Presentation to the
Committee to Review Dietary Reference Intakes for Vitamin D and Calcium

Vitamin D and Cancer

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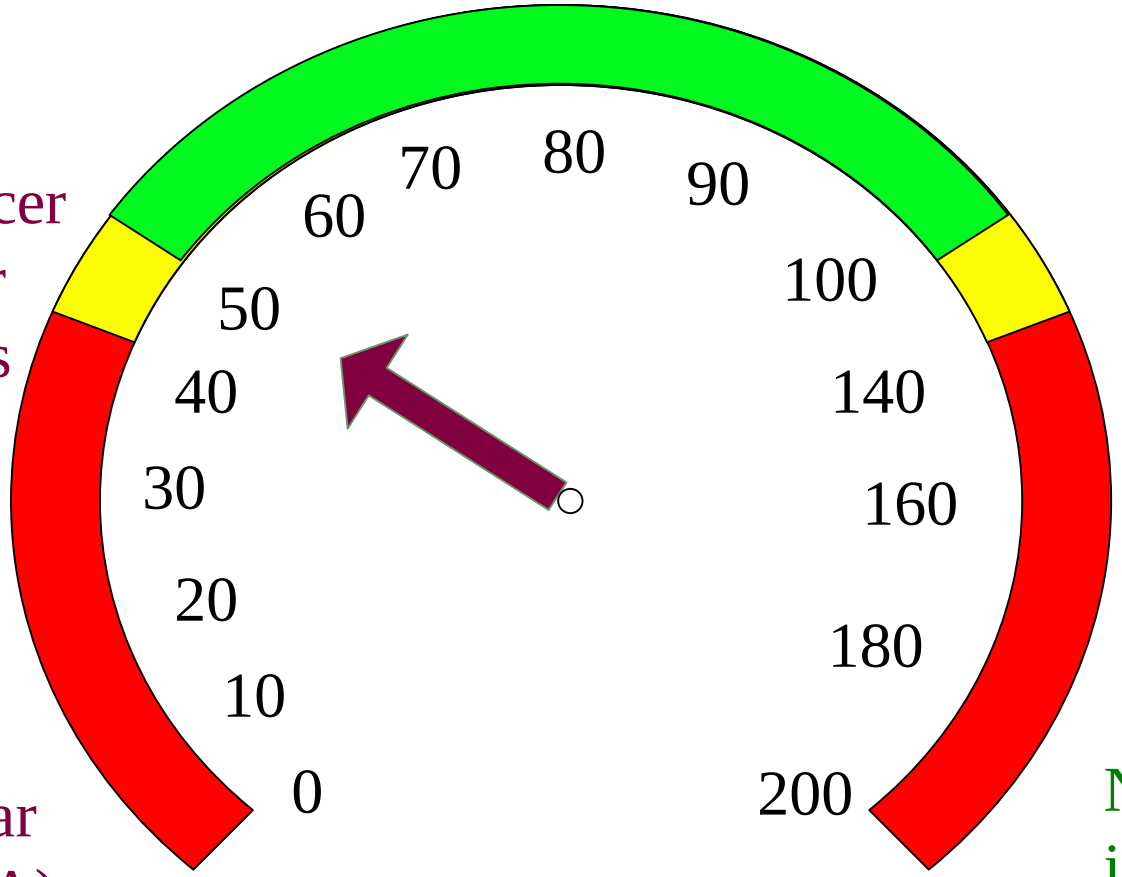
Serum 25(OH)D Safety Limits for Healthy Adults

Breast cancer
Colorectal cancer
Ovarian cancer
Type I diabetes
Multiple sclerosis
Fractures
Myocardial infarction
Cerebrovascular accident (CVA)
Metabolic syndrome
Rickets



Serum 25(OH)D level, ng/ml
(1 ng/ml = 2.5 nmol/L)

No down side in green.
Renal stones in red arc?

Optimal Vitamin D Status for Colorectal Cancer Prevention

A Quantitative Meta Analysis

Edward D. Gorham, MPH, PhD, Cedric F. Garland, DrPH, Frank C. Garland, PhD, William B. Grant, PhD, Sharif B. Mohr, MPH, Martin Lipkin, MD, Harold L. Newmark, ScD, Edward Giovannucci, MD, ScD, Melissa Wei, BS, Michael F. Holick, MD, PhD

Background: Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.

Methods: Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Peto's Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose–response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.

Results: Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.82, 0.66, 0.59, and 0.46 ($p_{trend}<0.0001$) for colorectal cancer. According to the DerSimonian-Laird test for homogeneity of pooled data, the studies were homogeneous ($chi^2=1.09$, $df=4$, $p=0.90$). The pooled odds ratio for the highest quintile versus the lowest was 0.49 ($p<0.0001$, 95% confidence interval, 0.35–0.68). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level ≥33 ng/mL, compared to ≤12 ng/mL.

Conclusions: The evidence to date suggests that daily intake of 1000–2000 IU/day of vitamin D_3 could reduce the incidence of colorectal with minimal risk.

(Am J Prev Med 2007;32(3):210–216) © 2007 American Journal of Preventive Medicine

Introduction

The Women's Health Initiative[1] demonstrated that a low dose of vitamin D did not protect against colorectal cancer within 7 years of follow-up; however, a meta-analysis indicates that a higher dose may reduce its incidence.

There were approximately 145,300 new cases and 56,300 deaths from colorectal cancer in the United States during 2006.[2] An observation of higher age-adjusted mortality rates of colorectal cancer in the northern and northeastern United States compared to the southwest, Hawaii, and Florida led to a theory that vitamin D of mainly solar origin may reduce risk of colorectal cancer[3] through a mechanism involving calcium metabolism, intercellular adherence, and contact inhibition. Since then, five observational studies have explored the association of serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25[OH]D) with risk of colorectal cancer.[1,4–7] However, an overall dose–response gradient for the effect of serum levels of 25(OH)D on colorectal cancer risk has not been determined. This meta-analysis provides an estimated dose–response gradient that may be of help in planning for a useful role of vitamin D in control of colorectal cancer.

Methods

Study Inclusion

The PubMed database was searched for the period from January 1966 to December 2006 by using the terms ("vitamin

From the University of California San Diego, Department of Family and Preventive Medicine, School of Medicine (Gorham, C.F. Garland, F.C. Garland, Mohr) La Jolla, California; SUNARC/Sunlight, Nutrition and Health Research Center (Grant), San Francisco, California; Strang Cancer Prevention Center (Lipkin), New York, New York; Susan Lehman Cullman Laboratory for Cancer Research, Rutgers, The State University of New Jersey (Newmark), Piscataway, New Jersey, and Cancer Institute of New Jersey, New Brunswick, New Jersey; Harvard School of Public Health, Departments of Nutrition and Epidemiology (Giovannucci, Wei); and Vitamin D Laboratory, Section of Endocrinology, Nutrition and Diabetes, Department of Medicine, Boston University School of Medicine (Holick), Boston, Massachusetts

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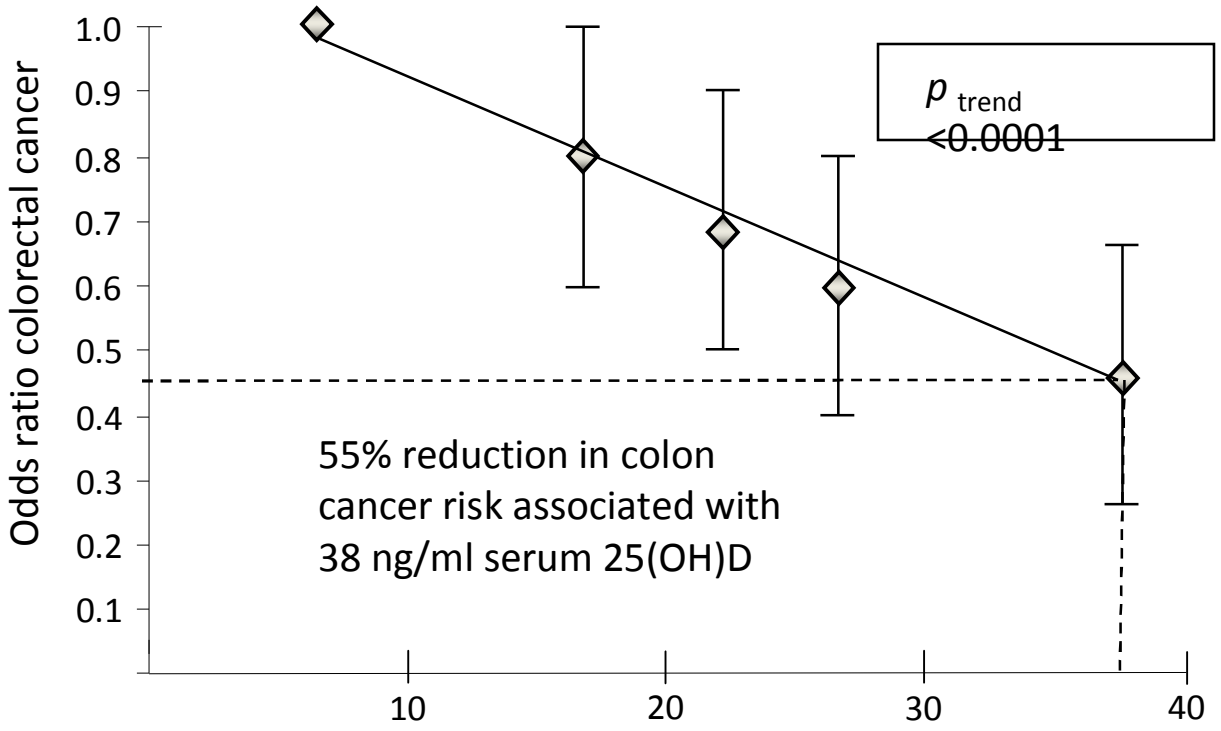
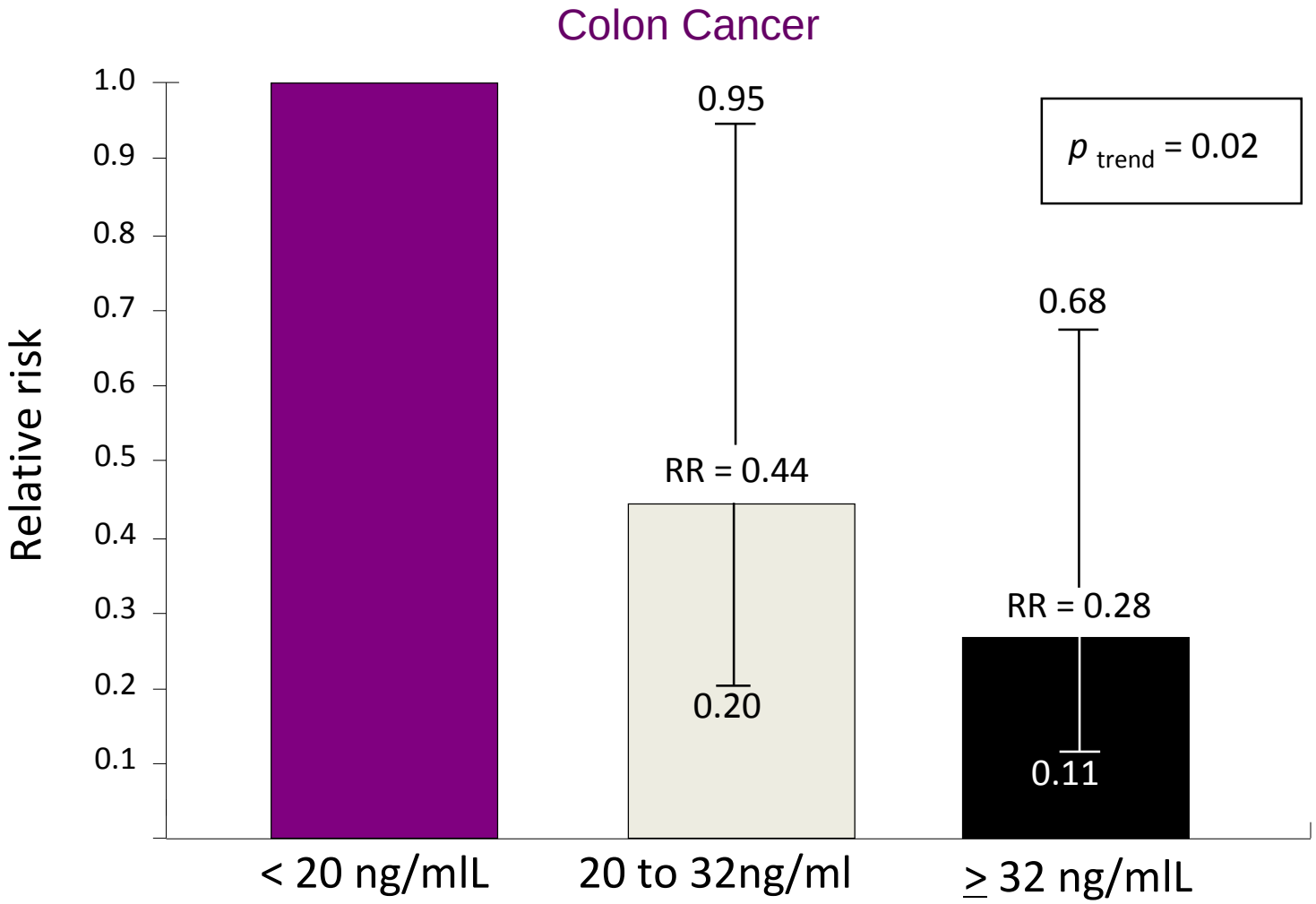
0749-3797/07/$–see front matter
doi:10.1016/j.amepre.2006.11.004

Colon Cancer



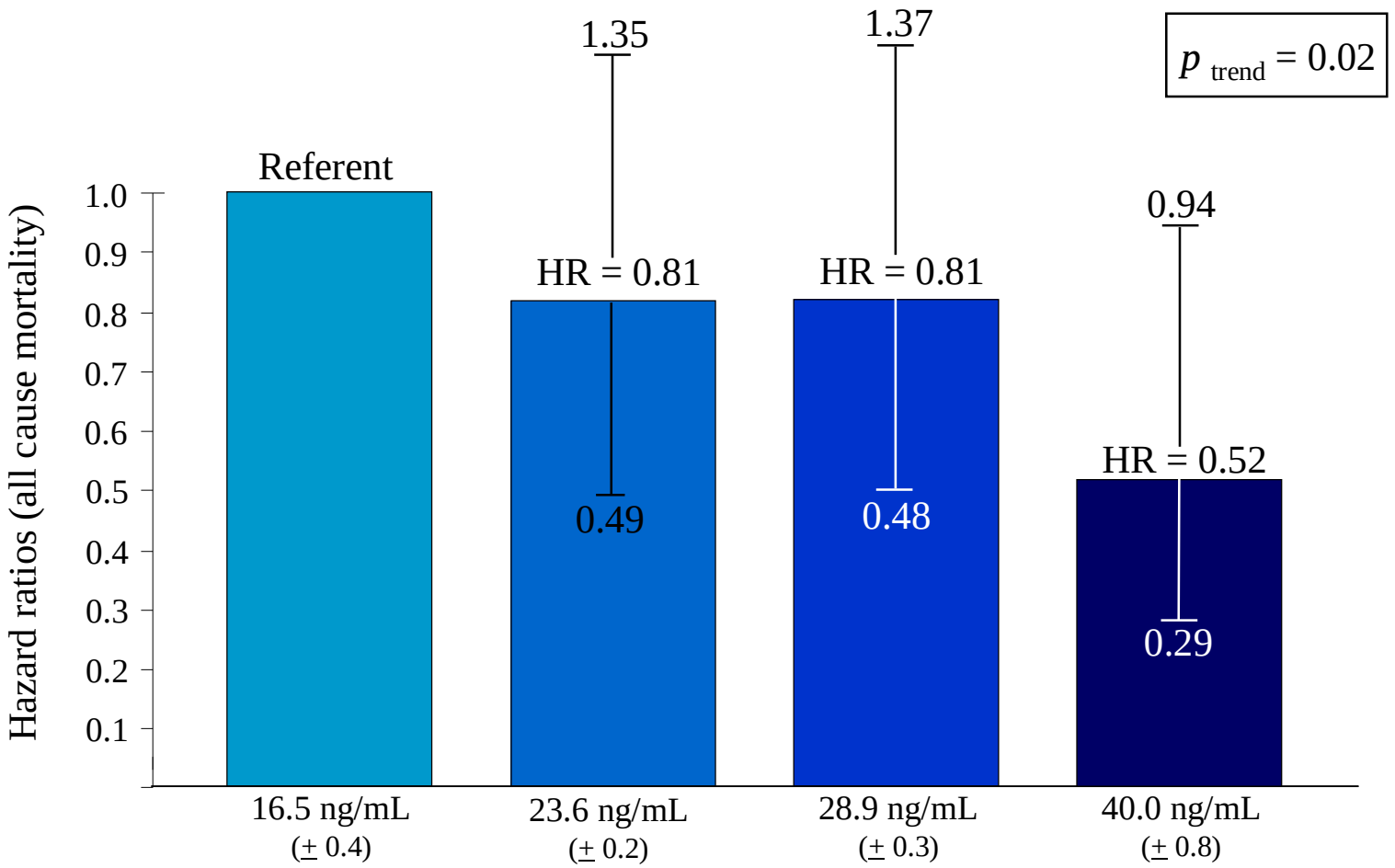
Pooled odds ratio for colorectal cancer, according to serum 25(OH)D concentration (Source: meta-analysis of 6 studies, Gorham et al. Am J Prev Med 2007)



Relative risk of colon cancer mortality, by baseline serum 25-hydroxyvitamin D concentration, in tertiles, NHANES III cohort, 1988-2000.

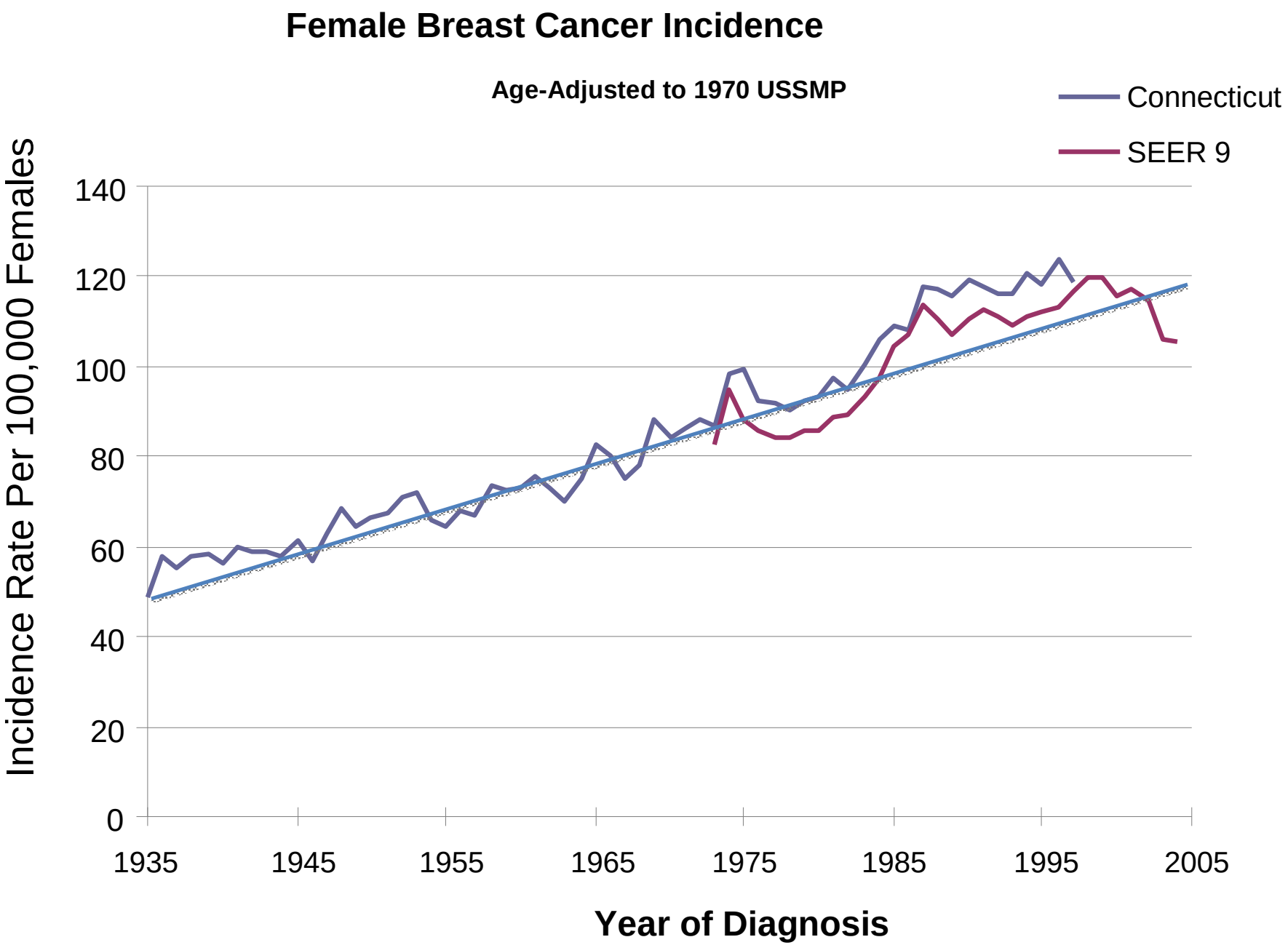
Source: Freedman DM, Looker AC, Shih-Chen C, et al. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007;99:1594-602.

Colon Cancer Survival

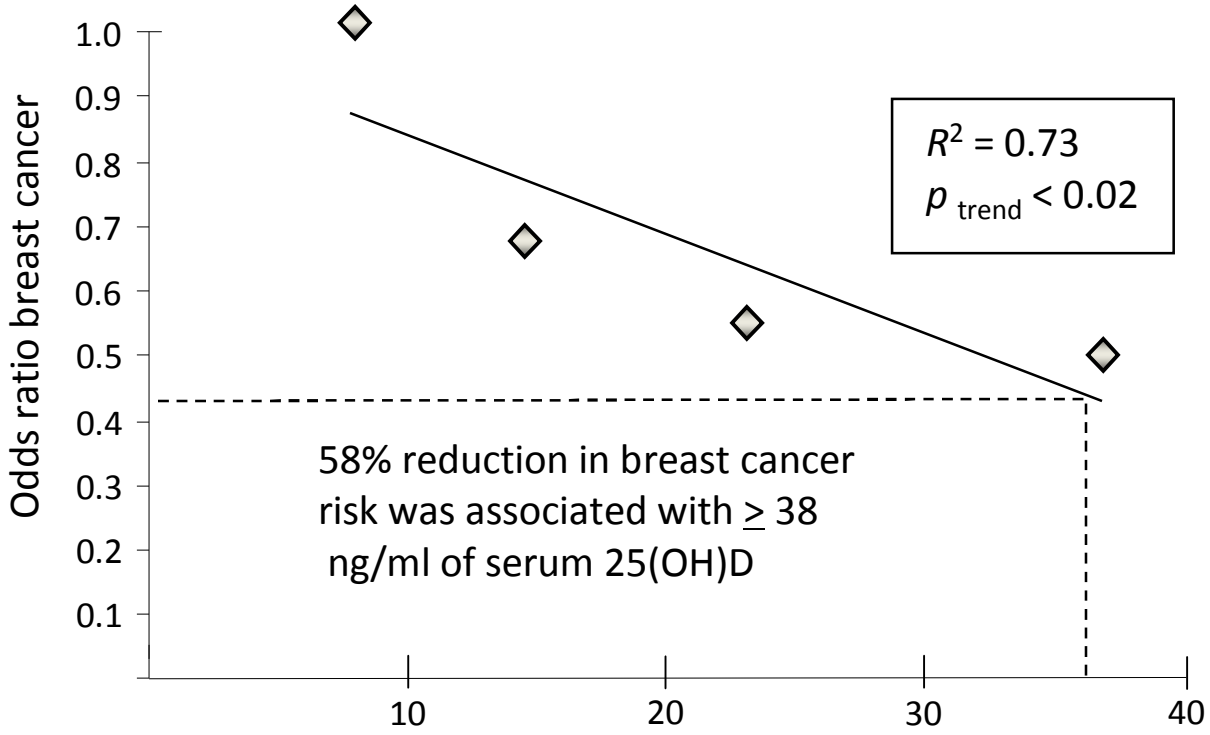


Hazard ratios for all cause mortality among 304 colorectal cancer patients by prediagnostic mean plasma 25-hydroxyvitamin D concentration by quartiles, multiple-adjusted, Nurses Health and Health Professionals Study Cohorts

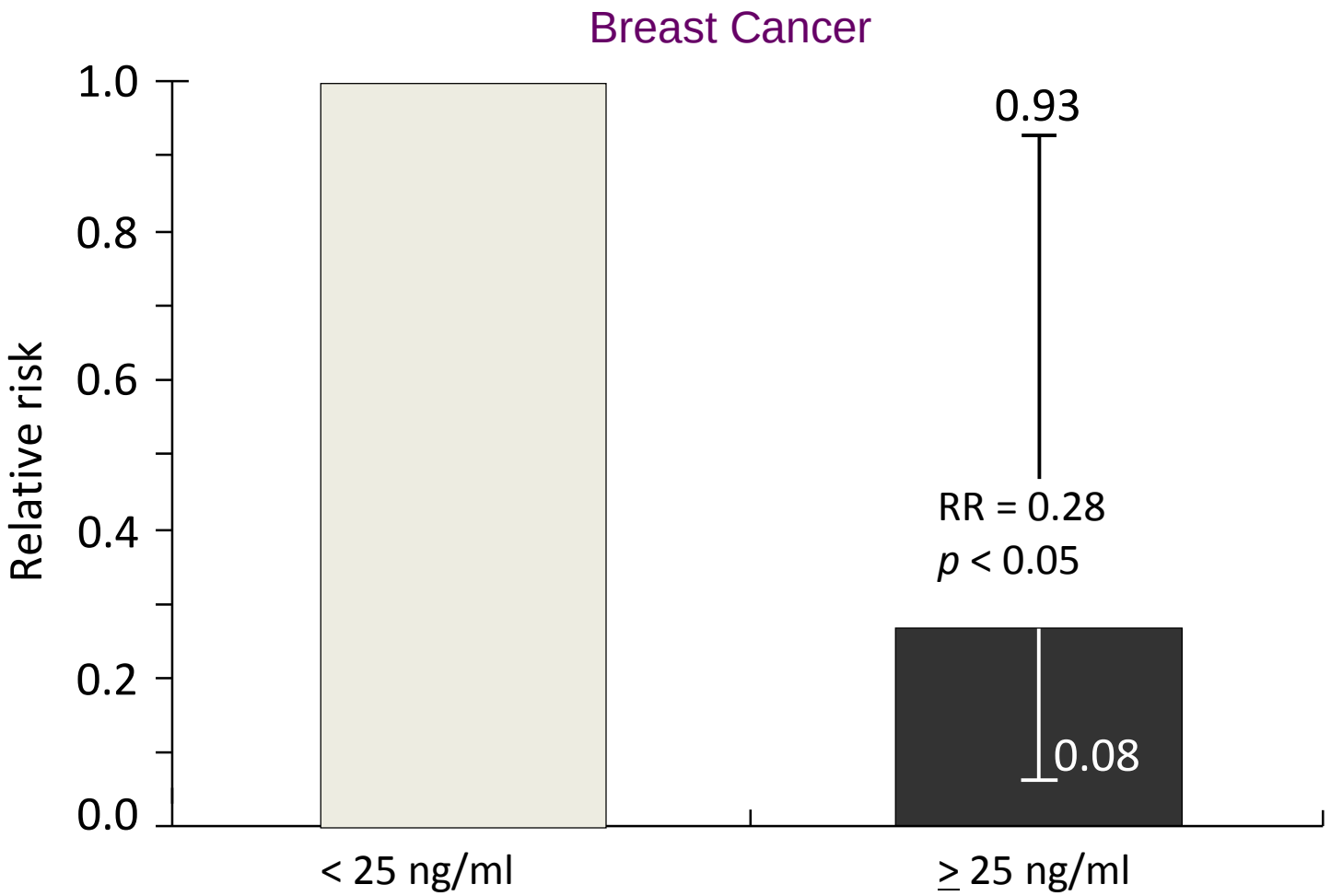
Source: Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, Fuchs CS. Circulating 25-hydroxyvitamin D levels and survival in patients with colorectal cancer J Clin Oncol 2008; 26: 2984-91.


Female Breast Cancer Incidence
Age-Adjusted to 1970 USSMP
Connecticut
SEER 9
Incidence Rate Per 100,000 Females
140
120
100
80
60
40
20
0
1935
1945
1955
1965
1975
1985
1995
2005
Year of Diagnosis

Breast Cancer

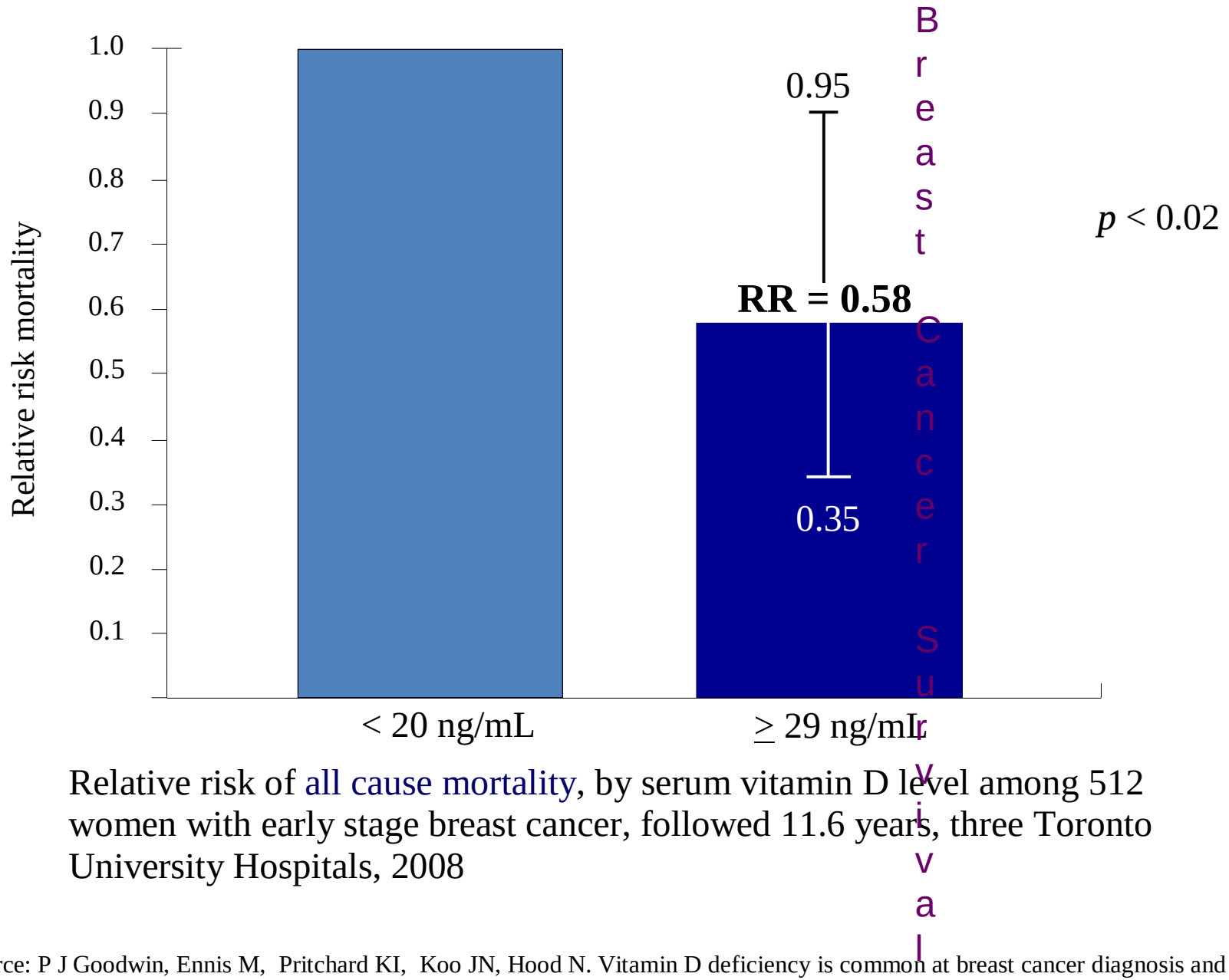


Pooled odds ratios for breast cancer, according to serum 25(OH)D concentration, meta-analysis, 2008 (Sources: Garland et al. meta-analysis, J Steroid Biochem Mol Biol 2007. Includes data from Bertone-Johnson et al. 2005, Lowe et al. 2005)



Relative risk of breast cancer mortality, by baseline serum 25-hydroxyvitamin D concentration, divided at the median, NHANES III cohort, 1988-2000

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.



Relative risk of all cause mortality, by serum vitamin D level among 512 women with early stage breast cancer, followed 11.6 years, three Toronto University Hospitals, 2008

Source: P J Goodwin, Ennis M, Pritchard KI, Koo JN, Hood N. 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 of T1-3, N0-1, M0 BC. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, May 30-June 3, 2008. Abstract number: 08-AB-31397-ASCOAM.

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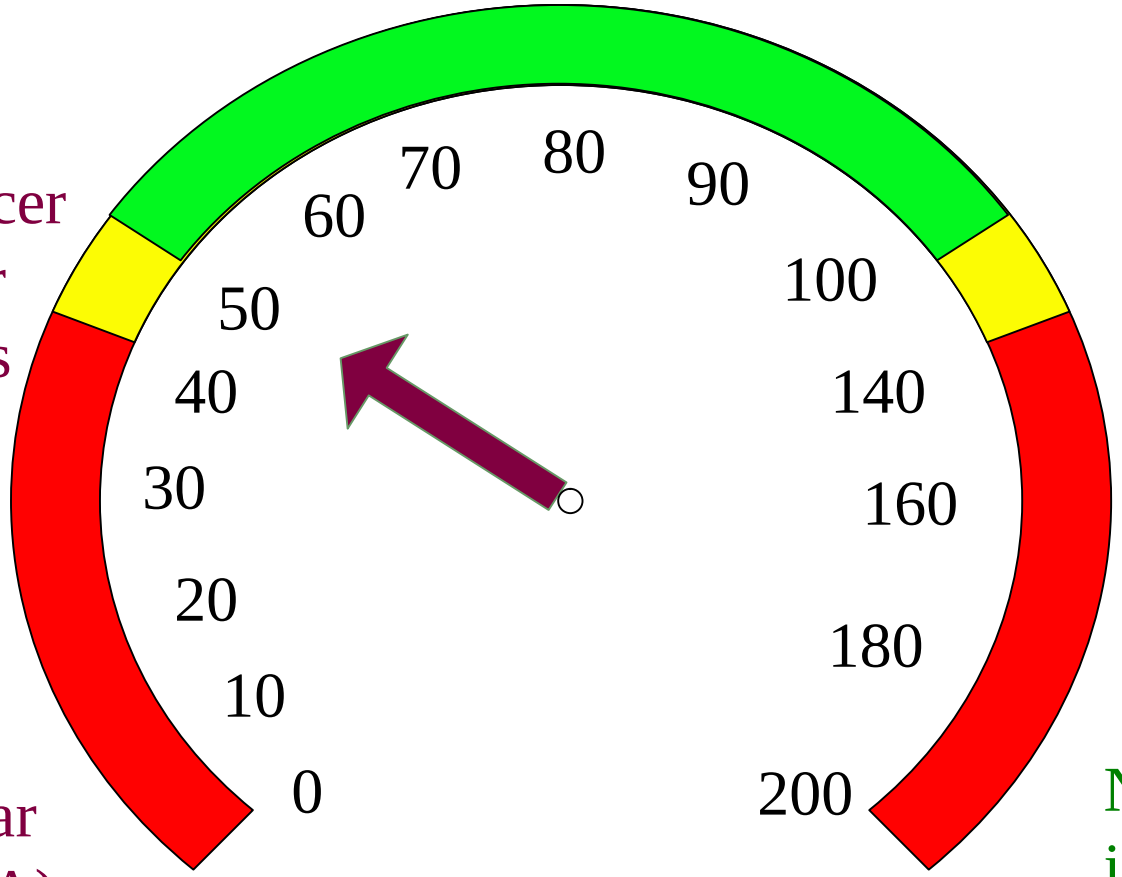

Serum 25(OH)D level, ng/ml
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Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial[1,2]

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

ABSTRACT

Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking.

Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types.

Design: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4°N. Subjects were randomly assigned to receive 1400–1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1100 IU vitamin D_3/d (Ca + D), or placebo.

Results: When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects ($P < 0.03$). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 ($P = 0.01$) and 0.532 ($P = 0.06$), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; $P < 0.005$) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk.

Conclusions: Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women. This trial was registered at clinicaltrials.gov as NCT00352170. *Am J Clin Nutr* 2007;85:1586–91.

KEY WORDS Serum 25-hydroxyvitamin D, cancer, women, calcium and vitamin D_3 supplementation

INTRODUCTION

The relation of solar radiation to reduced cancer mortality in North America was identified >60 y ago (1). Garland and Garland (2) were the first to propose that vitamin D was responsible, specifically for the association with colon cancer. The inverse association between ambient solar radiation and cancer mortality rates has subsequently been described for cancers of the breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, and uterus, as well as for non-Hodgkin lymphoma and multiple myeloma (3–10).

This seeming protection was presumed to be mediated by the effect of solar radiation on vitamin D status. Exploration of the connection between vitamin D nutriture and chronic disease in humans received a critical stimulus with the availability of a physiologically stable indicator of vitamin D status [serum 25-hydroxyvitamin D, or 25(OH)D] and the designation of 25(OH)D as the functional indicator of vitamin D status by the Institute of Medicine (11). These developments have facilitated a more precise definition of the relation between cancer risk and vitamin D status. The inverse association has now been established for incident colorectal cancer (12) and for prostate cancer (13), among others. Gorham et al (14), quantifying the inverse relation between serum 25(OH)D and risk of colorectal cancer, calculated a 50% reduction in cancer risk at serum 25(OH)D concentrations ≥80 nmol/L.

Giovannucci (15, 16) and Holick (17, 18) have each recently reviewed the now large body of evidence linking low vitamin D status to increased risk of cancer. Similar associations were earlier noted for high calcium intake and reduced cancer risk (19–21), most prominently for colorectal cancer, whereby a luminal effect of high calcium intake provided a plausible mechanism.

The human evidence to date linking cancer and vitamin D has been observational in character, although several of the many positive studies linking vitamin D and cancer have been prospective. We had the opportunity to examine the relation of these nutrients to cancer incidence in a 4-y, double-blind, placebo-controlled trial of calcium and vitamin D supplementation for which cancer was the principal secondary endpoint. The null hypothesis was that there would be no difference in all-cancer incidence between the 3 calcium and vitamin D treatment groups.

SUBJECTS AND METHODS

Participants

The participants have been described in detail in an article describing their vitamin D status (22). Briefly, participants were recruited as a population-based sample from a 9-county, largely rural area in eastern Nebraska (latitude 41.4°N), with the use of random telephone dialing of all listed telephones in the counties

[1] From the Osteoporosis Research Center, Creighton University, Omaha, NE.

[2] Reprints not available. Address correspondence to JM Lappe, Creighton University, 601 North 30th Street, Suite 4820, Omaha, NE 68131. E-mail: jmlappe@creighton.edu.

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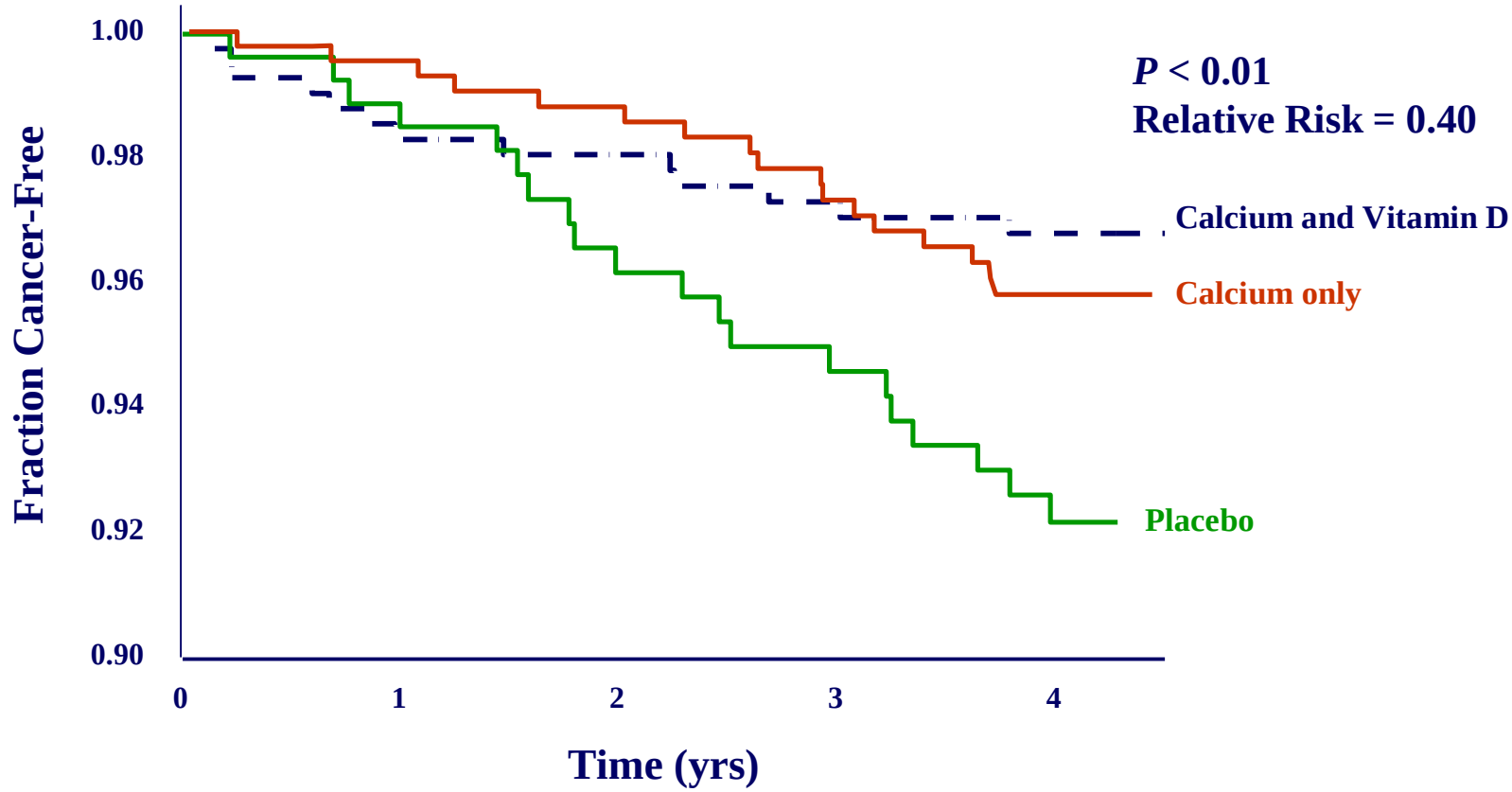
Accepted for publication February 1, 2007.

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)

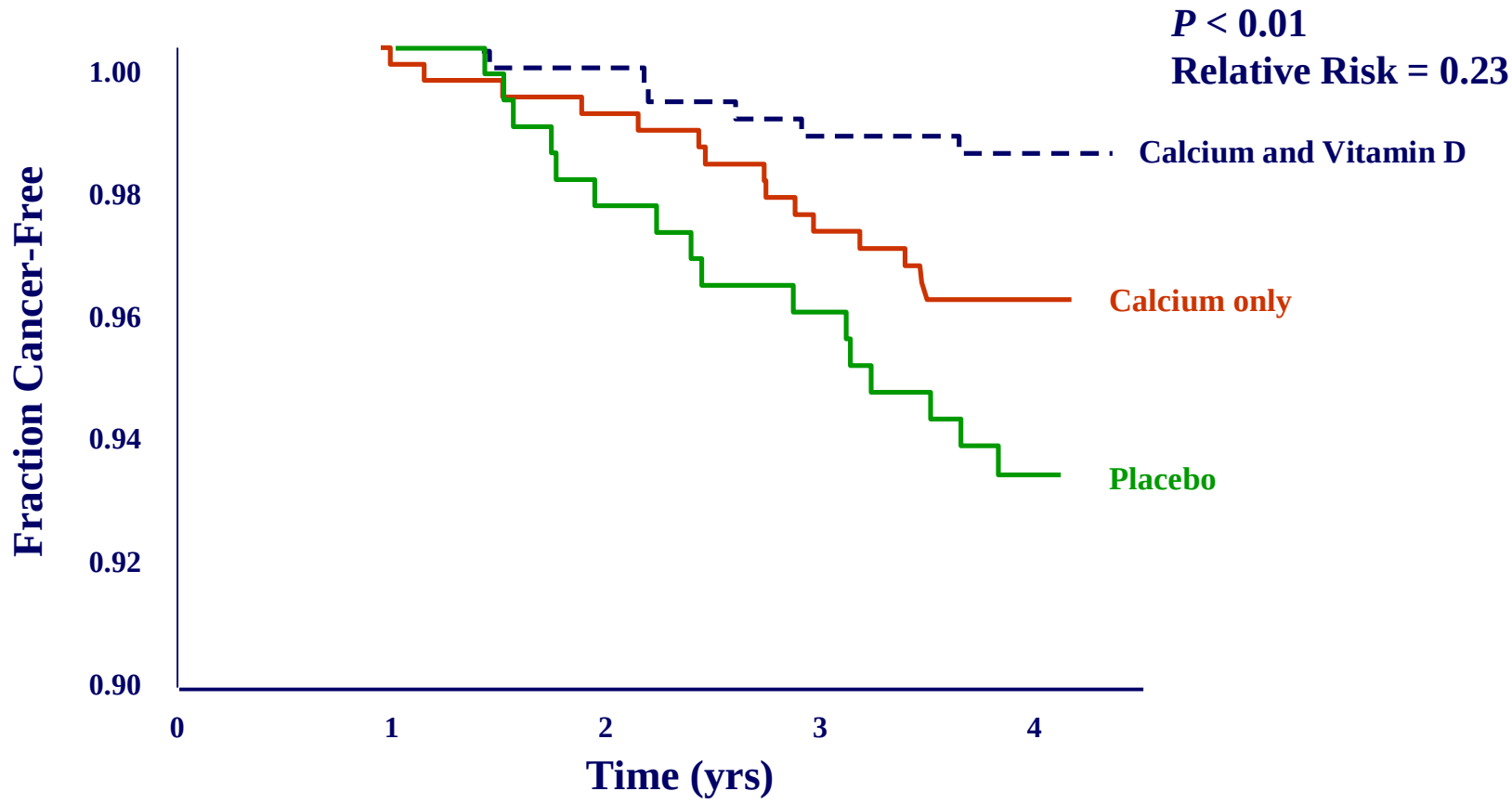
Source: Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586-91.

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



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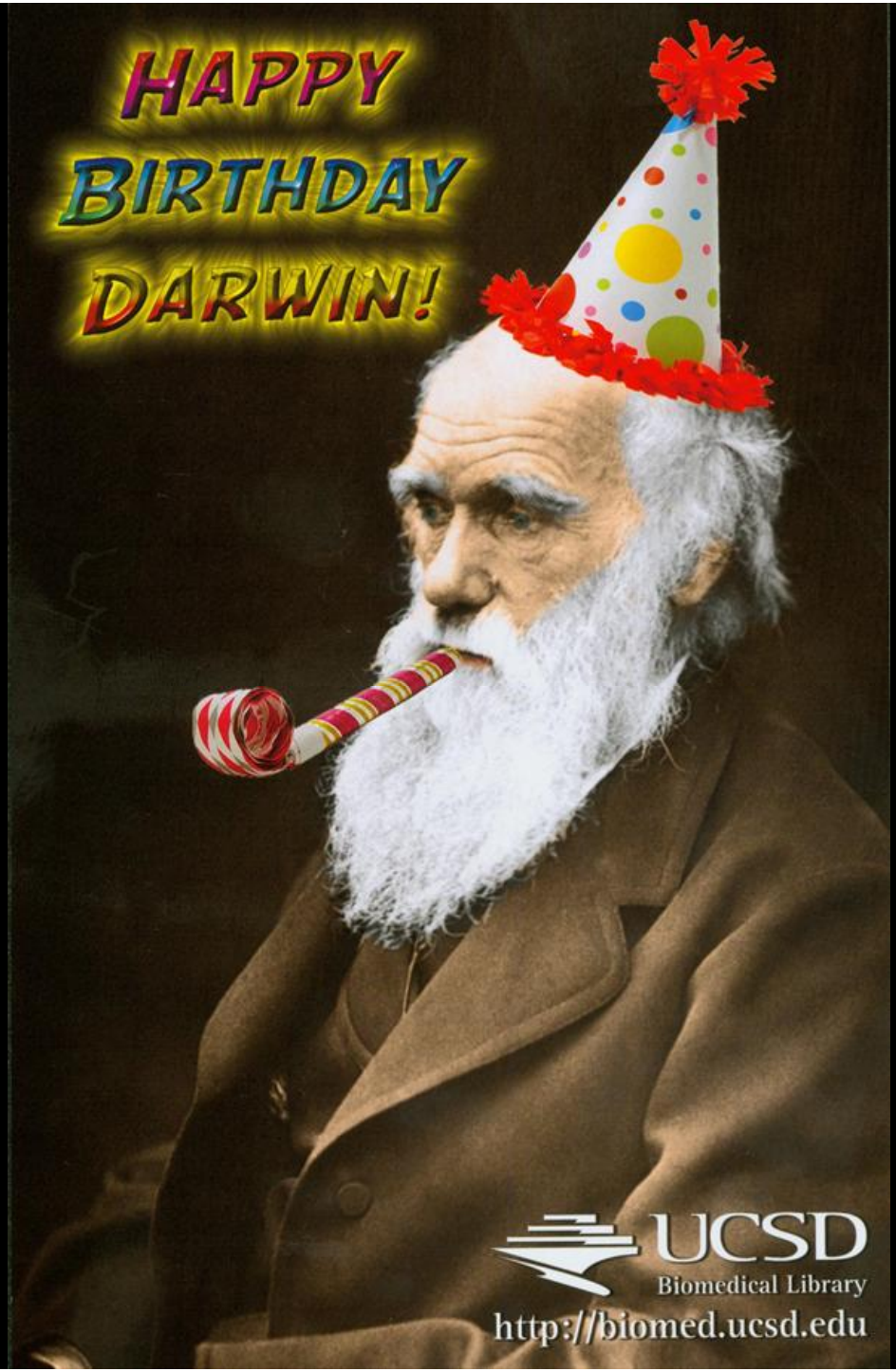
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BIRTHDAY
DARWIN!
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Figure 9A. Disjunction–Initiation–Natural Selection–Overgrowth–Metastasis-Involution-Transition (DINOMIT) Cancer Model

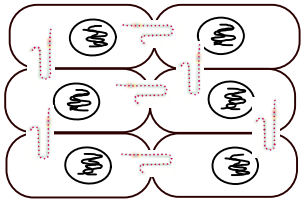
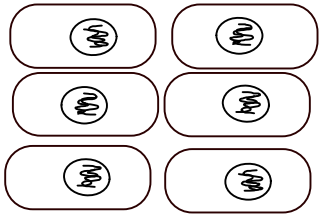
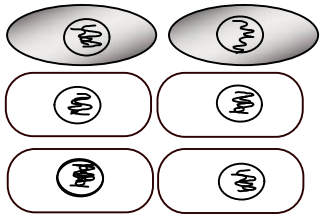
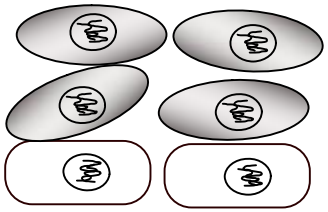
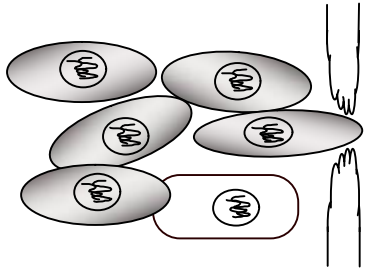
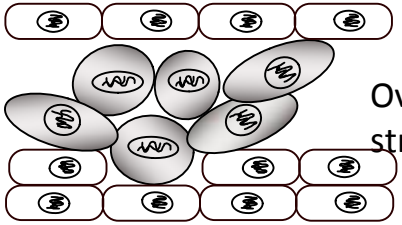
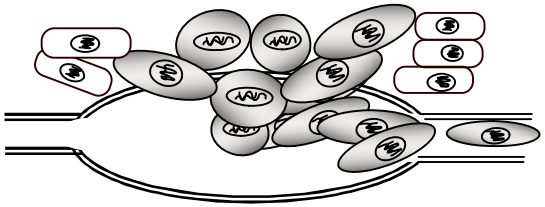
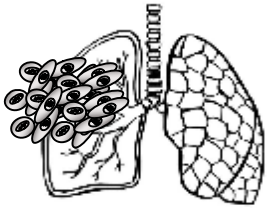
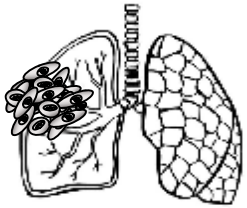
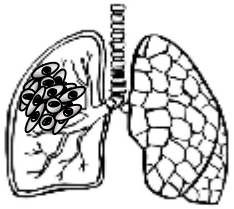
Phase	Diagram	Process	Preventive or therapeutic action
Vitamin D replete (normal)		Tight junctions intact. Intercellular communication intact. Contact inhibition functional. Most mature cells not mitotic. Normally scheduled apoptosis.	Serum 25(OH)D level of 40-60 ng/ml maintains functions at left via 1,25(OH)D local biosynthesis.
1. Disjunction due to low vitamin D and calcium		Cells separate slightly. Tight junctions and E-cadherins are downregulated, intercellular communication is reduced or lost, contact inhibition is lost.	Upregulates E-cadherins, catenins, and intercellular junctions.
2. Initiation		DNA errors or epigenetic events occur that support faster mitosis of some mature or developing epithelial cells.	Upregulates E-cadherin, contact inhibition, and return of mature cells to postmitotic status.
3. Natural selection		Rapidly dividing, most aggressive progeny of these predominate; a cell with a 2% growth advantage will fill a tissue compartment in 9000 generations.	Inhibits mitosis of mature cells, reducing chances of natural selection of rapidly mitotic clone.
4. Overgrowth penetration of basement membrane		Rapidly mitotic cells compete for nutrients and blood supply, dissolve and penetrate basement membrane	Re-establishes intercellular junctions and contact inhibition

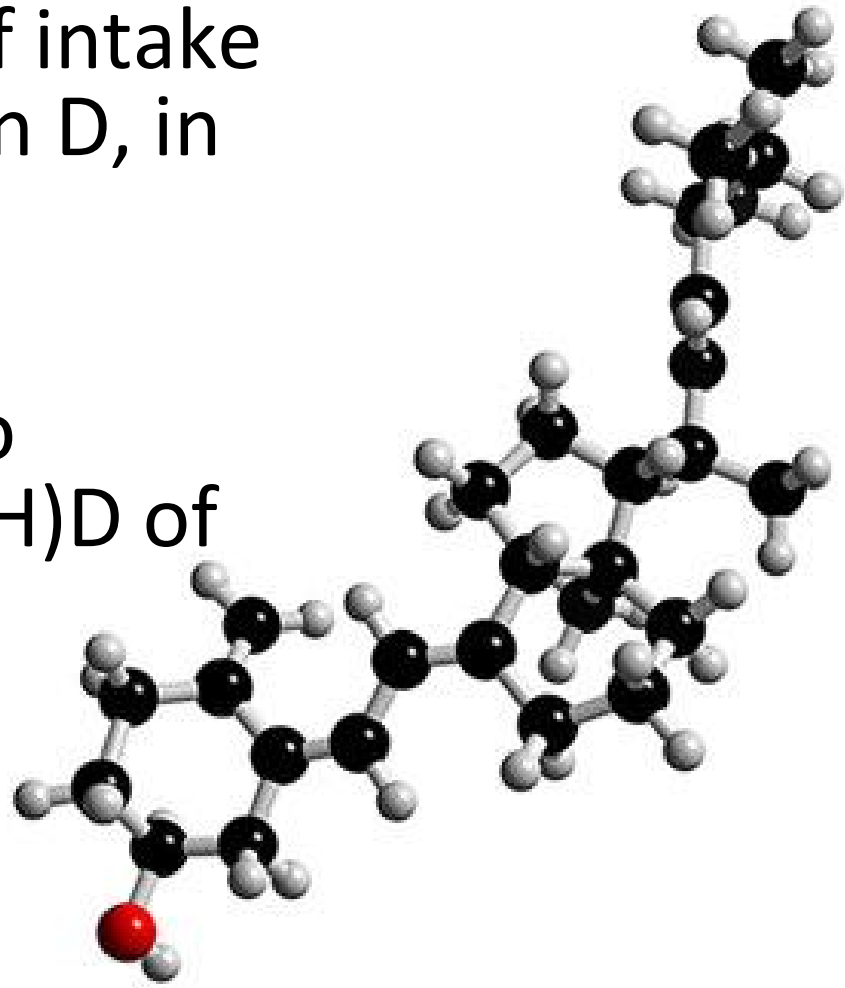
Figure 9B. Disjunction–Initiation–Natural Selection–Overgrowth–Metastasis-Involution-Transition (DINOMIT) Cancer Model

Phase	Diagram	Process	Preventive or therapeutic action
4. Overgrowth stromal invasion		Overgrowth into stroma	Re-establish tight junctions between cancer cells
4. (*cont.*) Overgrowth lymphatic entry and transport		Lymph vessel invasion, growth, and transport to lung, liver, brain	Re-establish tight junctions Prevent lymphatic entry Inhibit growth
5. Metastasis		Malignant cells colonize remote host site	If VDR still present, re-establish tight junctions, downregulate VEGF, reduce growth rate, restore contact inhibition
6. Involution (growth arrest)		Onset of summer levels of 25(OH)D slows or arrests growth of malignant cells	Re-establishment of tight junctions, Reduction in growth rate, restoration of contact inhibition
7. Transition		Temporary transition to quiescent status	Maintenance of adequate serum 25(OH)D would support temporary transition to quiescent status. Low 25 (OH)D would allow metastases to grow and spread

- Benefit/risk ratio for 2000 IU/day vitamin D is infinite

- There is no known risk of intake of 2000 IU/day of vitamin D, in healthy people

- There is no known risk to maintaining serum 25(OH)D of 50 ng/ml



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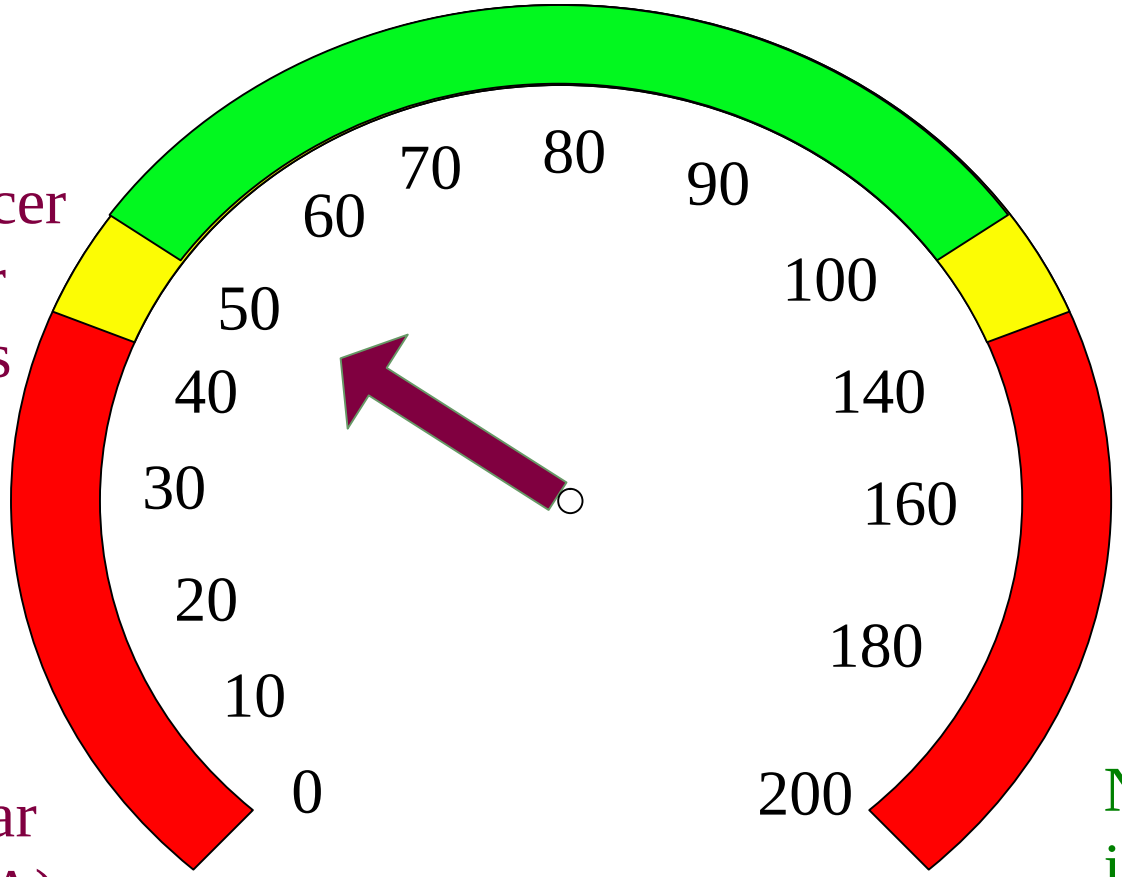
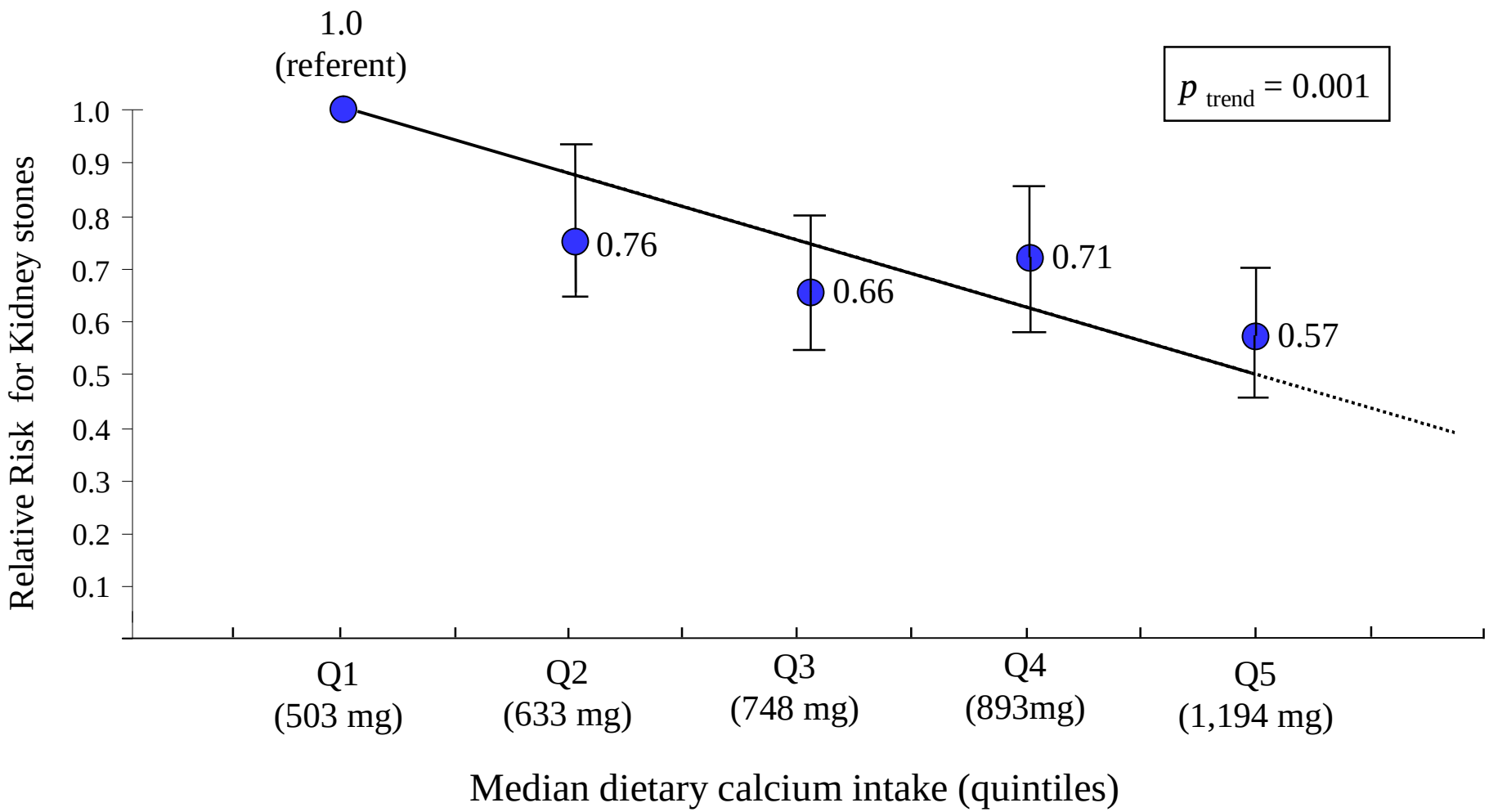


Serum 25(OH)D level, ng/ml
(1 ng/ml = 2.5 nmol/L)

No down side in green.
Renal stones in red arc?

Why can't we all get along?
-- Rodney King, 1991

2000 IU/day vitamin D3
50 ng/ml serum target 25(OH)D

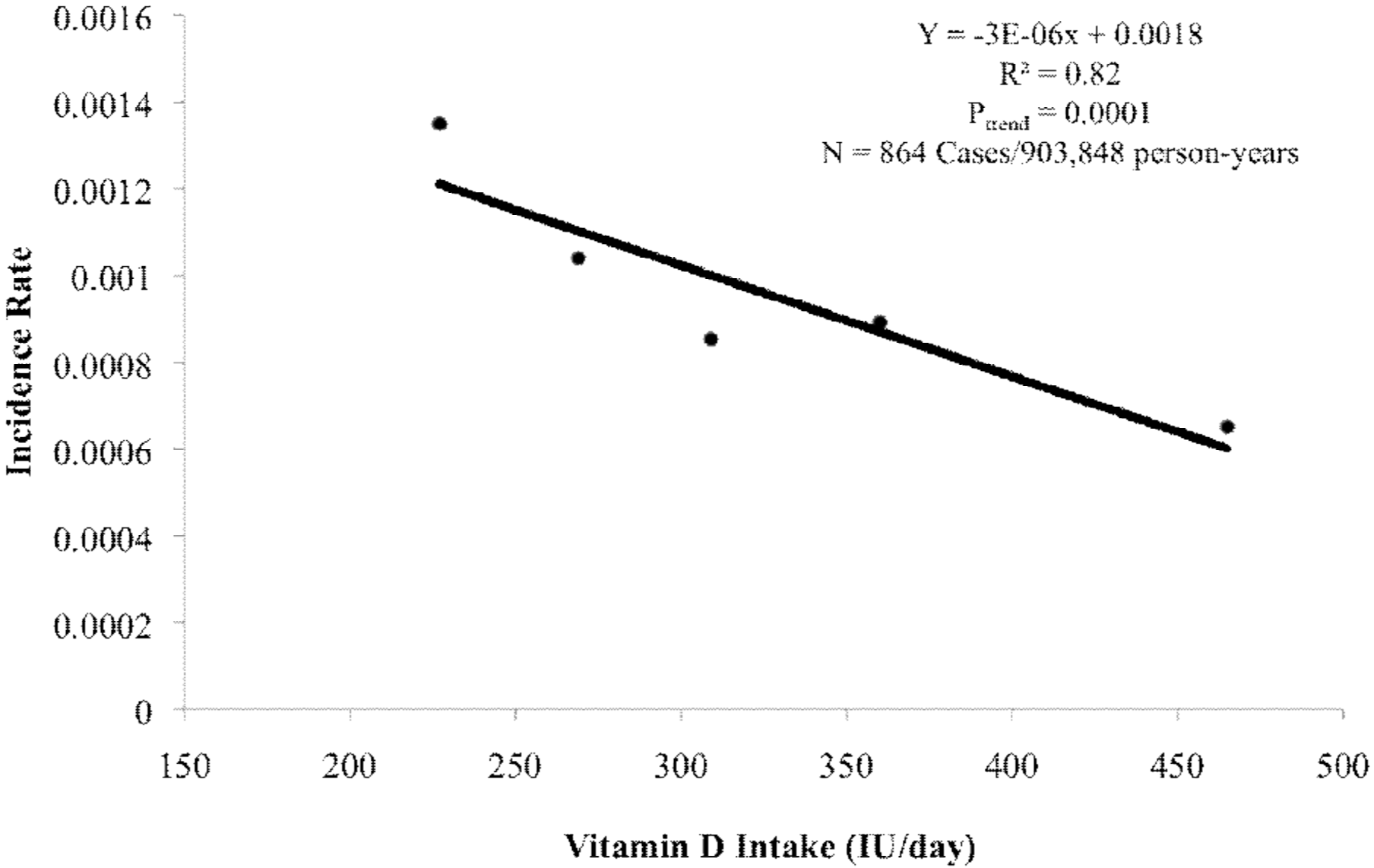


Relative risks* and 95% confidence limits for incident kidney stones by dietary calcium intake among men less than 60 years of age, N=1,496 incident cases in 266,772 participants, Health Professionals Follow-Up Study, 1986-2000

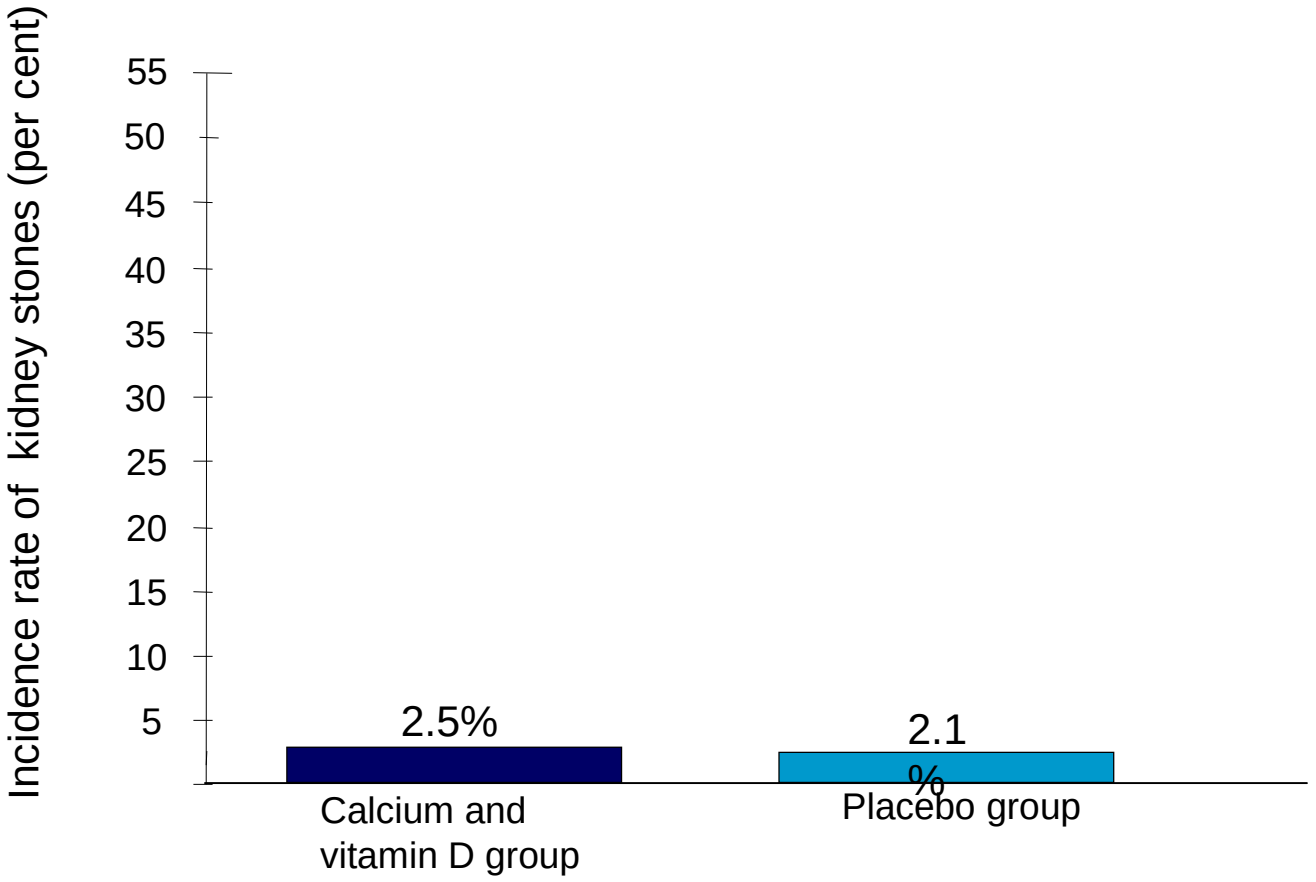
* Adjusted for age, body mass index, thiazide diuretics use, alcohol use, and intake of animal protein, potassium, sodium, vitamin C, and magnesium

Source: Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15:3225-32.

Incidence of Kidney Stones According to Oral Vitamin D Intake, Women, 1980 - 1992
Source: Curhan et al., 1997



Incidence rate of kidney stones according to group,
Women's Health Initiative clinical trial , 7-Year Follow-up



Source: Jackson et al. New Engl J Med 2006