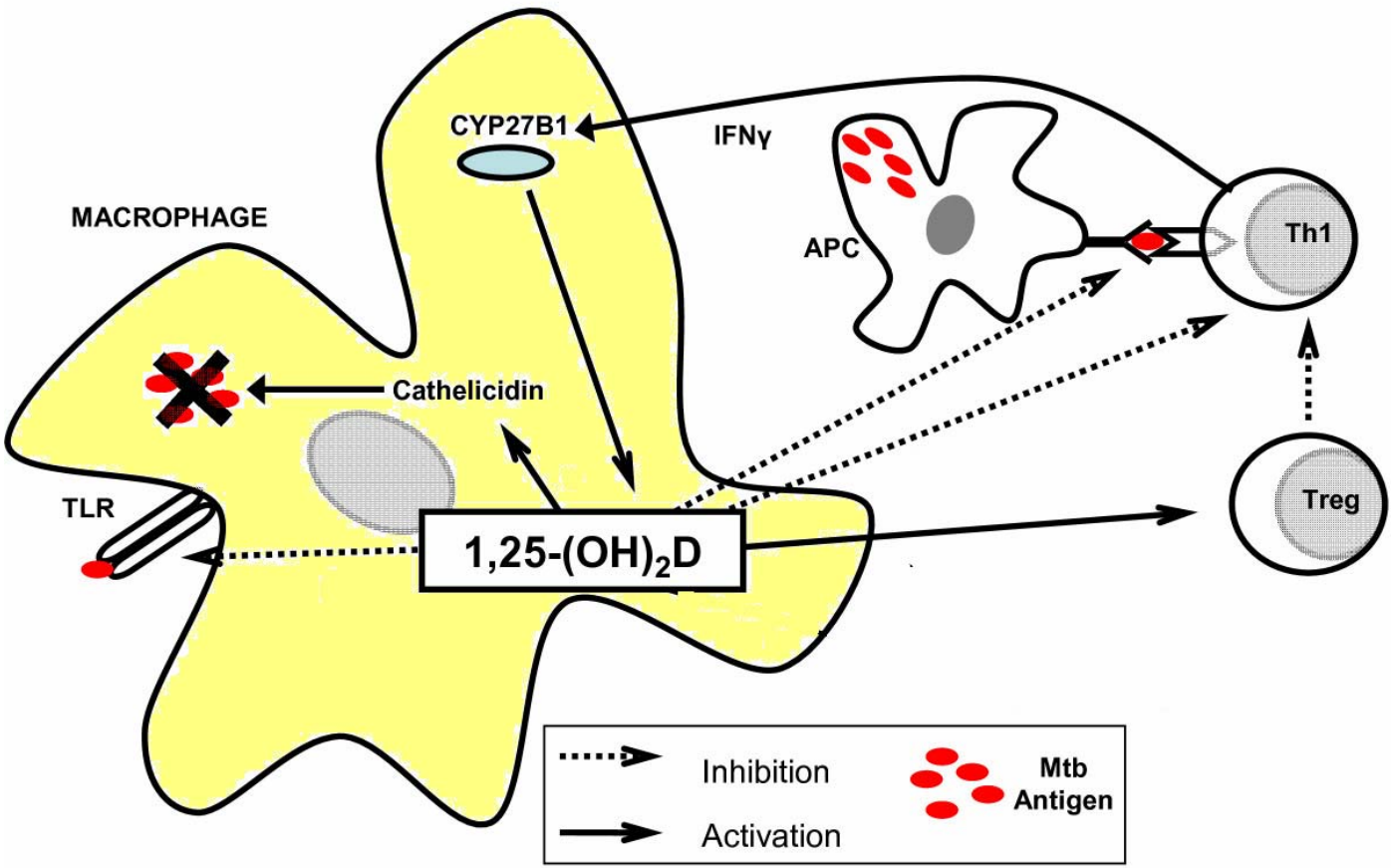


Modificado de Conesa et al, AIDS Res Ther 2009

Vitamin D como inmunomodulador



Modificado de Conesa et al, AIDS Res Ther 2009

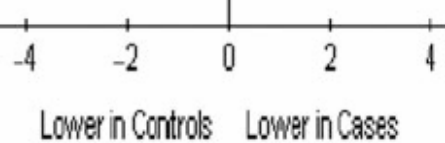
Deficiencia de vit D y tuberculosis

Table 4 Effect sizes of low serum vitamin D in tuberculosis patients and controls

Study or sub-category	Cases N	Control N	Effect Size (SE)	Weight %	Effect Size (random) 95% CI
Davies, UK	40	40	0.8600 (0.2300)	16.69	0.86 [0.41, 1.31]
Grange, Indonesia	40	38	0.1800 (0.2300)	16.69	0.18 [−0.27, 0.63]
Davies, Kenya	15	15	1.0400 (0.3900)	8.34	1.04 [0.28, 1.80]
Davies, Thailand	51	51	0.9600 (0.2100)	18.31	0.96 [0.55, 1.37]
Chan, Hong Kong	24	24	0.3300 (0.3000)	12.14	0.33 [−0.26, 0.92]
Wilkinson, UK	103	42	0.5900 (0.2300)	16.69	0.59 [0.14, 1.04]
Sasidharan, India	35	16	0.9400 (0.3200)	11.13	0.94 [0.31, 1.57]
Total (95% CI)	308	226		100.00	0.68 [0.43, 0.93]

Test for heterogeneity: $Chi^2 = 10.14$, df = 6 (P = 0.12), $I^2 = 40.8\%$

Test for overall effect: Z = 5.28 (P < 0.00001)



(Nnoaham, Int J Epidemiol 2008)

Vit D como “coadyuvante” al tto. de tuberculosis

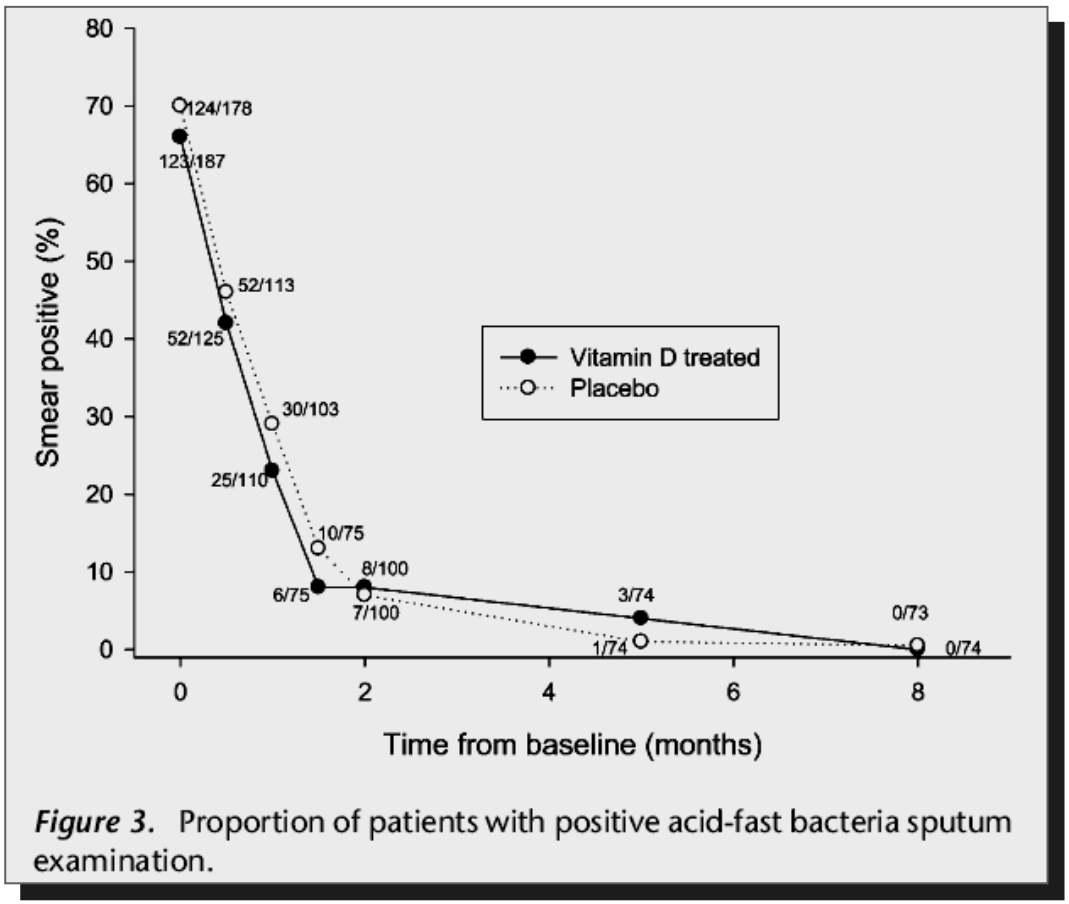


Figure 3. Proportion of patients with positive acid-fast bacteria sputum examination.

- 365 adultos con Tbc (Guinea-Bissau)
- Vit D 100.000 U al inicio y tras 5 y 8 meses

(Wejse, AJRCCM 2009)

Vit D como “coadyuvante” al tto. de tuberculosis

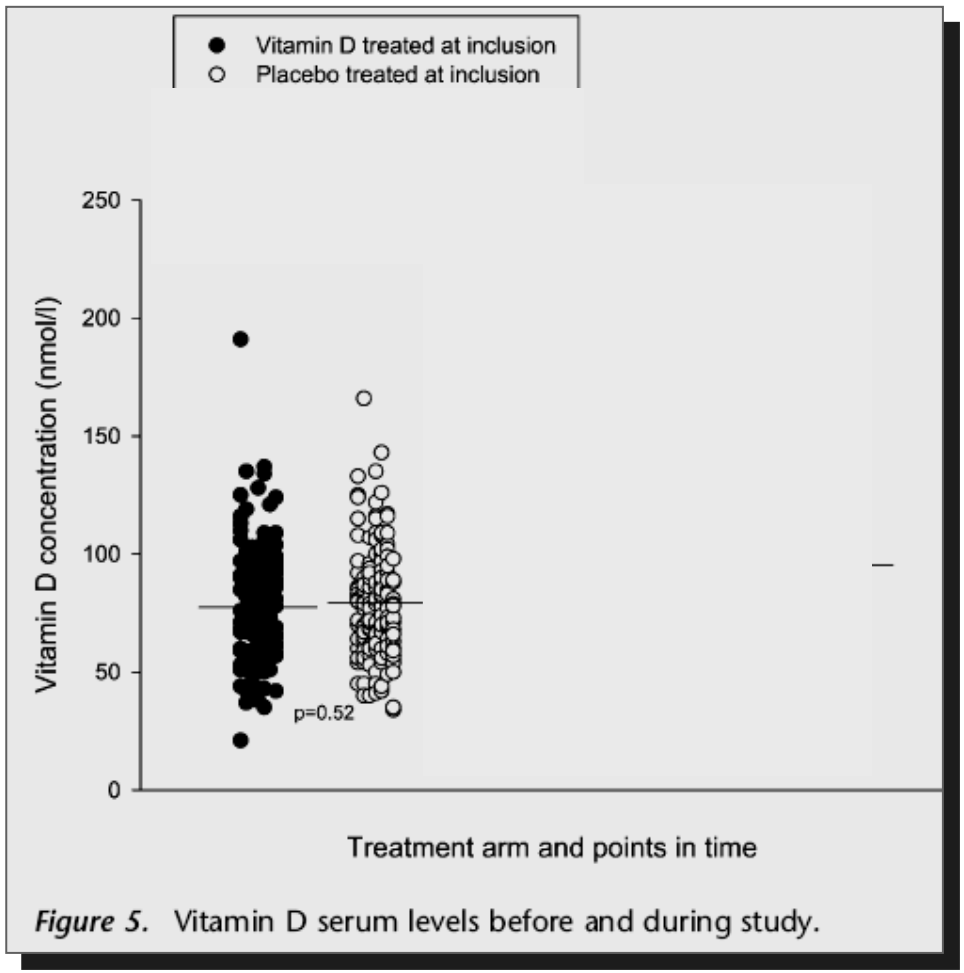
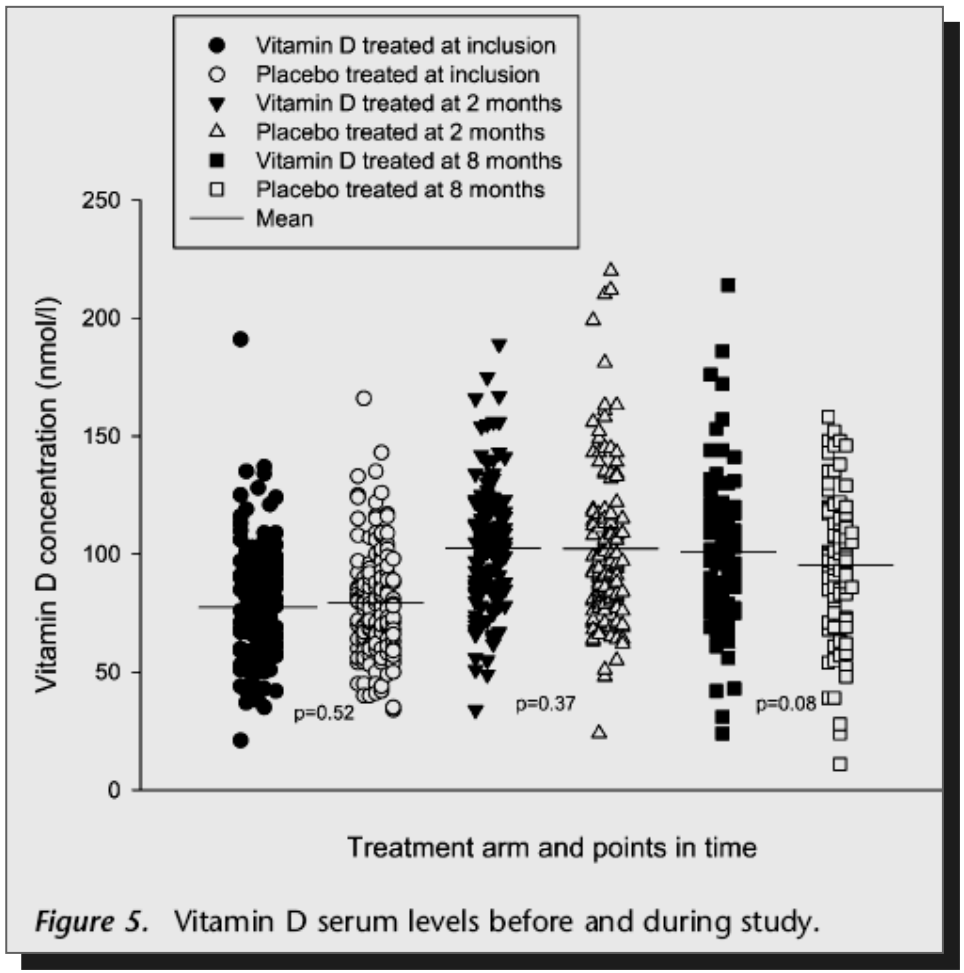


Figure 5. Vitamin D serum levels before and during study.

- 365 adultos con Tbc (Guinea-Bissau)
- Vit D 100.000 U al inicio y tras 5 y 8 meses

(Wejse, AJRCCM 2009)

Vit D como “coadyuvante” al tto. de tuberculosis



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Vit D y autoinmunidad

- Diabetes tipo 1
- Esclerosis múltiple

- LES
- Artritis experimental
- Enf inflamatoria intestinal
- Encefalomielitis experimental

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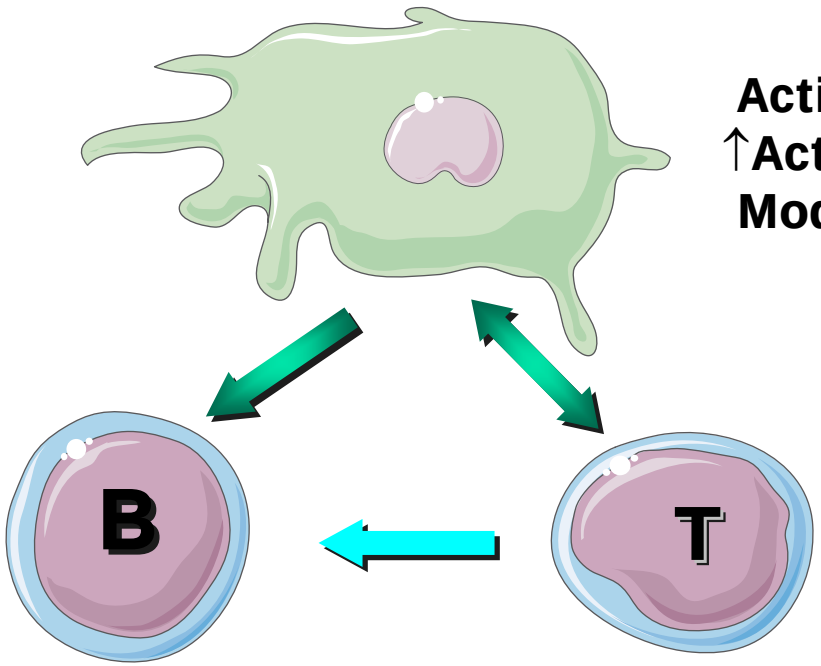

Activación
↑Activ. microbicida
Modula cel dendríticas

↓ Proliferación
↓ Síntesis Ig's

↓ Proliferación
↓ Th1
↑ Th2
↑ Treg

- Cáncer
- Infecciones
- Autoinmunidad
- **Diabetes**
- **Cardiovascular**
- Músculo

Niveles de 25(OH)D y síndrome metabólico

Table 1 —*Unadjusted prevalence and adjusted odds ratios and 95% confidence limits of having the metabolic syndrome by quintiles vitamin D concentration among 8,421 U.S. adults aged ≥20 years, NHANES III, 1988–1994*

	Quintiles of vitamin D (nmol/l)				
	1 (≤48.4)	2 (48.5–63.4)	3 (63.5–78.1)	4 (78.2–96.3)	5 (≥96.4)
Metabolic syndrome					
Unadjusted prevalence†	27.5 (1.7)	26.6 (1.4)	23.3 (1.5)	18.7 (1.3)	13.5 (1.7)
Model 1‡	1.00	0.91 (0.72, 1.17)	0.80 (0.62, 1.03)	0.65 (0.51, 0.83)	0.49 (0.37, 0.66)
Model 2§	1.00	0.82 (0.60, 1.10)	0.75 (0.55, 1.02)	0.60 (0.44, 0.83)	0.46 (0.32, 0.67)

(Ford et al. Diabetes Care 2005)

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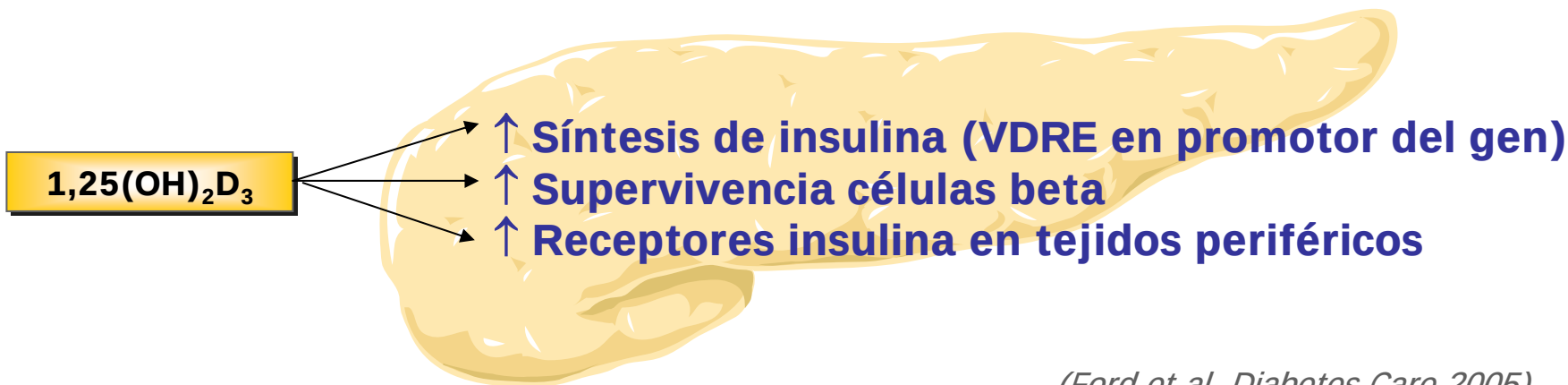
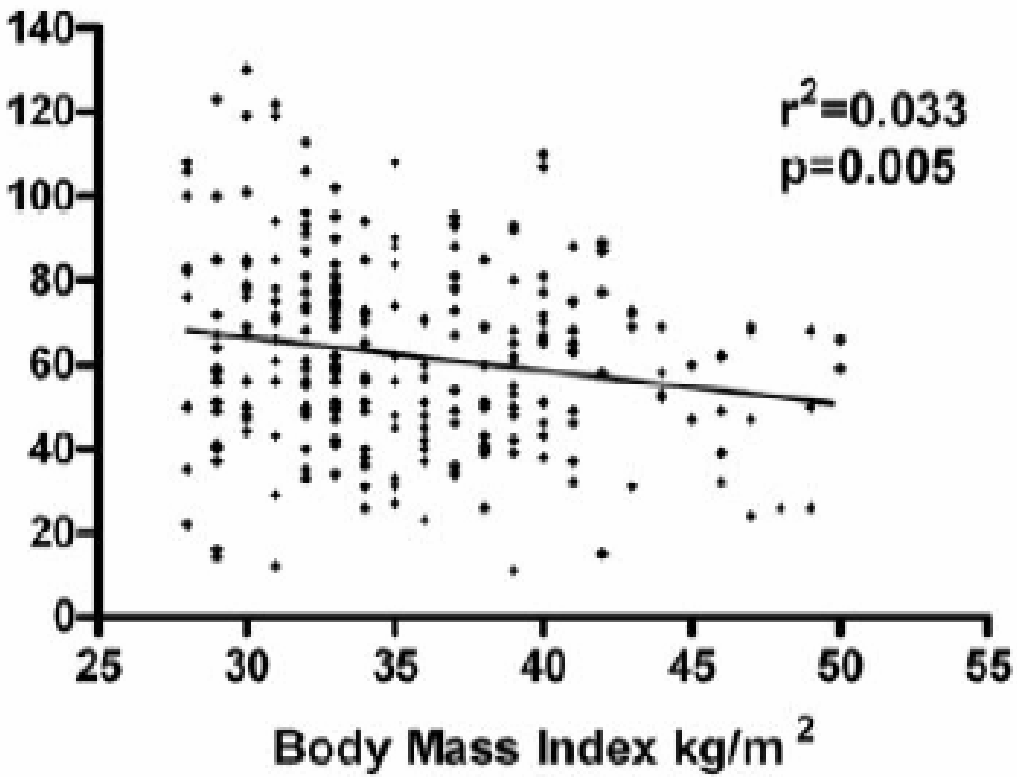


(Ford et al. Diabetes Care 2005)

Niveles de vitamina D y obesidad



(McGill et al, Nutrition J 2008)

Vit D y riesgo cardiovascular

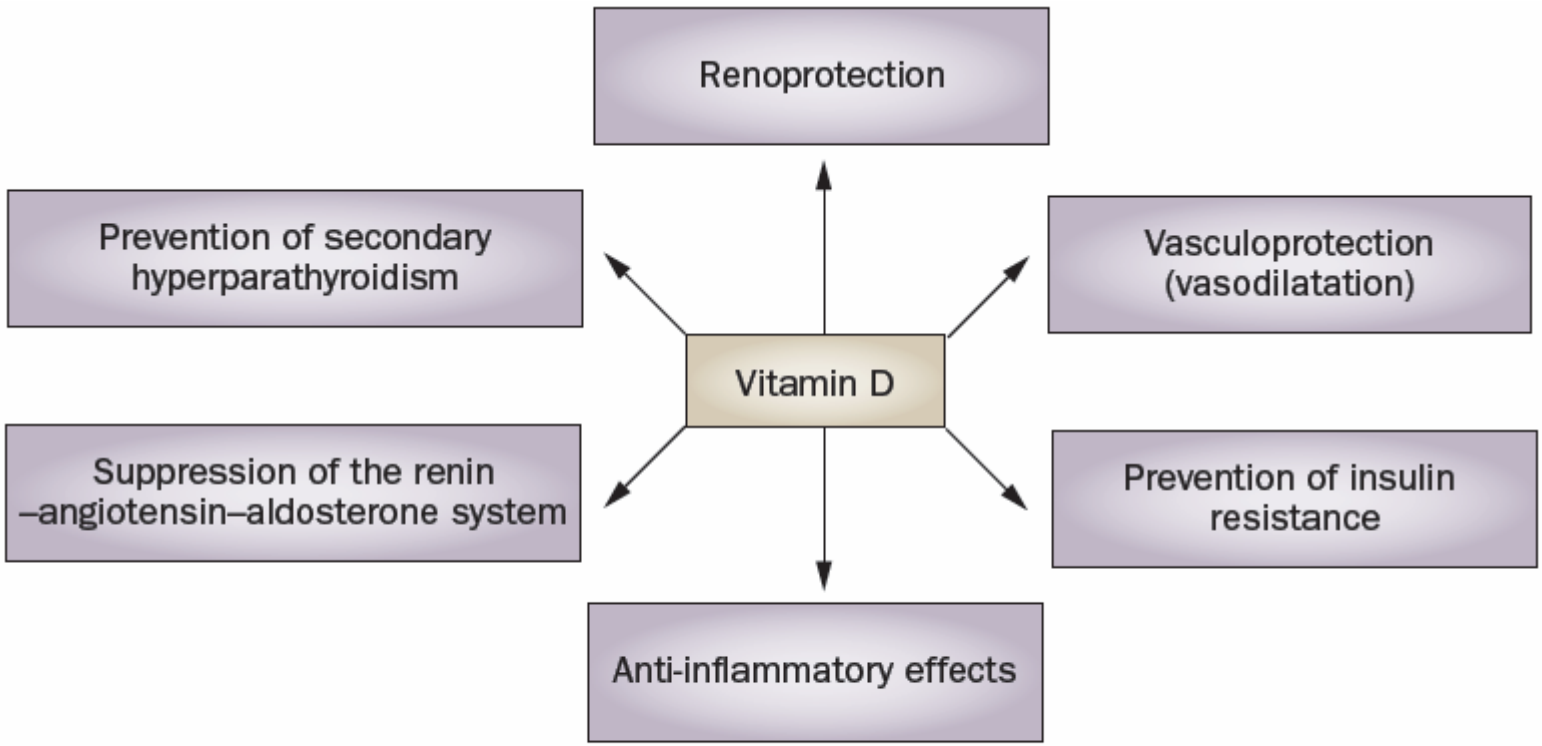


Figure 2 | The antihypertensive effects of vitamin D.

(Pilz et al. Nature Rev Cardiol 2009)

Niveles de 25(OH)D y mortalidad cardiovascular

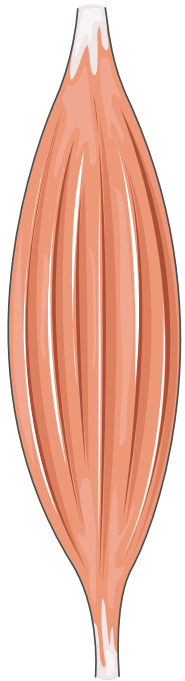
"Hazard ratio" frente a quintil 1

	Quintil 3	Quintil 5
Totales	**0,81** (0,66-1,0)	**0,76** (0,61-0,95)
ACVA	**0,97** (0,70-1,35)	**0,48** (0,31-0,75)
Coronarias	**0,73** (0,56-0,95)	**0,91** (0,70-1,18)

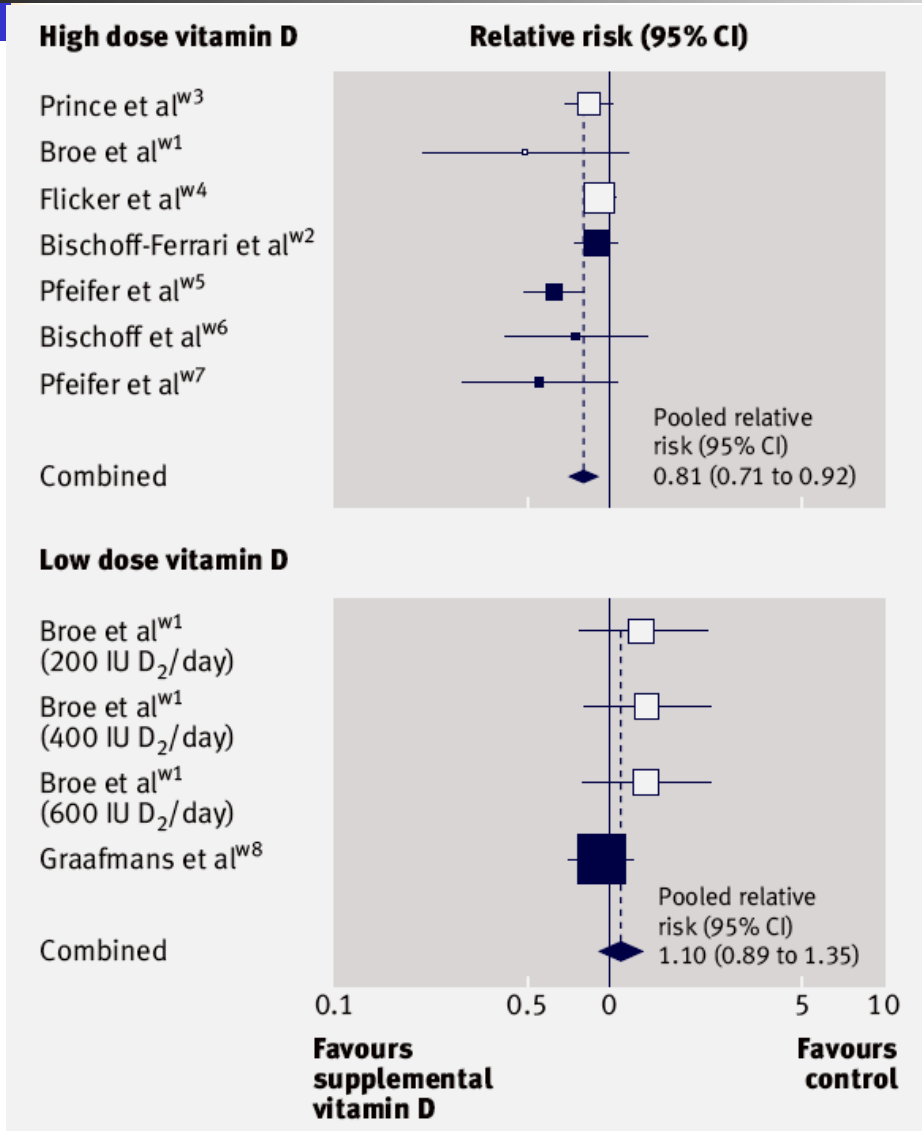
(Kilkkinen. Am J Epidemiol 2009)

Vit D y función muscular

- Cáncer
- Infecciones
- Autoinmunidad
- Diabetes
- Cardiovascular
- **Músculo**



Suplementos de vit. D y caídas

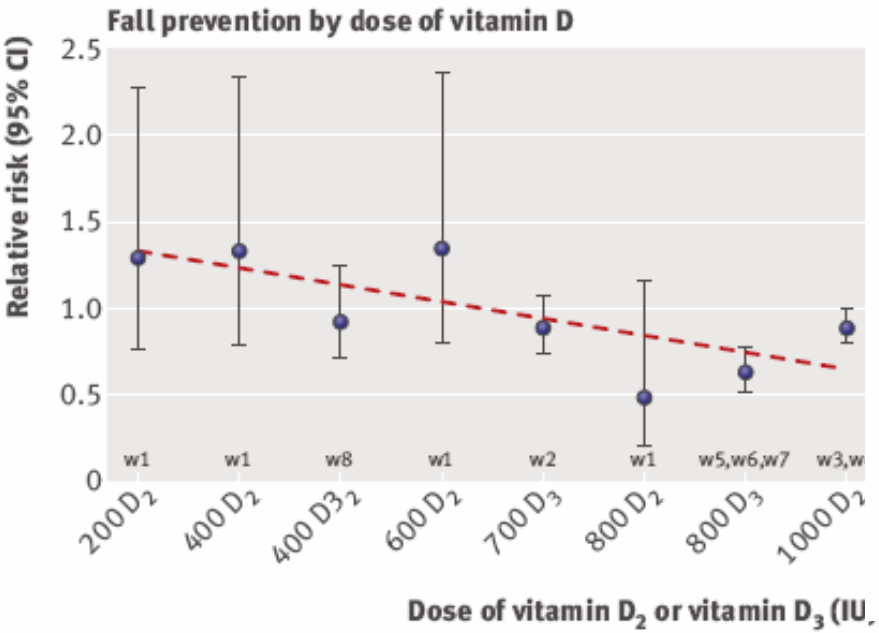


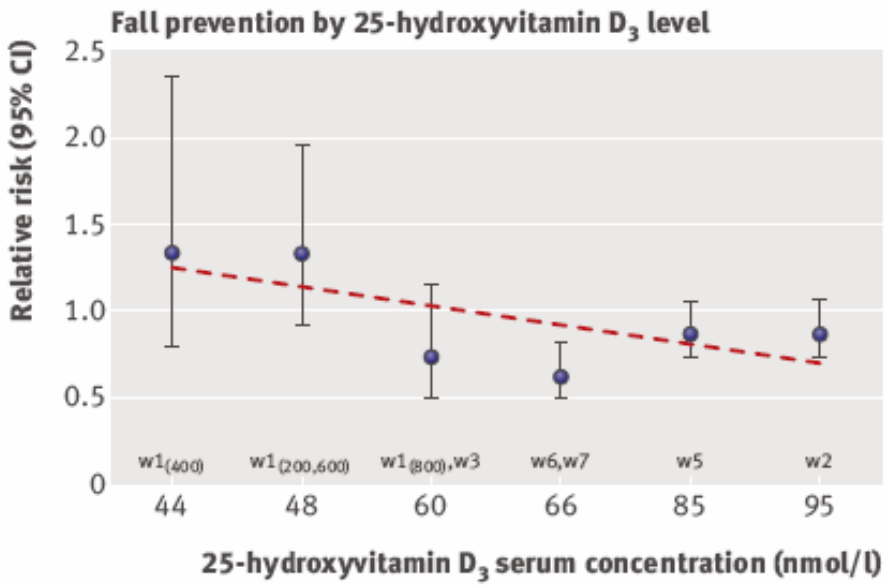
Meta-análisis

- 8 Ensayos clínicos controlados, doble ciego, en ancianos (n=2426)
- Edad media 80 años
- Mujeres 80%
- Dosis:
  - “Alta”: 700-1000 u/d
  - “Baja”: 200-600 u/d

(Bischoff-Ferrari et al, BMJ 2009)

Suplementos de vit. D y caídas





24 ng/ml

(Bischoff-Ferrari et al, BMJ 2009)

Respuesta a la suplementación con 25(OH)D

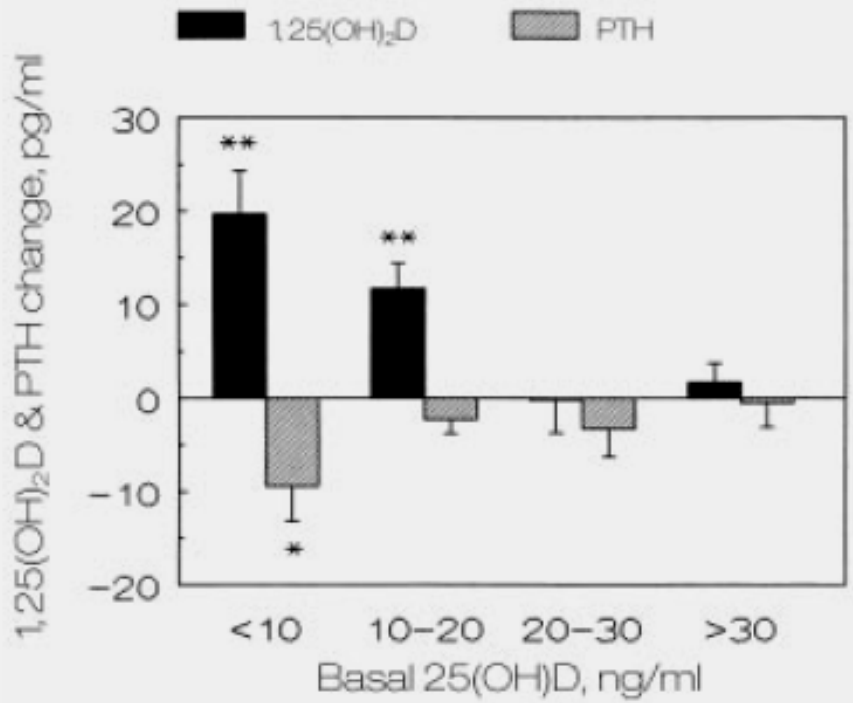


FIG. 2. Average changes in serum $1,25(OH)_2D$ (black bars) and PTH (dashed bars) induced by a 25(OH)D supplement, according to different intervals of basal 25(OH)D levels. $^{*}p < 0.05$; $^{**}p < 0001$.

(Docio et al, JBMR 1998)

En resumen

En resumen

Además de sus efectos sobre el aparato locomotor (hueso y músculo), numerosos estudios epidemiológicos y meta-análisis demuestran una asociación entre niveles bajos de vitamina D y mayor riesgo de

- **Cáncer (colon,** sobre todo**)**
- **Tuberculosis y otras infecciones**

Algunos estudios sugieren también una asociación con

- Diabetes tipo 2 y enfermedades cardiovasculares
- Enfermedades autoinmunes

¿ Una falacia ecológica?

En resumen

Muchos tejidos expresan receptores de vitamina D y 1-hidroxilasa, lo que sugiere un efecto (hormonal o paracrino) a esos niveles.

Los estudios de intervención controlados no han demostrado por ahora de manera convincente que la administración de suplementos de vitamina D disminuya esos riesgos.

Vitamina D: más allá de la osteoporosis

La importancia real “in vivo” de los efectos extraóseos de la vitamina D es todavía incierta