# Vitamin D and Cancer

서울대학교 의과대학

가정의학과 조 희 경

# Contents

- Introduction
- Biological Mechanisms
- Epidemiologic Studies
- Randomized Controlled Trials
- Guidelines on vitamin D intake

The NEW ENGLAND JOURNAL of MEDICINE

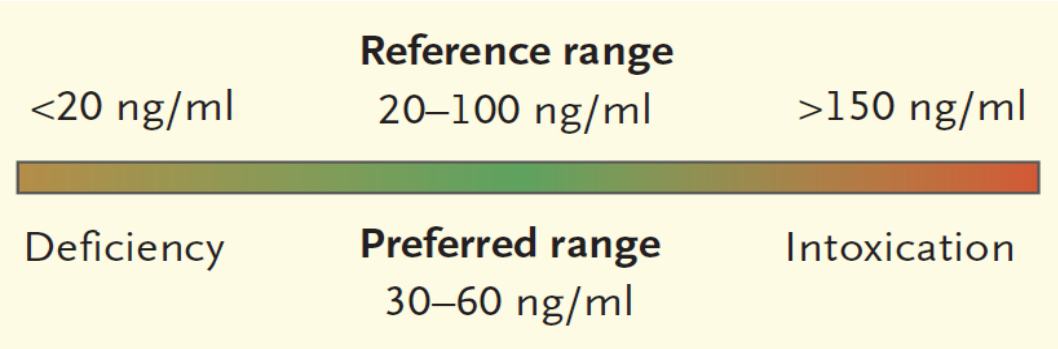
American Journal of Epidemiology


## Editorial

# Anticancer Vitamins du Jour—The ABCED's So Far

# Known and Unknowns

- WE KNOW – Vitamin D is important



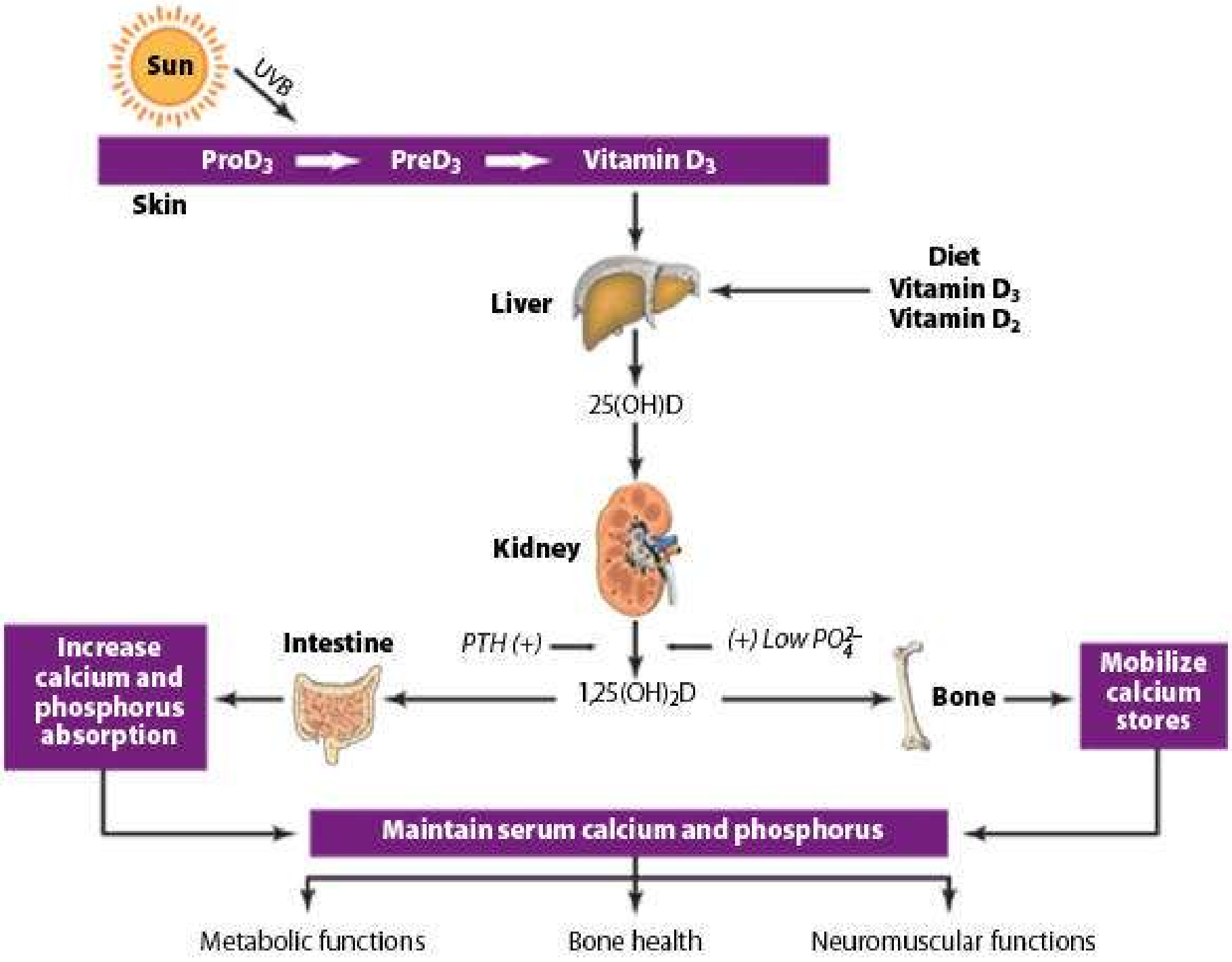

  - < 20 ng/mL : deficient or insufficient
  - Potentially harmful level: ≥150 ng/mL
    - hypercalcemia, vascular soft tissue calcification, hyperphosphatemia

- **UNKNOWNS**

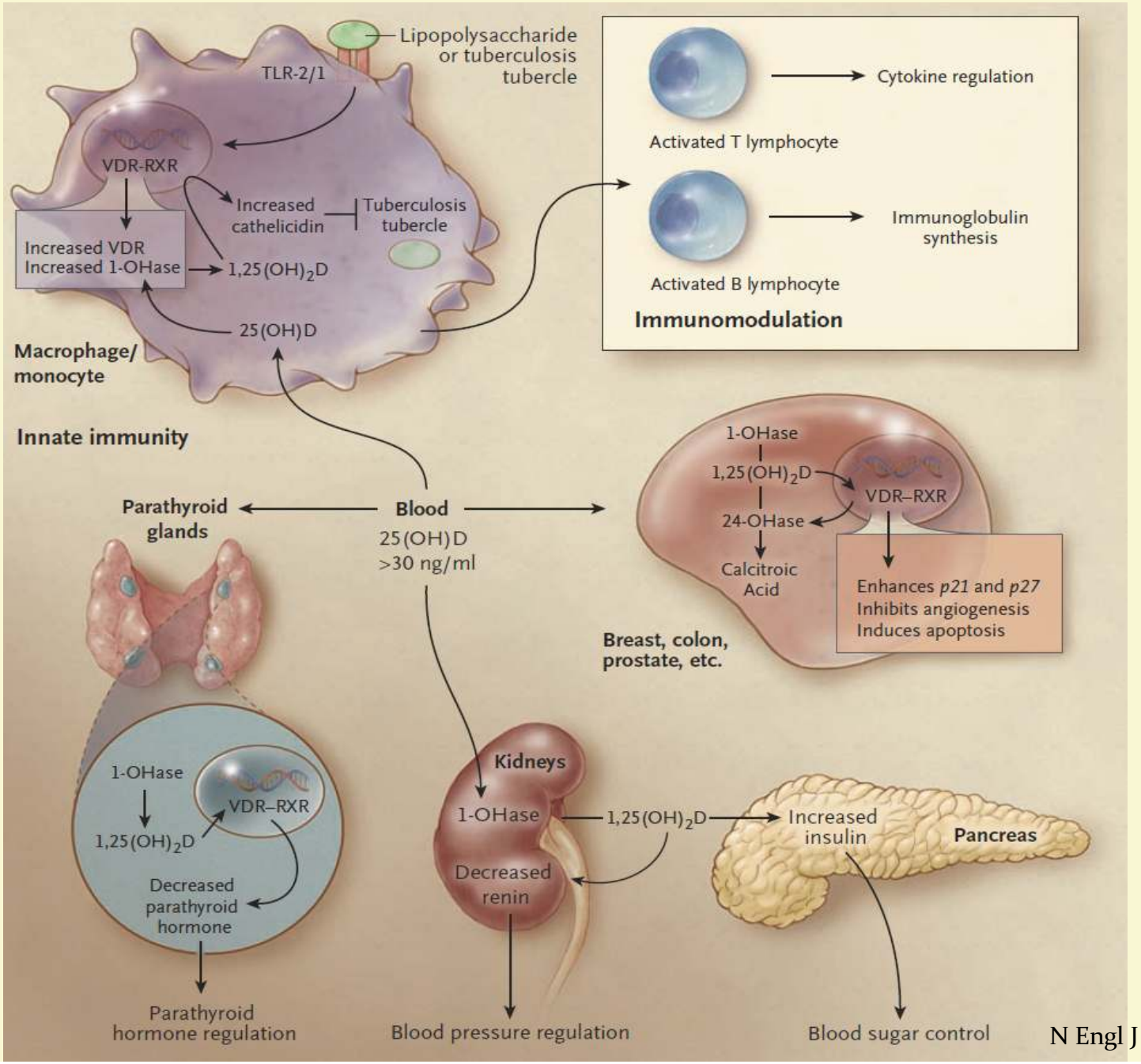
  **Optimal intake?**

  **Optimal blood 25(OH)D level?**

# Biological Mechanisms

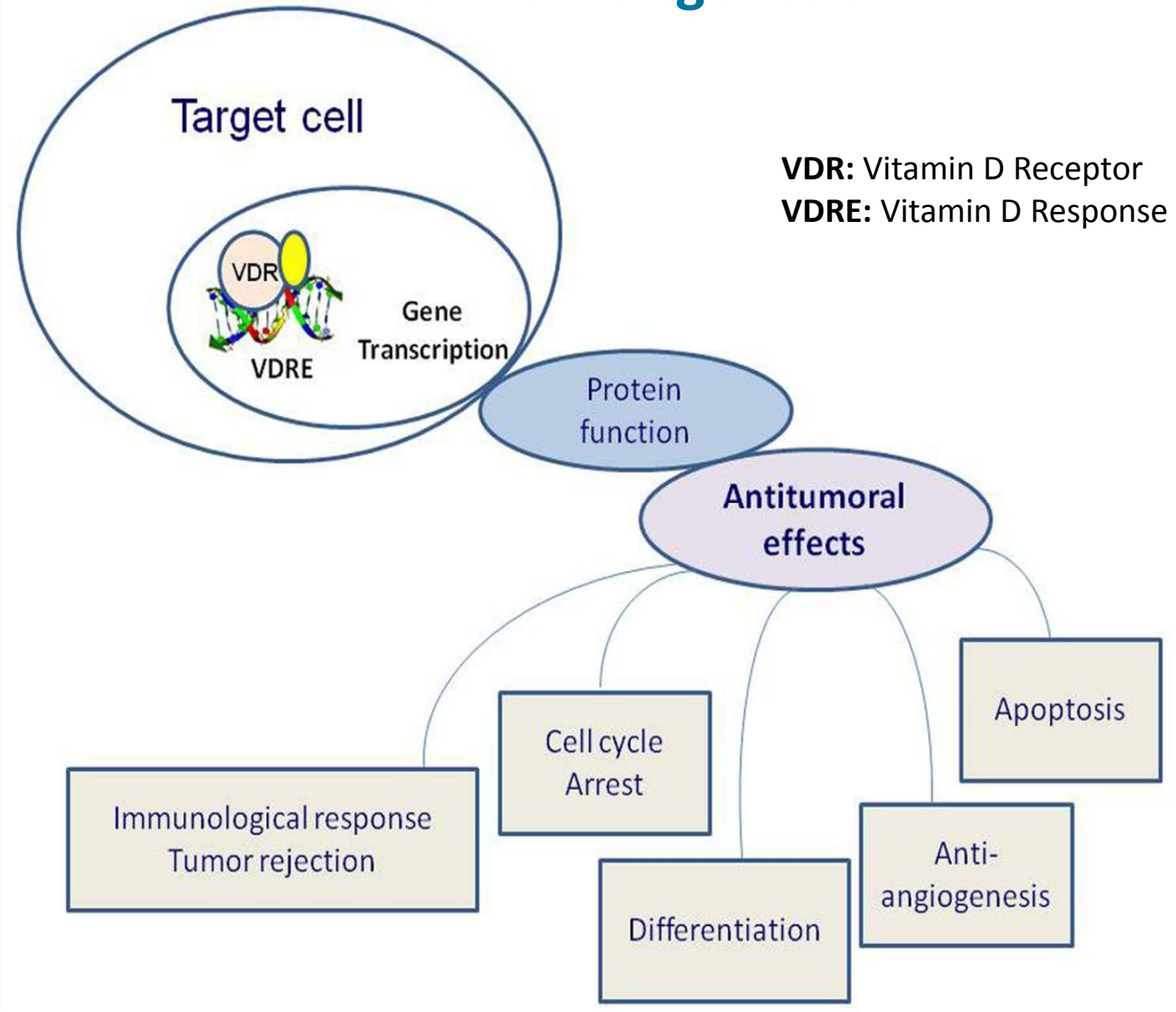

Sun
UVB
ProD3
PreD3
Vitamin D3
Skin
Liver
Diet
Vitamin D3
Vitamin D2
25(OH)D
Kidney
Intestine
PTH (+)
(+) Low PO4 2-
1,25(OH)2D
Bone
Increase calcium and phosphorus absorption
Mobilize calcium stores
Maintain serum calcium and phosphorus
Metabolic functions
Bone health
Neuromuscular functions

# Non-Skeletal Functions of Vitamin D



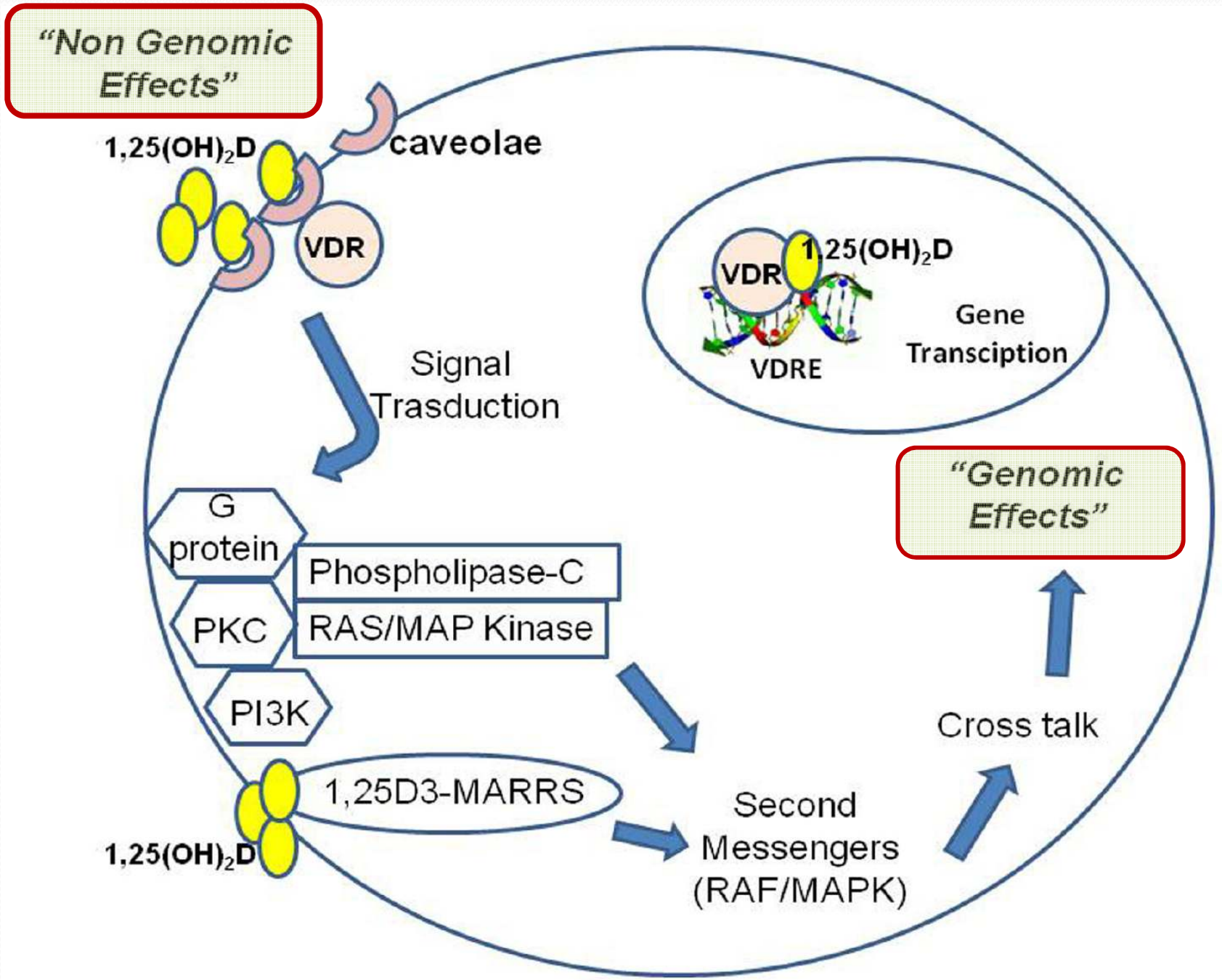

N Engl J Med 2007; 357;3

# Effects of Vitamin D Receptor(VDR) Activation on Tumorigenesis




**VDR:** Vitamin D Receptor
**VDRE:** Vitamin D Response Elements

Vuolo L. *Front Endocrinol* 2012;3:58




Vuolo L. *Front Endocrinol* 2012;3:58

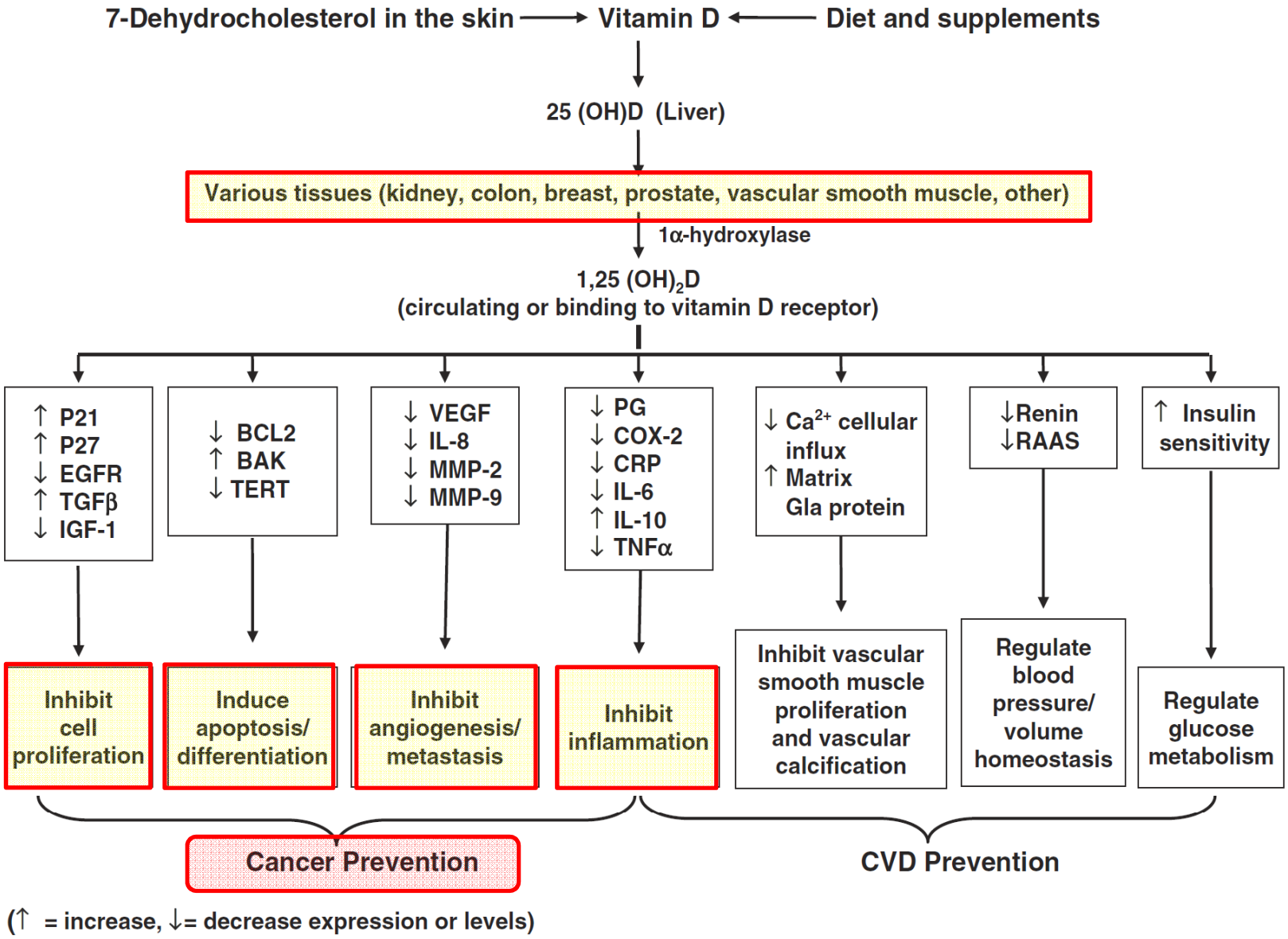



**Fig. 1.** Mechanisms by which vitamin D may lower cancer and cardiovascular risk. *BAK*, BCL2-antagonist/killer; *BCL2*, B-cell chronic lymphocytic leukemia/lymphoma 2; *COX-2*, cyclooxygenase-2; *CRP*, C-reactive protein; *EGFR*, epidermal growth factor receptor; *IGF-1*, insulin-like growth factor-1; *IL-6*, interleukin-6; *IL-8*, interleukin-8; *IL-10*, interleukin-10; *MMP-2*, matrix metalloproteinase-2; *MMP-9*, matrix metalloproteinase-9; *PG*, prostaglandin; *RAAS*, renin-angiotensin-aldosterone system; *TERT*, telomerase reverse transcriptase; *TGFß*, transforming growth factor-ß; *TNFα*, tumor necrosis factor-α; *VEGF*, vascular endothelial growth factor.

# Epidemiologic studies

# The Association of Solar Ultraviolet B (UVB) with Reducing Risk of Cancer: Multifactorial Ecologic Analysis of Geographic Variation in Age-adjusted Cancer Mortality Rates

WILLIAM B. GRANT[1] and CEDRIC F. GARLAND[2]

GRANT WB. *Anticancer Research* 2006; *26*: 2687-2700

- Colon cancer
- Breast cancer

- Prostate cancer
- NHL (Non-Hodgkin lymphoma)
- Pancreatic cancer
- Bladder cancer
- Kidney cancer
- Lung cancer
- Ovarian cancer
- Endometrial cancer
- Esophageal cancer
- Gastric cancer

# Colorectal Cancer

VOLUME 29 · NUMBER 28 · OCTOBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

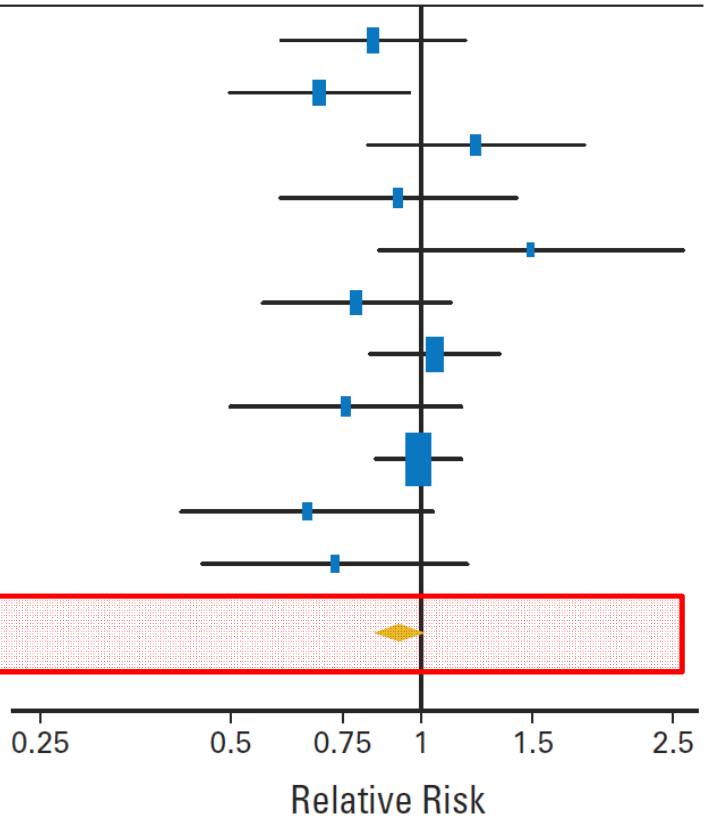
# Association Between Vitamin D and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies

*Yanlei Ma, Peng Zhang, Feng Wang, Jianjun Yang, Zhihua Liu, and Huanlong Qin*

**Vitamin D Intake**

| | Range (μg/d) | Relative Risk | 95% CI |
|---|---|---|---|
| Jenab et al[19] | 3.7 | 0.84 | 0.60 to 1.17 |
| Lipworth et al[20] (C) | 3.5 | 0.69 | 0.50 to 0.96 |
| Lipworth et al[20] (R) | 3.5 | 1.22 | 0.82 to 1.80 |
| Ishihara et al[21] (M) | 9.2 | 0.92 | 0.60 to 1.42 |
| Ishihara et al[21] (F) | 8.7 | 1.49 | 0.86 to 2.60 |
| Mizoue et al[22] | 7.7 | 0.79 | 0.56 to 1.11 |
| Terry et al[23] | 0.8 | 1.05 | 0.83 to 1.33 |
| Zheng et al[24] | 6.3 | 0.76 | 0.50 to 1.16 |
| Martínez et al[25] | 4.2 | 0.99 | 0.85 to 1.16 |
| Kearney et al[26] | 5.6 | 0.66 | 0.42 to 1.05 |
| Bostick et al[27] | 6.2 | 0.73 | 0.45 to 1.18 |
| Overall | | 0.88 | 0.80 to 0.96 |

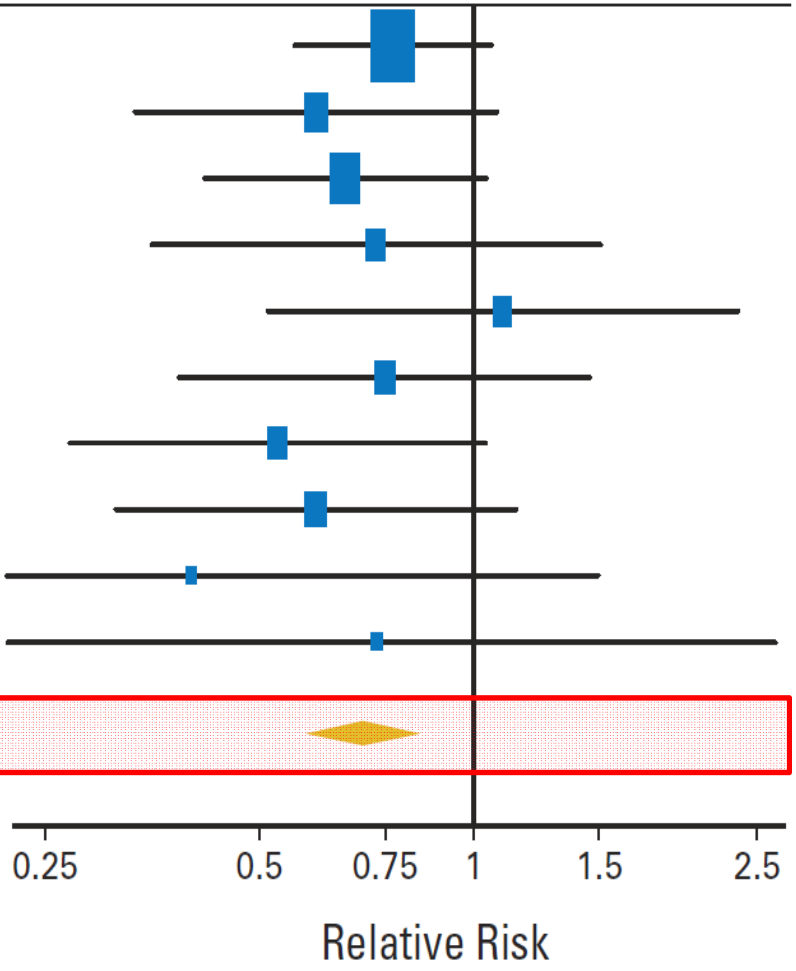
Test for heterogeneity: Q = 3.62; $P = .191$; $I^2 = 26.6\%$



## Blood 25(OH)D Levels

| | Range (ng/mL) | Relative Risk | 95% CI |
|---|---|---|---|
| Jenab et al[19] | 8.0 | 0.77 | 0.56 to 1.06 |
| Woolcott et al[28] | 16.0 | 0.60 | 0.33 to 1.07 |
| Wu et al[29] | 21.0 | 0.66 | 0.42 to 1.05 |
| Otani et al[30] (M) | 9.2 | 0.73 | 0.35 to 1.50 |
| Otani et al[30] (F) | 8.3 | 1.10 | 0.50 to 2.30 |
| Wactawski-Wende et al[31] | 11.0 | 0.75 | 0.39 to 1.48 |
| Feskanich et al[34] | 20.4 | 0.53 | 0.27 to 1.04 |
| Tangrea et al[32] | 9.5 | 0.60 | 0.30 to 1.10 |
| Braun et al[33] | 12.9 | 0.40 | 0.10 to 0.40 |
| Garland et al[35] | 23.0 | 0.73 | 0.20 to 2.66 |
| Overall | | 0.67 | 0.54 to 0.80 |

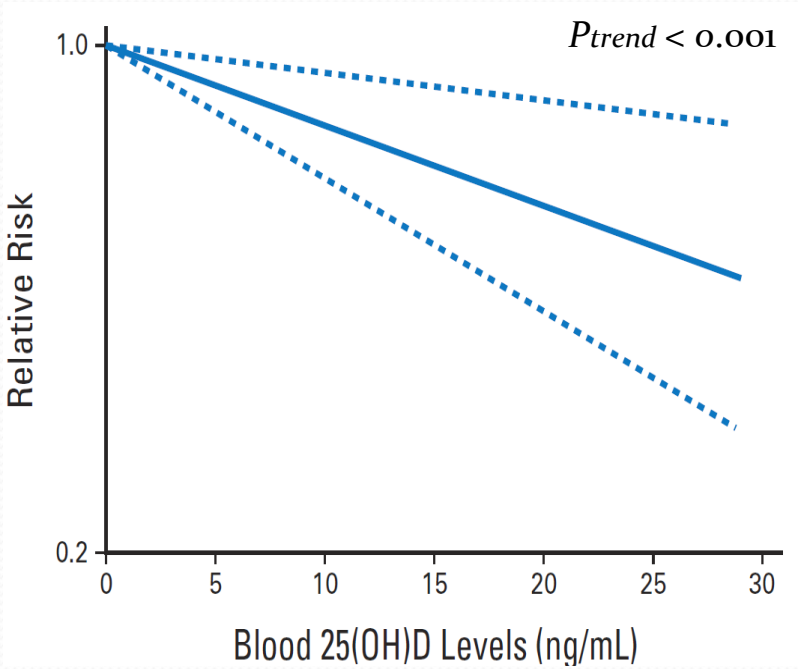
Test for heterogeneity: Q = 3.637; $P$ = .934; $I^2$ =0.0%




Ma Y. *J Clin Oncol 2011;29:3775-3782.*

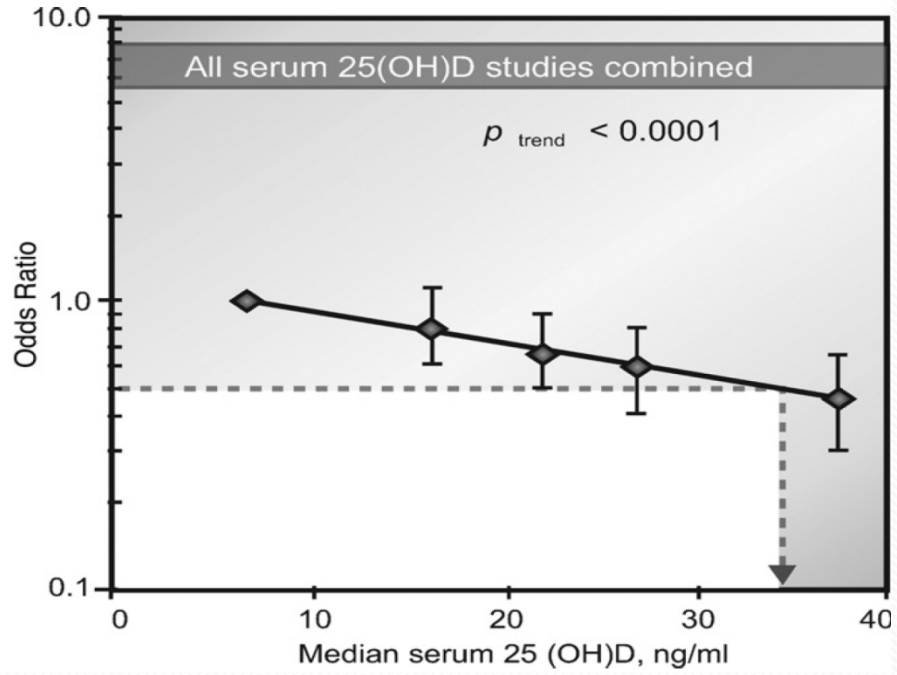
# Meta-regression

## Dose-Response Relationship




**Per 10 ng/mL increment in blood 25(OH)D , RR = 0.74 (95% CI, 0.63-0.89)**

Ma Y. *J Clin Oncol 2011;29:3775-3782.*




**50% projected reduction in CRC incidence with 33 ng/ml, compared to ≤12 ng/ml**

Gorham ED. Am J Prev Med 2007;32(3):210–216

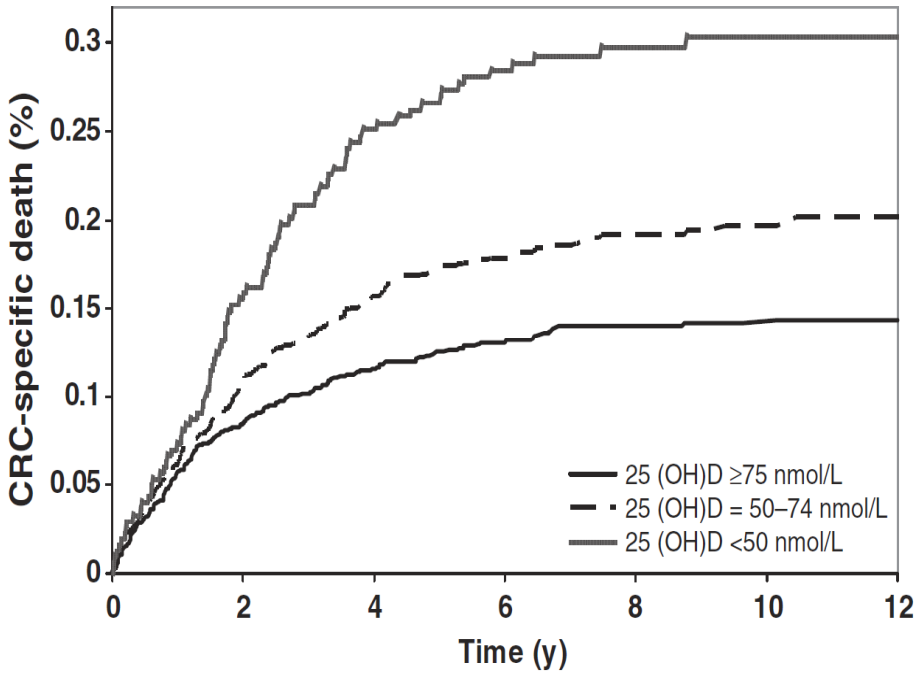
# Colorectal Cancer Mortality

Research Article

Cancer Epidemiology, Biomarkers & Prevention

## Prediagnostic 25-Hydroxyvitamin D, *VDR* and *CASR* Polymorphisms, and Survival in Patients with Colorectal Cancer in Western European Populations

Veronika Fedirko[1], Elio Riboli[2], Anne Tjønneland[3], Pietro Ferrari[1], Anja Olsen[3], H. Bas Bueno-de-Mesquita[4,5],




**Adjusted cumulative incidence curve of CRC-specific mortality by prediagnostic 25(OH)D levels in the EPIC cohort**

Fedirko. *Cancer Epidemiol Biomarkers Prev* 2012; 21(4)

# CRC and Overall Mortality

**Table 2.** HRs and 95% CIs for CRC-specific and overall mortality according to quintiles of blood 25(OH)D in the EPIC study ($N = 1,202$)

| 25(OH)D category | Category range, nmol/L | No. | Event | HR (95% CI) | $P_{trend}$[a] |
|---|---|---|---|---|---|
| CRC-specific mortality | | | | | |
| Multivariable[c] | | | | | |
| Quintile 1 | <36.3 | 242 | 104 | 1.00 (ref.) | 0.04 |
| Quintile 2 | 36.4–48.6 | 239 | 85 | 0.76 (0.56–1.02) | |
| Quintile 3 | 48.7–60.5 | 241 | 95 | 0.93 (0.69–1.24) | |
| Quintile 4 | 60.6–76.8 | 240 | 78 | 0.78 (0.58–1.06) | |
| Quintile 5 | >76.8 | 240 | 82 | 0.69 (0.50–0.93) | |
| Overall mortality | | | | | |
| Multivariable[c] | | | | | |
| Quintile 1 | <36.3 | 242 | 128 | 1.00 (ref.) | <0.01 |
| Quintile 2 | 36.4–48.6 | 239 | 108 | 0.82 (0.63–1.07) | |
| Quintile 3 | 48.7–60.5 | 241 | 117 | 0.91 (0.70–1.18) | |
| Quintile 4 | 60.6–76.8 | 240 | 95 | 0.78 (0.59–1.03) | |
| Quintile 5 | >76.8 | 240 | 93 | 0.67 (0.50–0.88) | |

**CRC:** Colorectal Cancer

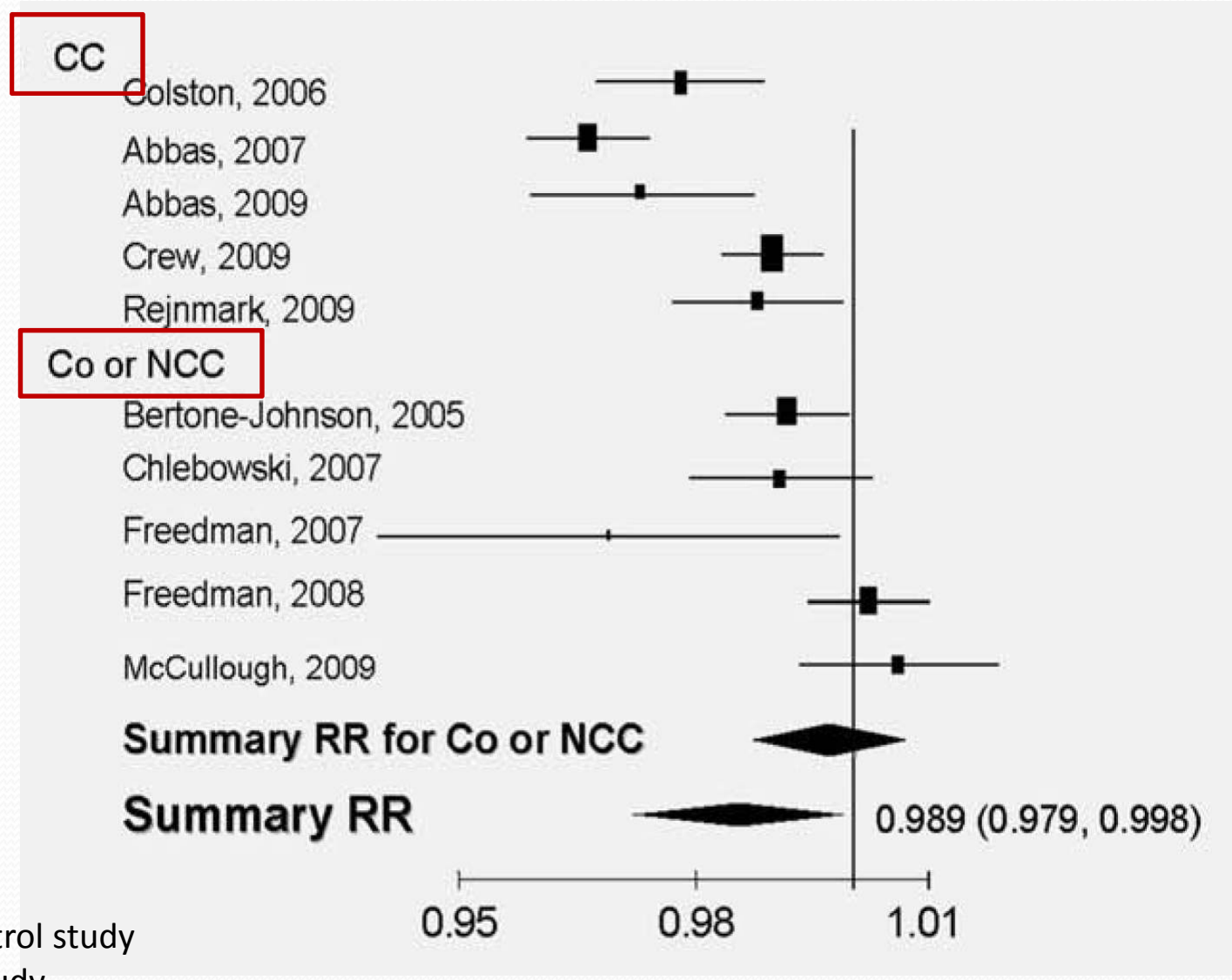
Fedirko. *Cancer Epidemiol Biomarkers Prev* 2012; 21(4)

# Summary of Colorectal Cancer in epidemiologic studies

- Consistently inverse relationship
- Between vitamin D levels and CRC risk or mortality

# Breast Cancer

# Relative Risks of Breast Cancer per 1 ng/ml Increase in Serum 25(OH)D




CC: Case-Control study
Co: Cohort study
NCC: Nested Case Control study within a prospective cohort study

Gandini S. *Int. J. Cancer* 2011; 128:1414–24

RESEARCH ARTICLE Open Access

# Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II

A Heather Eliassen[1,2*], Donna Spiegelman[2,3], Bruce W Hollis[5], Ronald L Horst[6], Walter C Willett[1,2,4] and Susan E Hankinson[1,2]

- prospective nested case-control study within the Nurses' Health Study II
- 613 cases vs. 1,218 matched controls

**Relative Risks (95% CI) of Breast Cancer by Quartile of Pre-diagnostic Plasma 25(OH)D**

| Cut points (ng/mL)§ | Quartile 1 < 18.4 | Quartile 2 18.4 to < 24.6 | Quartile 3 24.6 to < 30.6 | Quartile 4 ≥ 30.6 | *P*-value, test for trend |
|---|---|---|---|---|---|
| Cases/controls | 141/300 | 151/305 | 145/307 | 176/306 | |
| Simple | 1.00 (ref) | 1.06 (0.80 to 1.40) | 1.02 (0.77 to 1.36) | 1.26 (0.94 to 1.69) | 0.14 |
| Multivariate* | 1.00 (ref) | 1.05 (0.79 to 1.39) | 0.95 (0.71 to 1.29) | 1.20 (0.88 to 1.63) | 0.32 |

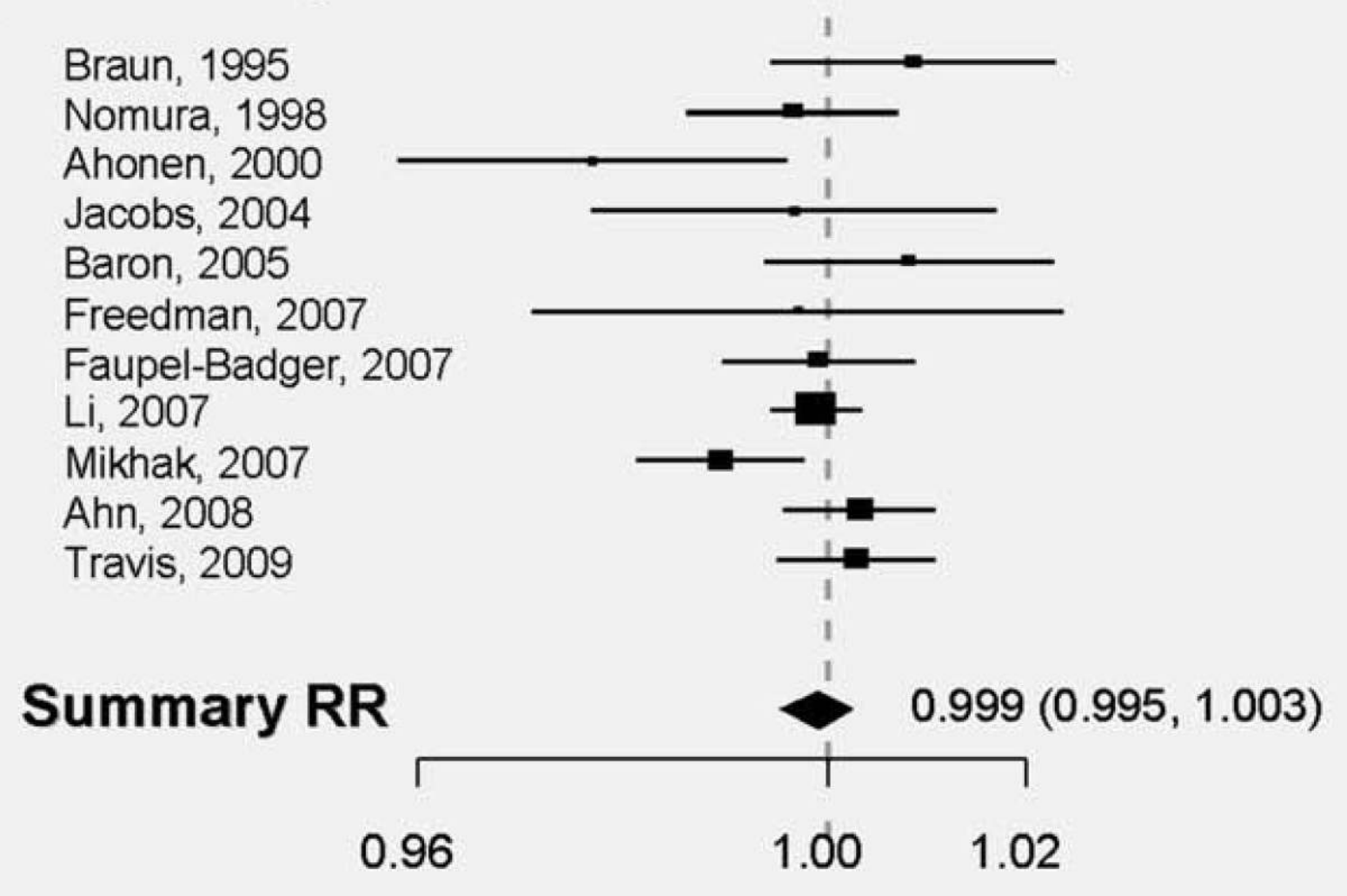
Eliassen AH. *Breast Cancer Research* 2011;13:R50

# Summary of  Breast Cancer in epidemiologic studies

- **Inconsistent relationship**

# Other Cancers

# Relative Risks of Prostate Cancer
## per 1 ng/ml Increase in Serum 25(OH)D




Gandini S. *Int. J. Cancer* 2011; 128:1414–1424

# A pooled nested case-control study

## (the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers)

**Kidney cancer**

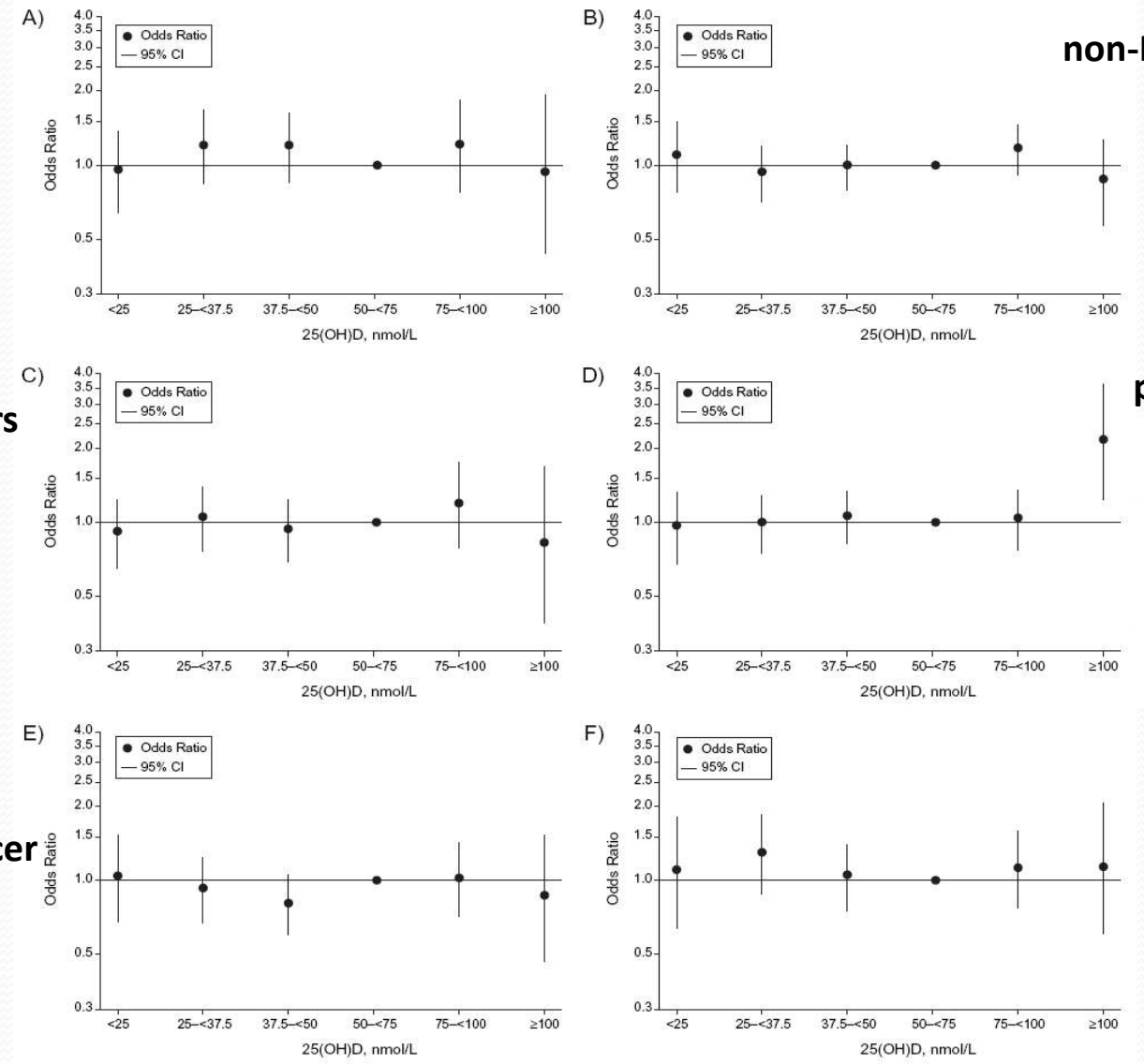
**non-Hodgkin lymphoma**

**Upper GI cancers**

**pancreatic cancer**

**Endometrial cancer**

**ovarian cancer**




*Am J Epidemiol* 2010;172:4–9

# Limitations in Observational Studies

- **Single serum 25(OH)D measurement** at a time of enrollment

  → CANNOT represent **LONG-TERM vitamin D levels**

- In large-scale epidemiological studies
  - For whole population
  - multiple measurement of blood 25(OH)D
  - for a long-term period

might be **UNFEASIBLE**

**Predicted 25(OH)D scores**

- Combined influences of major determinants of circulating 25(OH)D
- Can be used in a large population without blood samples
- Can be updated multiple times during follow-up

ARTICLE

# Predicted Plasma 25-Hydroxyvitamin D and Risk of Renal Cell Cancer

Hee-Kyung Joh, Edward L. Giovannucci, Kimberly A. Bertrand, Soo Lim, Eunyoung Cho

*Natl Cancer Inst* 2013; Apr 8 [Epub]

**Derivatives of predicted plasma 25(OH)D score**

- Race
- UV-B radiation flux at residence
- Leisure-time physical activity
- Body mass index
- Dietary and supplemental vitamin D intakes
- Alcohol intake
- Post-menopausal hormone use (in women)

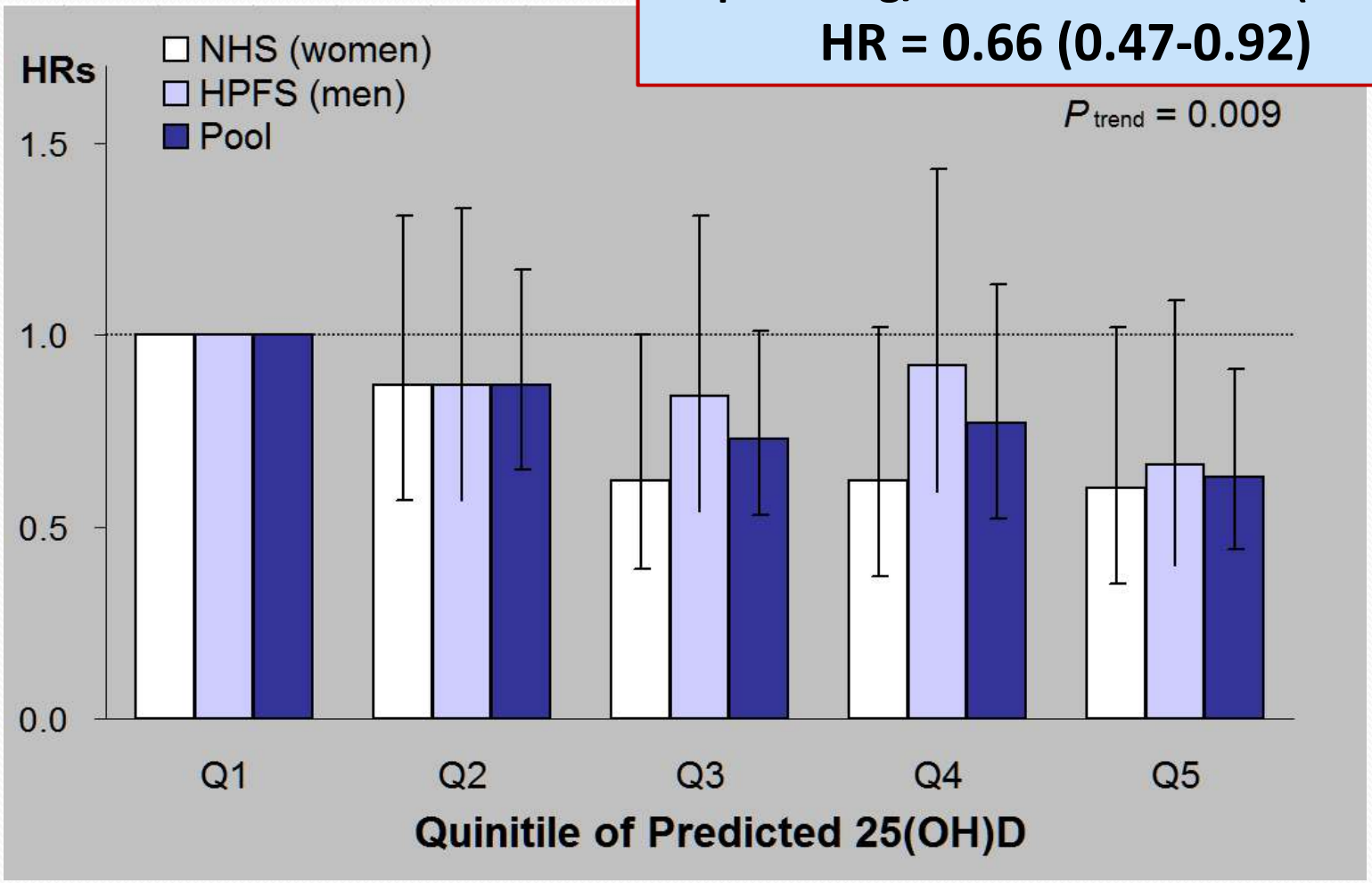
# METHODS

- **STUDY POPULATION**
  - Two independent prospective cohorts in the US
    - 72,051 women (Nurses' Health Study)
    - 46,380 men (Health Professionals Follow-Up Study)
- **Follow-up : 1986 - 2008 (22 years)**
- **Predicted 25(OH)D score & all covariables :**

  updated every 2 years
- **No. of incident RCC cases**
  - 201 cases in women
  - 207 cases in men

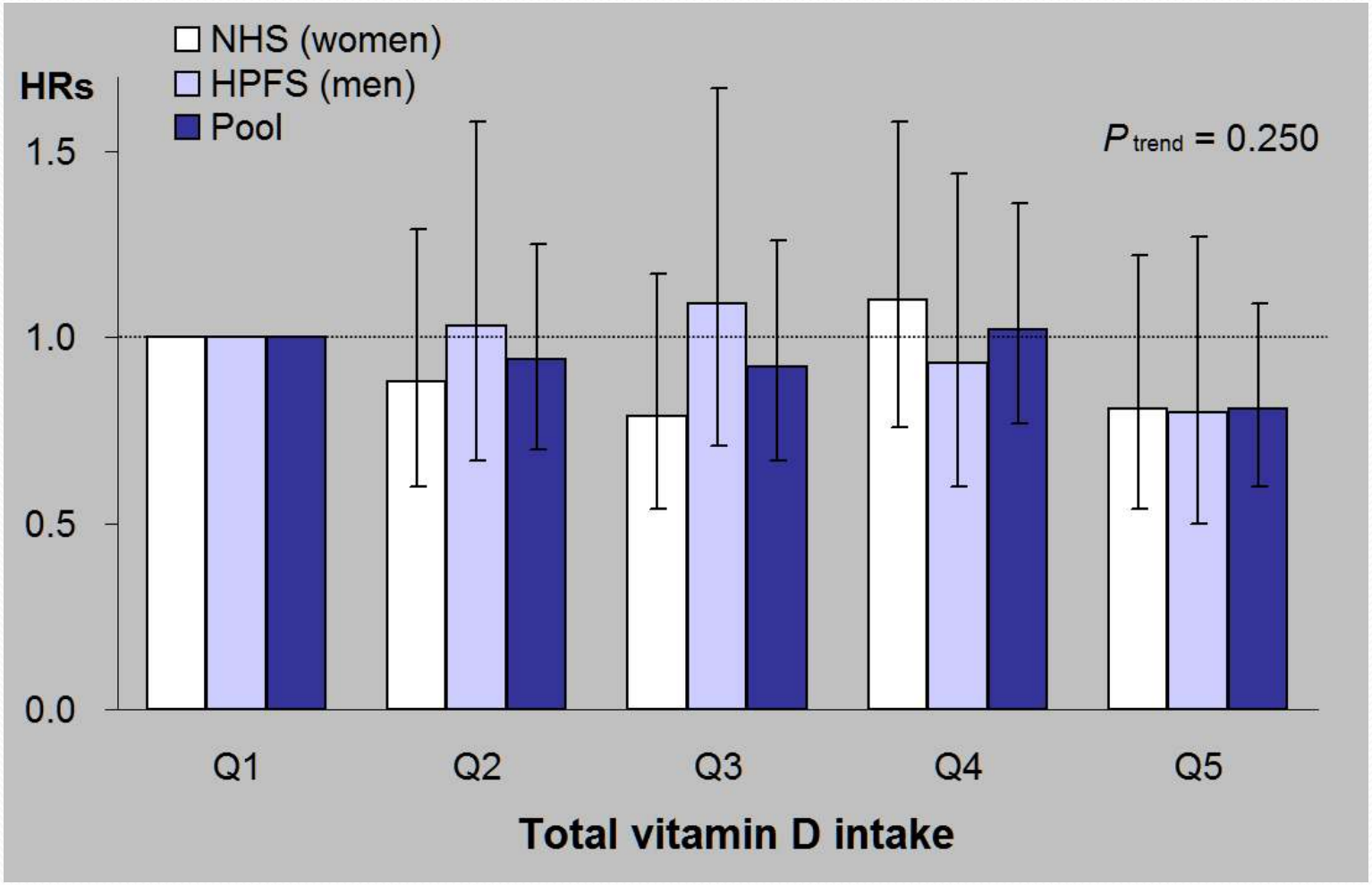
# Predicted Plasma 25(OH)D and Risk of Renal Cell Cancer

**per 10 ng/ml increment in 25(OH)D**
**HR = 0.66 (0.47-0.92)**




Joh HK. *J Natl Cancer Inst* 2013; Apr 8 [Epub]

# Vitamin D Intake and Risk of Renal Cell Cancer




Joh HK. *J Natl Cancer Inst* 2013; Apr 8 [Epub]

# RCTs

**No RCT in vitamin D** has been completed with **cancer** as the pre-specified **primary outcome**.

- **All** evidence are from **secondary analyses**

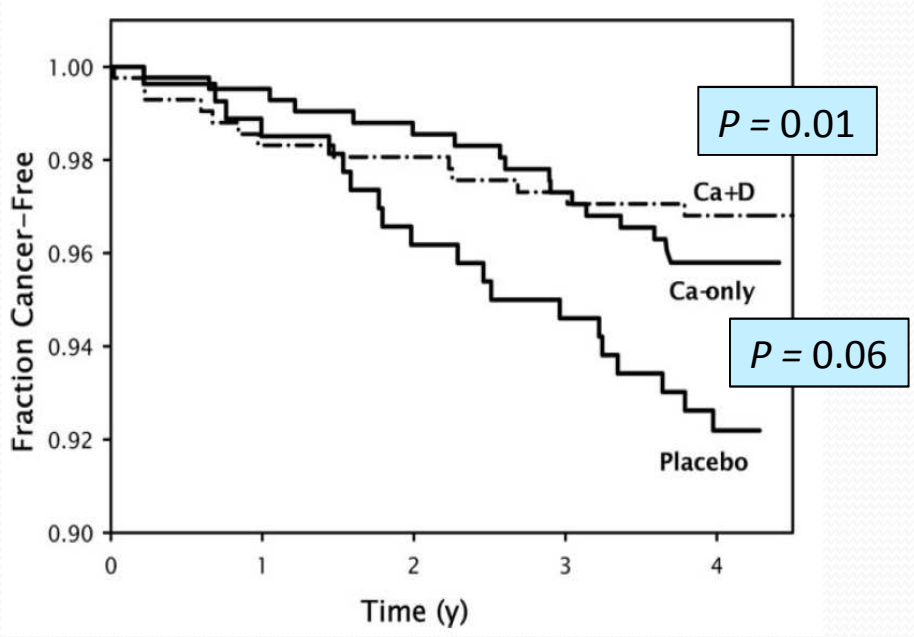
# Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial[1,2]

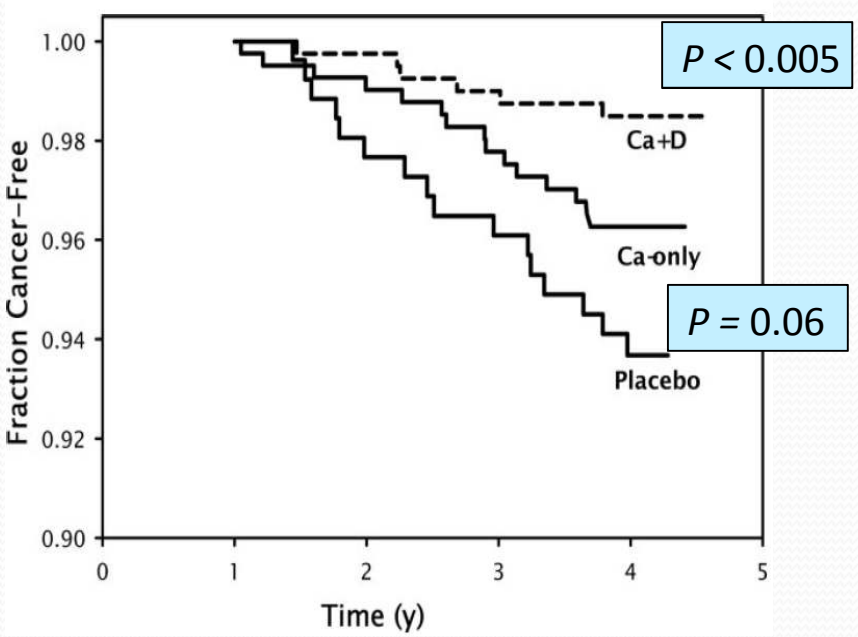
*Joan M Lappe, Dianne Travers-Gustafson, K Michael Davies, Robert R Recker, and Robert P Heaney*

*Am J Clin Nutr* 2007;85:1586–91

- Population & Follow-up
  - 1179 postmenopausal women aged >55 y followed 4 years
- Intervention
  - Ca-only : 1400-1500 mg/d Calcium
  - Ca + D : 1400-1500 mg/d Calcium + 1100 IU/d cholecalciferol
  - Placebo
- Outcome variables
  - Primary outcome: fracture incidence
  - Secondary outcome: **total cancer incidence**

| Site | Years 1–4 | | | Years 2–4 | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 288) | Calcium only ($n$ = 445) | Vitamin D plus calcium ($n$ = 446) | Placebo ($n$ = 266) | Calcium only ($n$ = 416) | Vitamin D plus calcium ($n$ = 403) |
| Breast($n$) | 8 | 6 | 5 | 7 | 6 | 4 |
| Colon ($n$) | 2 | 0 | 1 | 2 | 0 | 0 |
| Lung ($n$) | 3 | 3 | 1 | 3 | 2 | 1 |
| Lymph, leukemia, myeloma ($n$) | 4 | 4 | 2 | 4 | 4 | 2 |
| Uterus ($n$) | 0 | 2 | 1 | 0 | 1 | 0 |
| Other ($n$) | 3 | 2 | 3 | 2 | 2 | 1 |
| Total[1] | 20 (6.9) | 17 (3.8) | 13 (2.9) | 18 (6.8) | 15 (3.6) | 8 (2.0) |

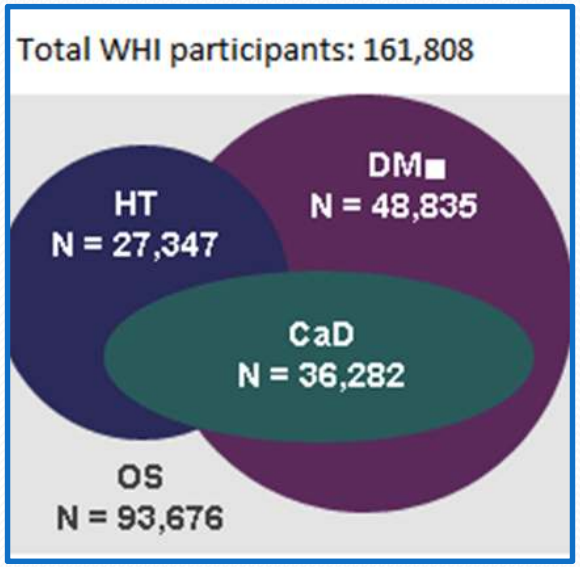


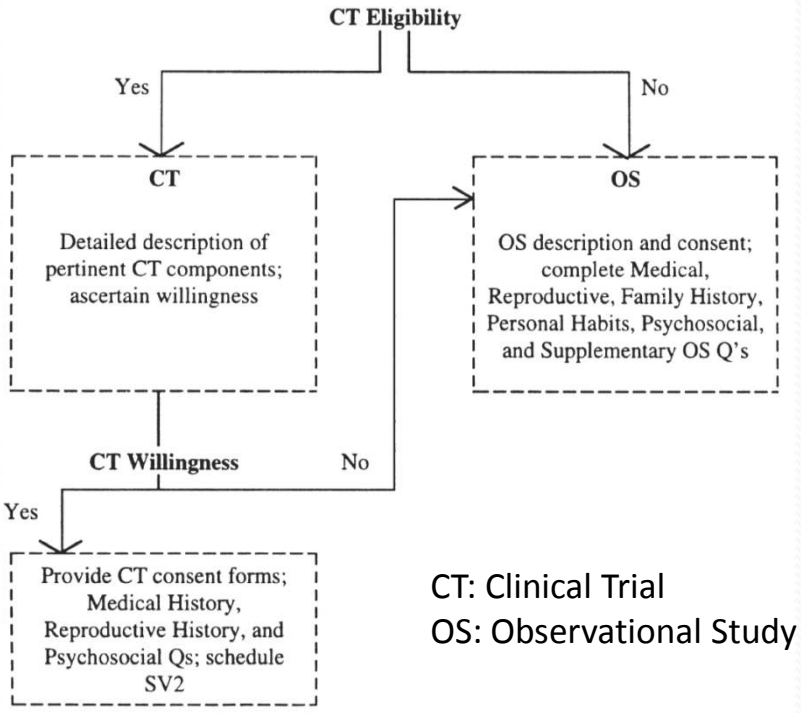

Lappe JM. *Am J Clin Nutr* 2007;85:1586–91

# Women's Health Initiative (WHI) Study

1994-1999 (average 7 years)
in the US postmenopausal women (50-79y)




HT: Hormone Therapy
DM: Dietary Modification
CaD: Calcium + Vitamin D supplementation




CT: Clinical Trial
OS: Observational Study

**CaD supplementation**: in 36,282 women
- 18,176 received **1000 mg** of elemental calcium and **400 IU** of vitamin D3 daily
- 18,106 received placebo

**- Primary outcome**: hip fracture
**- Secondary outcome**: total fracture and **colorectal cancer**

# Critics of WHI study

- **LOW dosage** of vitamin D supplementation (400 IU/d)
- More than half (57%) of the participants were taking personal calcium or vitamin D supplements at randomization
- **Poor adherence** :
  - 1/3 of the intervention group did not take supplements.
  - Off-study use of additional vitamin D and calcium supplements during the trial in placebo group

  → minimize the difference between placebo and supplement
- **Lack of blood 25-(OH)D measurement**
- **No regular or end-of-study colonoscopy**
  - 15% had no bowel assessment
- **Short length of follow-up**

# Colorectal Cancer – WHI study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Calcium plus Vitamin D Supplementation and the Risk of Colorectal Cancer

Jean Wactawski-Wende, Ph.D., Jane Morley Kotchen, M.D., Garnet L. Anderson, Ph.D., Annlouise R. Assaf, Ph.D., Robert L. Brunner, Ph.D., Mary Jo O'Sullivan, M.D., Karen L. Margolis, M.D., Judith K. Ockene, Ph.D., Lawrence Phillips, M.D., Linda Pottern, Ph.D., Ross L. Prentice, Ph.D., John Robbins, M.D., Thomas E. Rohan, Ph.D., Gloria E. Sarto, M.D., Santosh Sharma, M.D., Marcia L. Stefanick, Ph.D., Linda Van Horn, Ph.D., Robert B. Wallace, M.D., Evelyn Whitlock, M.D., Tamsen Bassford, M.D., Shirley A.A. Beresford, Ph.D., Henry R. Black, M.D., Denise E. Bonds, M.D., Robert G. Brzyski, M.D., Bette Caan, Dr.P.H., Rowan T. Chlebowski, M.D., Barbara Cochrane, Ph.D., Cedric Garland, Dr.P.H., Margery Gass, M.D., Jennifer Hays, Ph.D., Gerardo Heiss, M.D., Susan L. Hendrix, D.O., Barbara V. Howard, Ph.D., Judith Hsia, M.D., F. Allan Hubbell, M.D., Rebecca D. Jackson, M.D., Karen C. Johnson, M.D., Howard Judd, M.D., Charles L. Kooperberg, Ph.D., Lewis H. Kuller, M.D., Andrea Z. LaCroix, Ph.D., Dorothy S. Lane, M.D., Robert D. Langer, M.D., Norman L. Lasser, M.D., Cora E. Lewis, M.D., Marian C. Limacher, M.D., and JoAnn E. Manson, M.D., for the Women's Health Initiative Investigators*

N Engl J Med 2006;354:684-96.

ORIGINAL ARTICLE

# Calcium plus Vitamin D Supplementation and the Risk of Colorectal Cancer

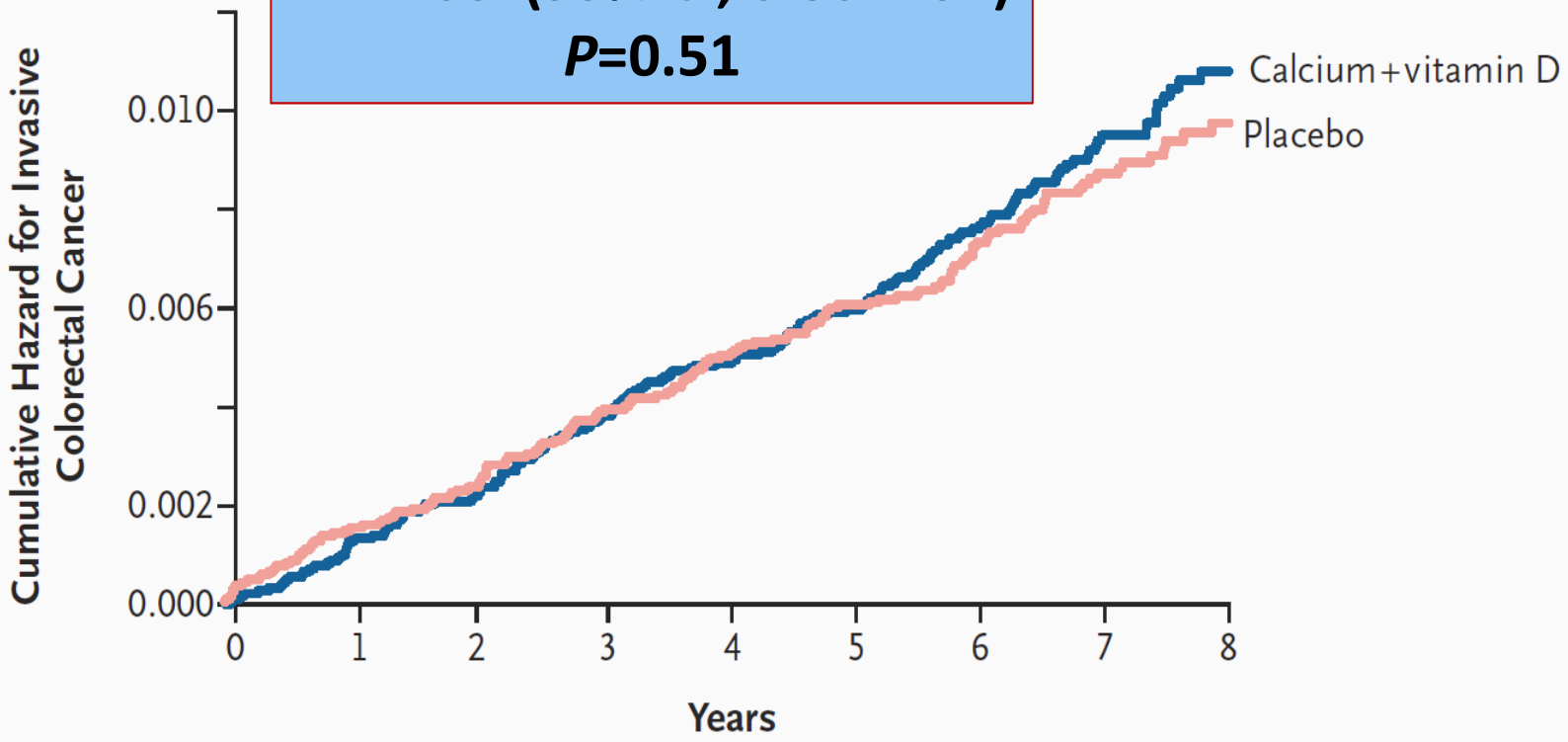
## RCT

- Effect of CaD supplementation ?
  - Colorectal cancer: secondary outcome
  - A Cox proportional hazards model

## Nested Case-Control Study

- Effect of Baseline serum 25(OH)D levels?
  - 306 cases
  - 306 controls
  - logistic regression model

**HR 1.08 (95% CI, 0.86-1.34)**
***P*=0.51**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **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 |

N Engl J Med 2006;354:684-96.

# Odds Ratios for Invasive Colorectal Cancer by the Quartile of Baseline Serum 25(OH)D Level in a Nested Case–Control Study

| Baseline Serum 25-Hydroxyvitamin D | Main-Effect Odds Ratio (95% CI)† | Calcium + Vitamin D | Placebo | Intervention Odds Ratio (95% CI)‡ |
|---|---|---|---|---|
| | | No. with Colorectal Cancer/ No. of Controls | | |
| ≥58.4 nmol/liter | 1.00 | 33/48 | 27/45 | 1.15 (0.58–2.27) |
| 42.4–58.3 nmol/liter | 1.96 (1.18–3.24) | 44/41 | 34/32 | 1.12 (0.59–2.12) |
| 31.0–42.3 nmol/liter | 1.95 (1.18–3.24) | 35/32 | 45/41 | 0.99 (0.51–1.91) |
| <31.0 nmol/liter | 2.53 (1.49–4.32) | 46/39 | 42/28 | 0.75 (0.39–1.48) |
| | *P* for trend = 0.02 | | | *P* for interaction = 0.54 |

Significantly increased risk of colorectal cancer in the lower baseline serum 25(OH)D levels

However, findings from the nested case–control study revealed no significant interaction between serum 25(OH)D levels at baseline and treatment assignment.

N Engl J Med 2006;354:684-96.

# **Breast cancer** – WHI

**Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer**

Chleboswski RT. *J Natl Cancer Inst* 2007; 100: 1581 – 1591

## RCT

- Effect of CaD supplementation ?

## Nested Case-Control Study

- Effect of Baseline serum 25(OH)D levels?
  - 1067 cases
  - 1067 controls

# Cumulative Hazard Ratio for Invasive Breast Cancer with Supplemental Calcium + Vitamin D

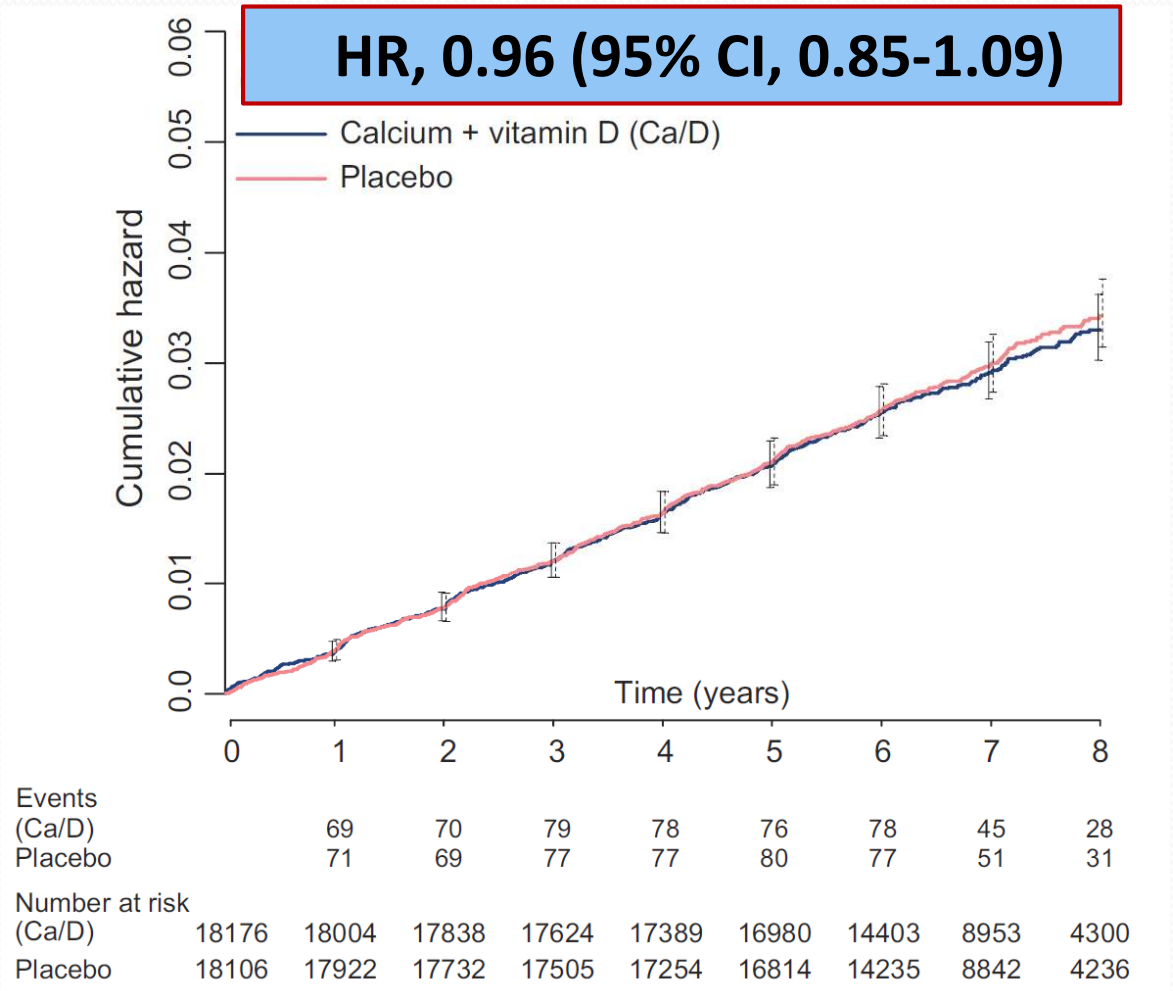
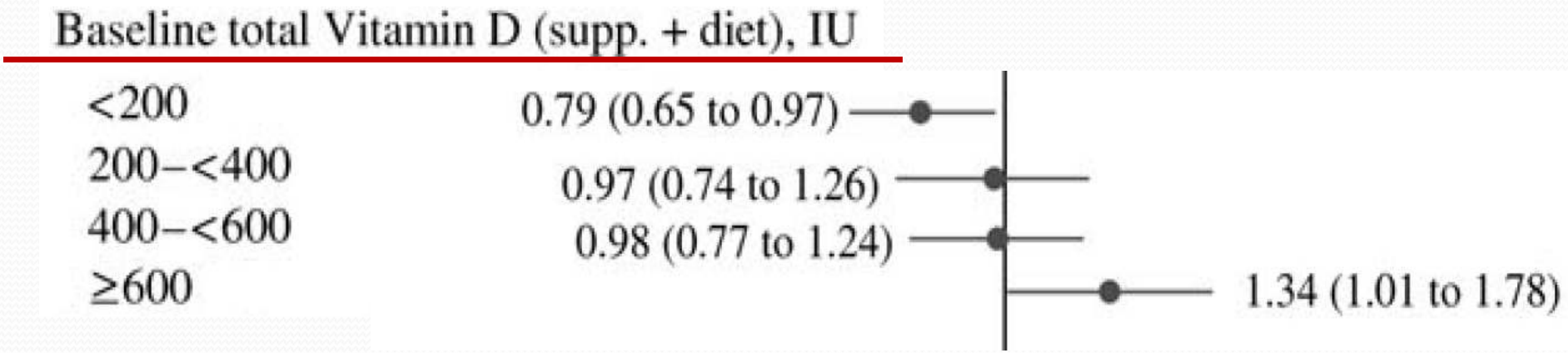



**Figure 2.** Kaplan–Meier estimates of the cumulative hazard ratio for invasive breast cancer with supplemental calcium plus vitamin D (Ca/D) as compared with placebo. HR, hazard ratio; CI, confidence interval.

# Subgroup Analysis




*P* interaction = 0.003

Chleboswski RT. *J Natl Cancer Inst* 2007; 100: 1581 – 1591

# Baseline Serum 25(OH)D Levels

| Baseline 25-hydroxyvitamin D, nmol/L | | Calcium + vitamin D | | |
|---|---|---|---|---|
| Determinate quintile | Main effect OR (95% CI)† | No. of mpatients/ no. of control subjects | Placebo | Intervention OR (95% CI)‡ |
| ≥67.6 | 1.00 (referent) | 86/109 | 76/86 | 0.89 (0.58 to 1.36) |
| 55.4≤67.6 | 1.15 (0.86 to 1.55) | 95/87 | 86/98 | 1.25 (0.83 to 1.90) |
| 43.9≤55.4 | 1.35 (0.99 to 1.82) | 102/87 | 92/84 | 1.07 (0.70 to 1.62) |
| 32.4≤43.9 | 1.17 (0.86 to 1.60) | 71/84 | 102/87 | 0.69 (0.45 to 1.06) |
| <32.4 | 1.22 (0.89 to 1.67) | 94/94 | 91/82 | 0.91 (0.60 to 1.39) |

Baseline 25(OH)D levels were not associated with subsequent breast cancer risk

Chleboswski RT. *J Natl Cancer Inst* 2007; 100: 1581 – 1591

# **Invasive Cancer** – WHI Study

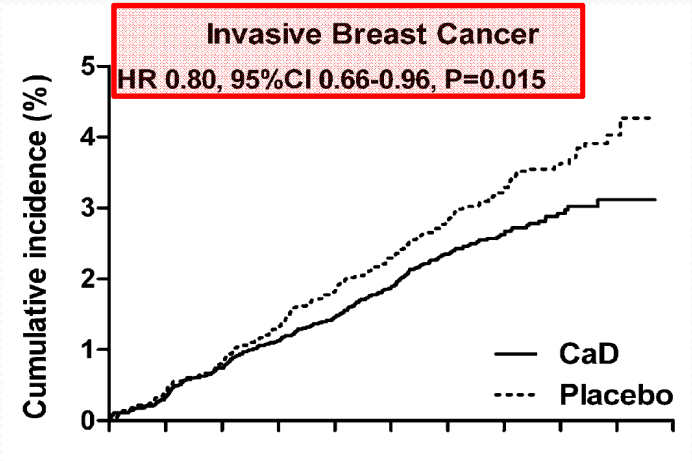
| Invasive cancer incidence | HR | (95% | CI) |
|---|---|---|---|
| Total cancer | 0.98 | (0.90 | - 1.05) |
| Breast | 0.96 | (0.85 | - 1.09) |
| Colon | 0.98 | (0.76 | - 1.27) |

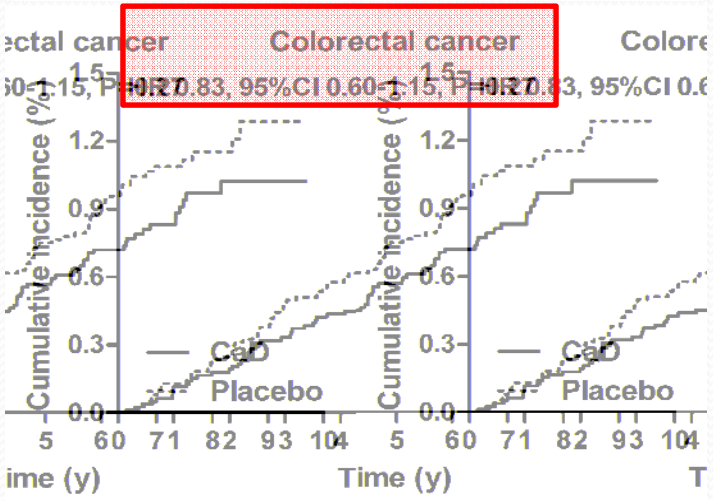
| Cancer mortality | HR | (95% | CI) |
|---|---|---|---|
| Total cancer | 0.90 | (0.77 | - 1.05) |

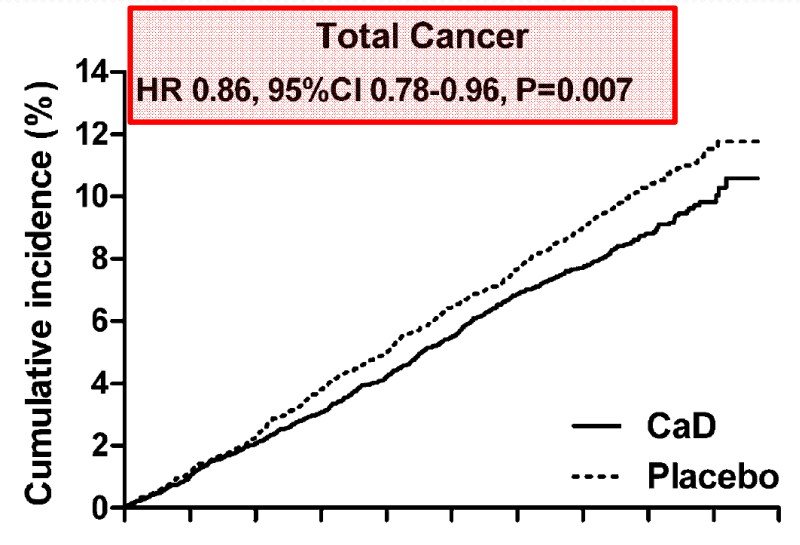
Brunner RL. *Nutrition and Cancer* 2011; 63(6): 827–841

# Calcium and Vitamin D Supplements and Health Outcomes: a Reanalysis of the WHI limited-access data set

Among 15,646 women who were **NOT** taking **personal calcium or vitamin D supplements at baseline.**




Bolland, MJ. *Am J Clin Nutr* 2011;94:1144–9.

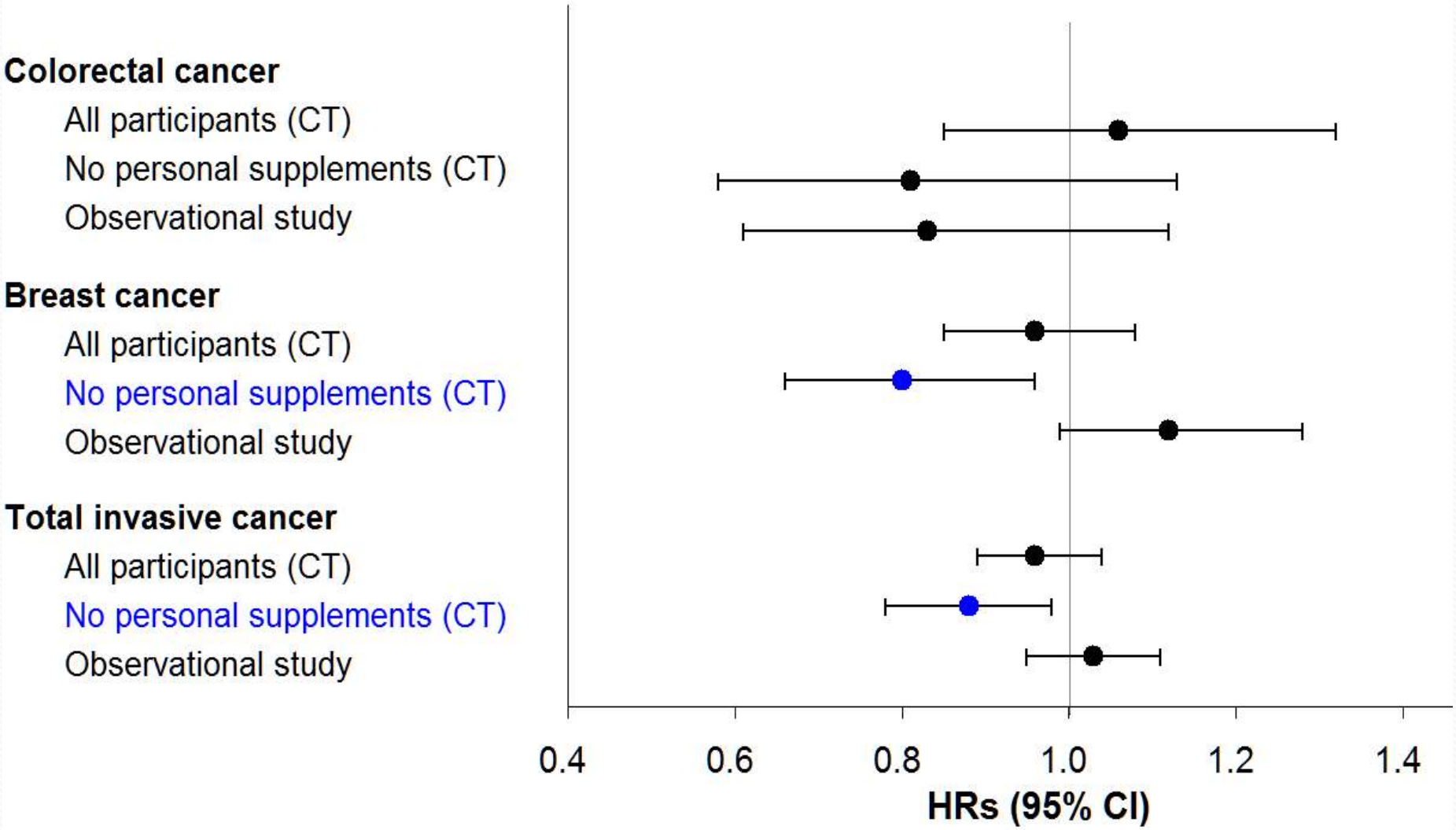
Osteoporos Int (2013) 24:567–580
DOI 10.1007/s00198-012-2224-2

ORIGINAL ARTICLE

# Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study

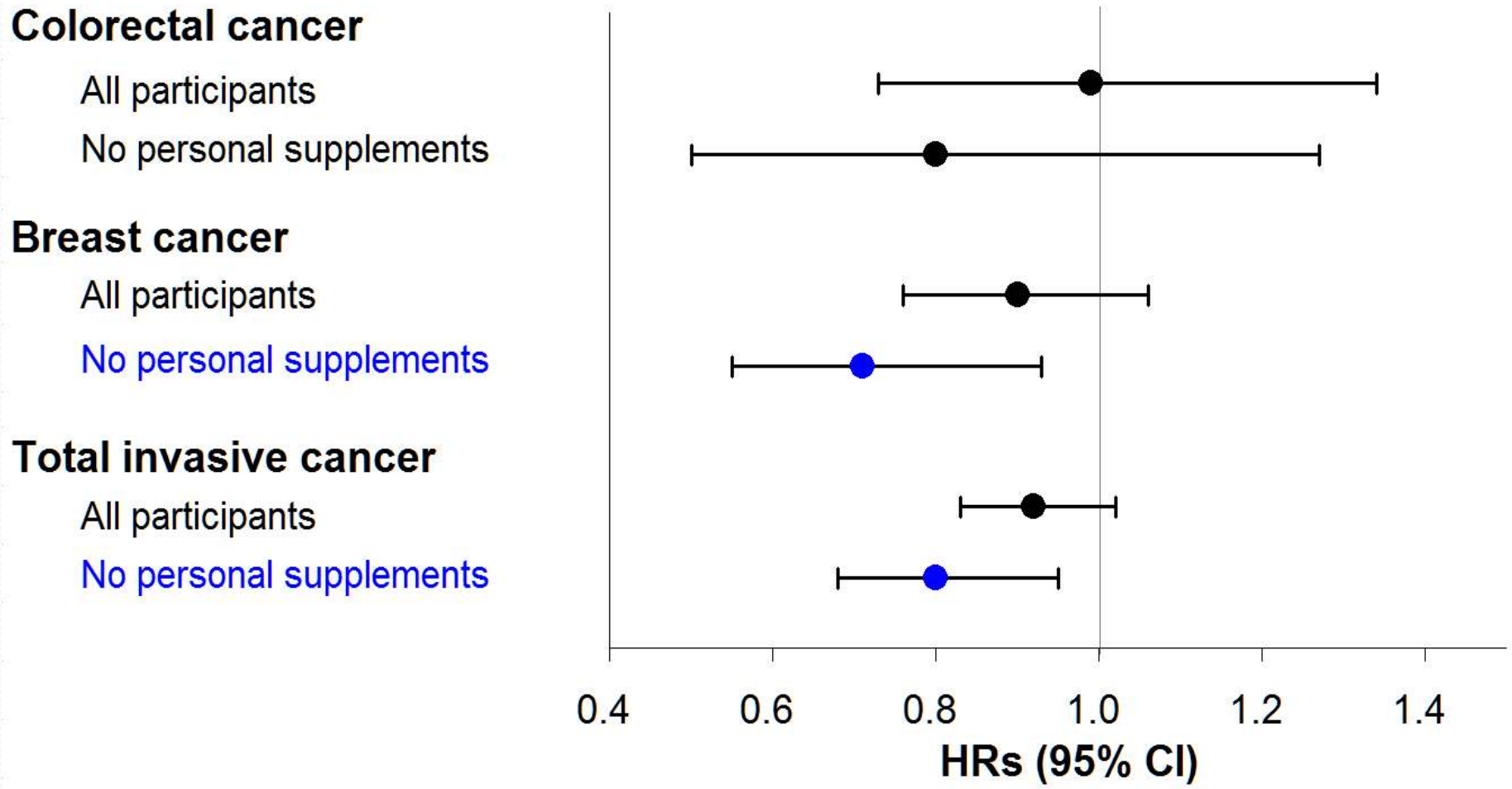
Prentice, R. L. *Osteoporos Int* 2013;24:567–580

# Hazard ratios (95% confidence intervals) for Invasive Cancer in the WHI CaD trial and Observational Study




Prentice, R. L. *Osteoporos Int* 2013;24:567–580

# Hazard ratios (95% confidence intervals) in the WHI CaD trial among Adherent Women




Prentice, R. L. *Osteoporos Int* 2013;24:567–580

# VITAL

THE VITAMIN D AND OMEGA-3 TRIAL (VITAL)

## The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL): Rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease

JoAnn E. Manson [a,b,*], Shari S. Bassuk [a], I-Min Lee [a,b], Nancy R. Cook [a,b], Michelle A. Albert [a,c], David Gordon [a], Elaine Zaharris [a], Jean G. MacFadyen [a], Eleanor Danielson [a], Jennifer Lin [a], Shumin M. Zhang [a], Julie E. Buring [a,b]

- 1st RCT for the primary prevention of cancer & CVD
- 20,000 healthy men (≥50yrs) and women (≥ 55yrs) in the US
- **2,000 IU/day** of **vitamin D3**
- **1 g/day** of marine **omega-3 fatty acids**
- **For 5 years**

Contemporary Clinical Trials 33 (2012) 159–171

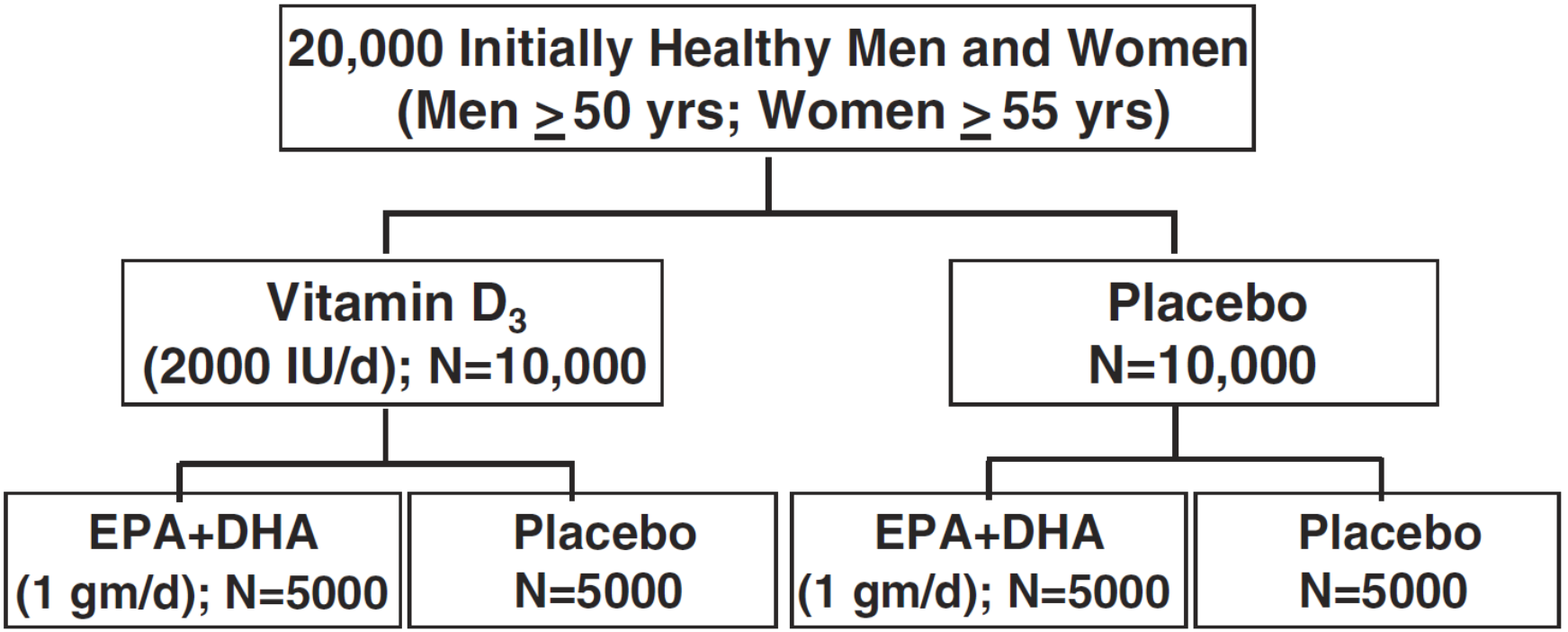



**Fig. 3.** The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) design.

# Limitations in RCTs

1. Generalizability
2. Low power
3. Single dose or a limited set of doses
4. Contamination between intervention and placebo group

# Guidelines

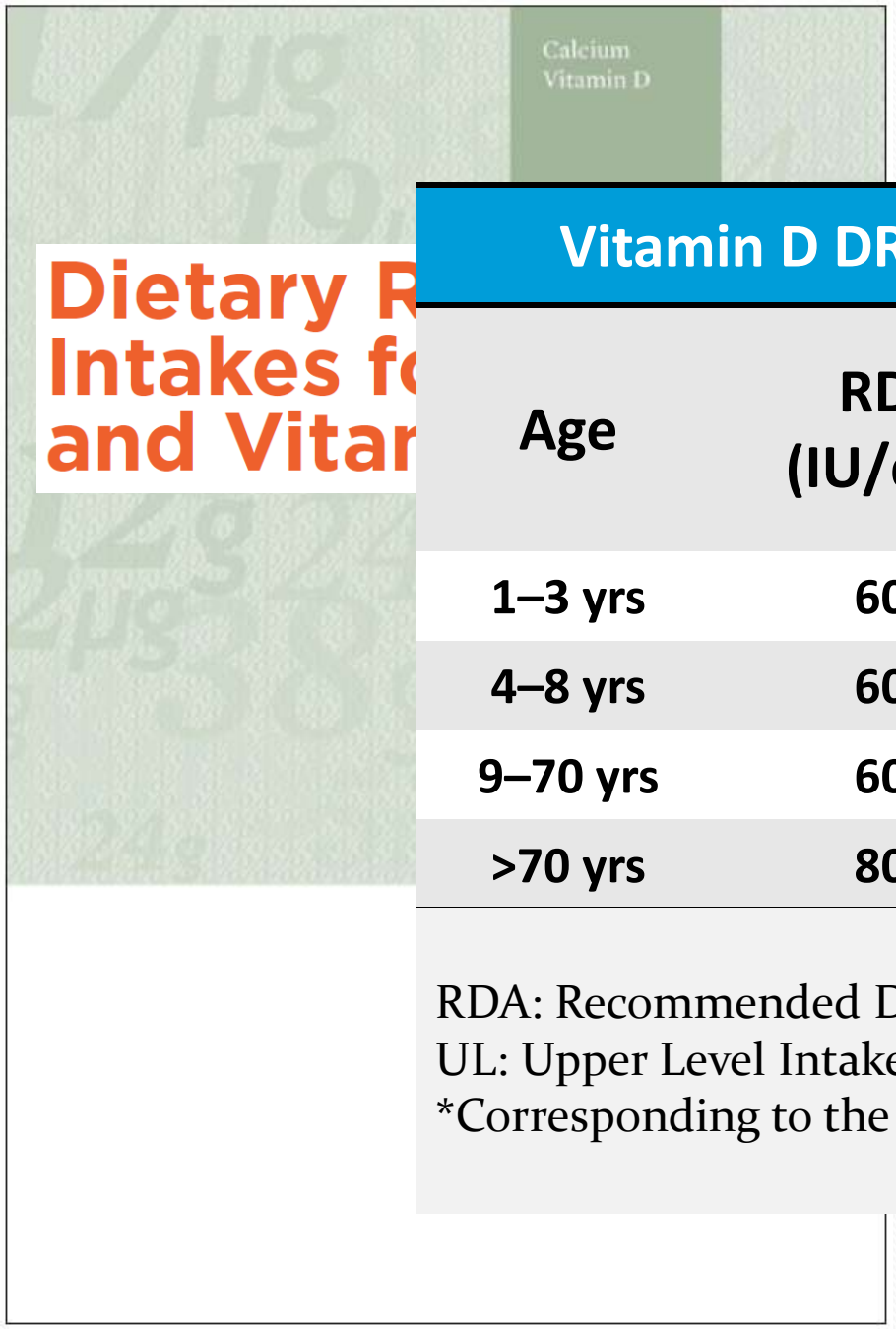
Osteoporos Int (2010) 21:1151–1154
DOI 10.1007/s00198-010-1285-3

POSITION PAPER

# IOF position statement: vitamin D recommendations for older adults

B. Dawson-Hughes · A. Mithal · J.-P. Bonjour · S. Boonen · P. Burckhardt · G. E.-H. Fuleihan · R. G. Josse · P. Lips · J. Morales-Torres · N. Yoshimura

- Optimal serum 25OHD level: **30 ng/ml**
- Efficacy of doses
  - Fractures : 800 IU/day
  - Falls : 1,000 IU/day
- Recommended dose for older adults: **800-1,000 IU/d**




## Vitamin D DRIs (Dietary Reference Intakes)

| Age | RDA (IU/day) | Serum 25(OH)D level (ng/ml)* | UL (IU/day) |
|---|---|---|---|
| 1–3 yrs | 600 | 20 | 2,500 |
| 4–8 yrs | 600 | 20 | 3,000 |
| 9–70 yrs | 600 | 20 | 4,000 |
| >70 yrs | 800 | 20 | 4,000 |

RDA: Recommended Dietary Allowance
UL: Upper Level Intake
*Corresponding to the RDA

# Screening for Vitamin D Deficiency

***This topic is in the process of being updated. Please go to the Update in Progress section to see the latest documents available.***

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This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) evidence on screening for vitamin D deficiency.

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## Update in Progress

In an effort to make the USPSTF recommendations clearer and its processes more transparent, the Task Force is sharing drafts of many of its documents for public comment, including draft Research Plans and draft Recommendation Statements. As a result, the final Recommendation Statement is not yet available.

SPECIAL FEATURE

Clinical Practice Guideline

# Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

- Optimal 25(OH)D : 40–60 ng/ml
  - 600 IU/d will raise and maintain blood concentrations of 25(OH)D > 20 ng/ml, but <30 ng/ml
- Recommended doses
  - Children: 400–1,000 IU/d
  - Adults: 1,500–2,000 IU/d

J Clin Endocrinol Metab 2011;96: 1911–1930

# Summary

- Most evidence for vitamin D and cancer is derived from laboratory studies, ecologic correlations, observational associations, and secondary analysis of RCTs.

- New trials assessing moderate-to-high dose vitamin D supplementation for cancer prevention are in progress.