Randomized Trial of Vitamin D3 & Calcium Supplementation to Reduce Risk of Cancer

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Solar Radiation and Cancer Mortality

- 1941 Apperly - Cancer mortality higher in northern than in southern US states.

Apperly, *Cancer Research* Vol 1, No 1 (1941); 1934–1938 health statistics

- 1989 Garland – Colon cancer mortality higher in the northeastern US than in the south.

Garland, 1989, *Lancet* 2.

Solar Radiation and Cancer Mortality

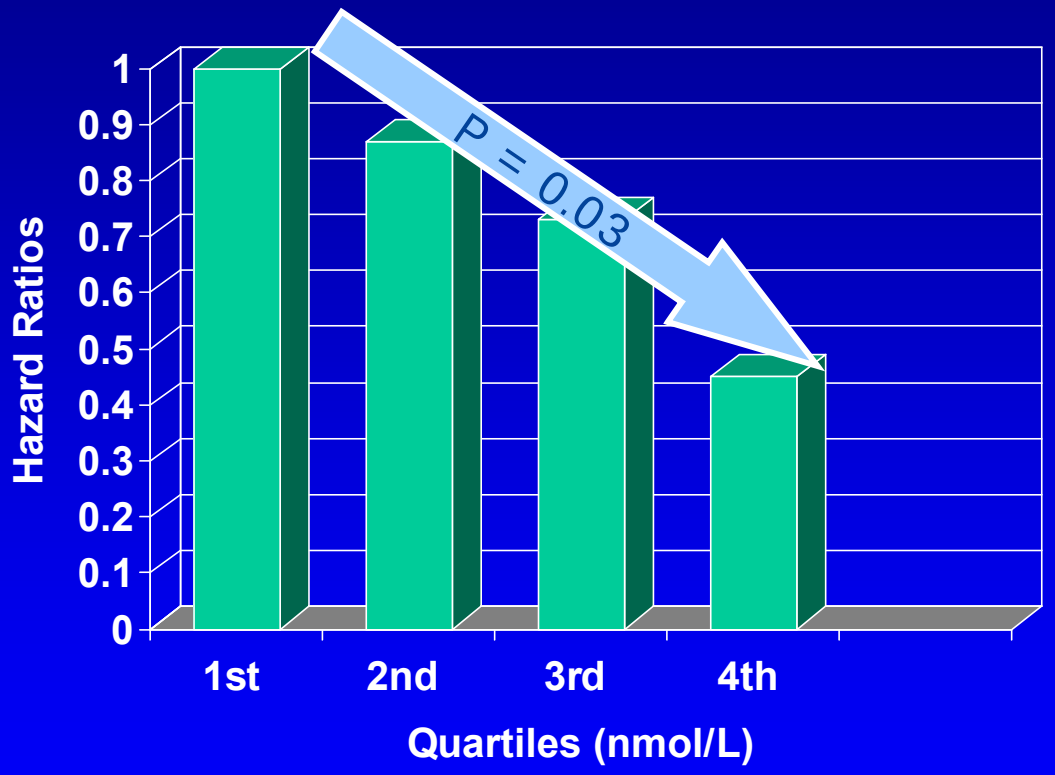
An inverse correlation between cancer death rates and sunlight exposure has been found for numerous cancers. Some of them include:

- breast
- colon
- rectum
- prostate
- stomach
- bladder
- thyroid
- non-Hodgkins lymphoma
- ovary
- lung
- pancreas
- uterus
- kidney
- esophagus
- multiple myeloma

Grant W. Cancer 2002;94
Holick M.. Prog Biophysics Mol Biol 2006;92:
Giovannucci E. Cancer Causes and Control 2005;16

Risk of Fatal Cancer by Quartile of 25OHD

- German men and women
- Referred for coronary angiography
- Age 62±10 yrs
- 3162 cases and 95 controls
- 1997-2000
- Median follow up of 7.5 yrs
- Death due to cancer confirmed by death certificates

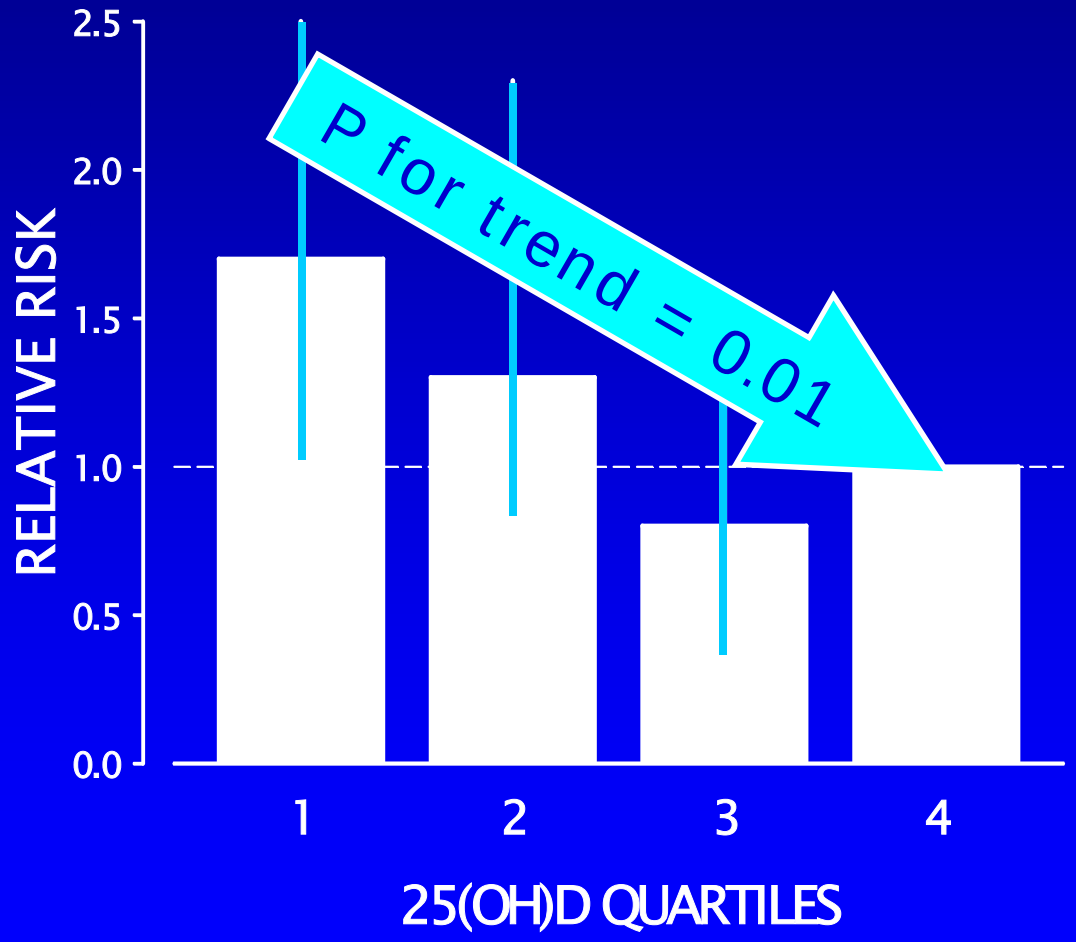


Pilz et al, 2008

Serum 25(OH)D & Prostate Cancer

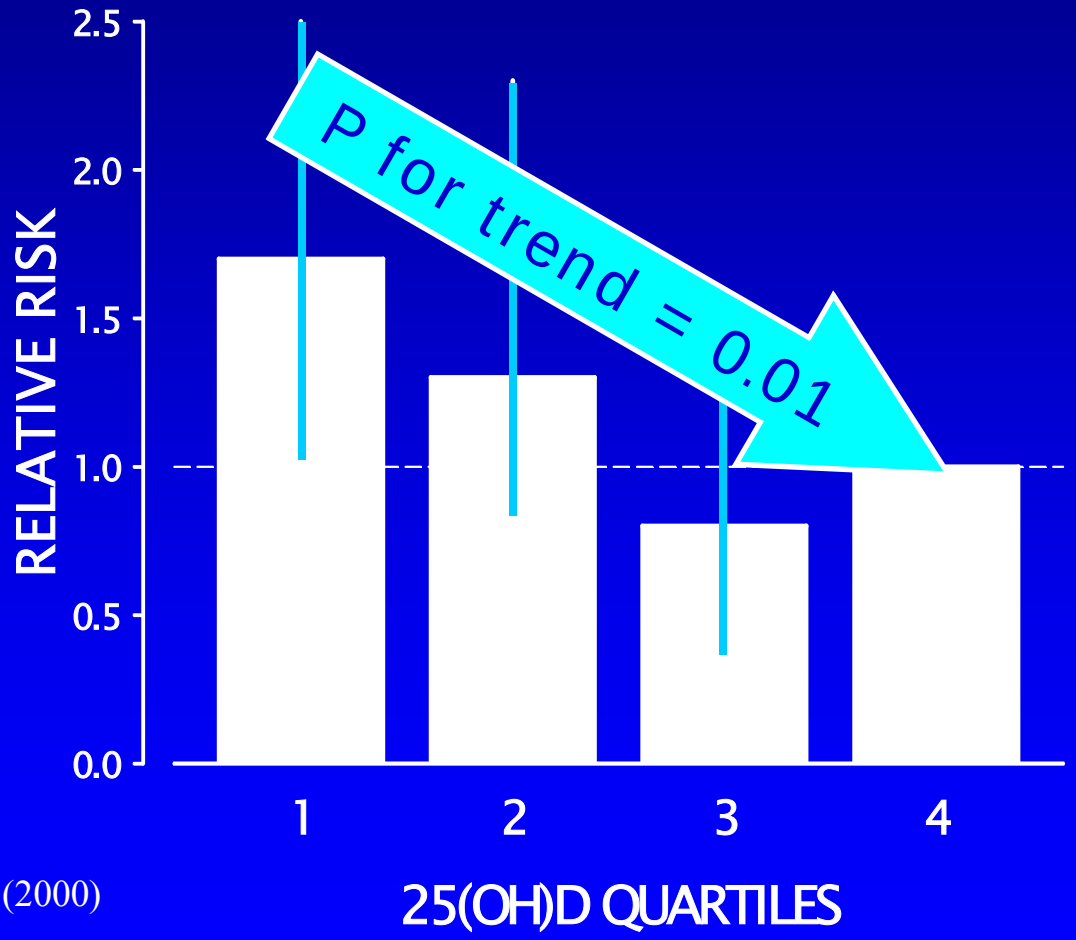
- 13 yr longitudinal study
- 19,000 men
- 149 cases prostate CA

Ahonen et al., 2000



Serum 25(OH)D & Prostate Cancer

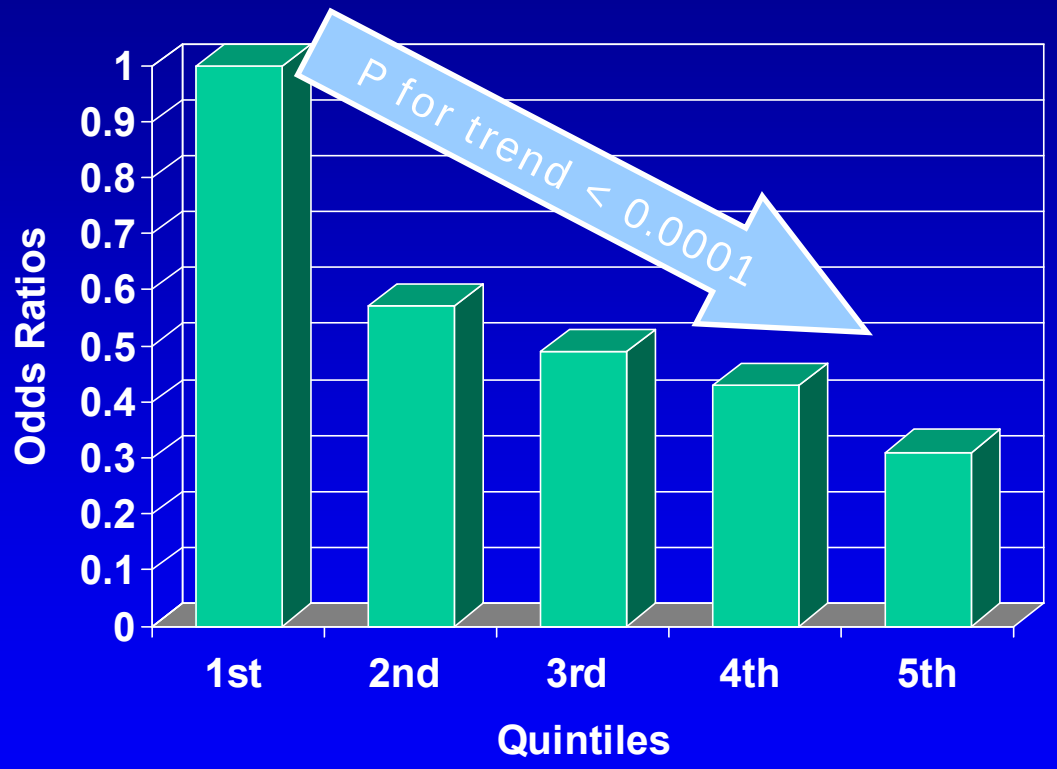
those with the lowest 25(OH)D level were 70% more likely to develop prostate CA than those in the highest quartile.



*Ahonen et al., CancerCauses&Control 11:847-852 (2000)

Risk of Breast Cancer by Quintile of 25OHD

- German women aged 50-74
- Postmenopausal
- 1394 cases and 1365 controls
- 2002-2005
- Histologically confirmed primary invasive or *in situ* breast cancer

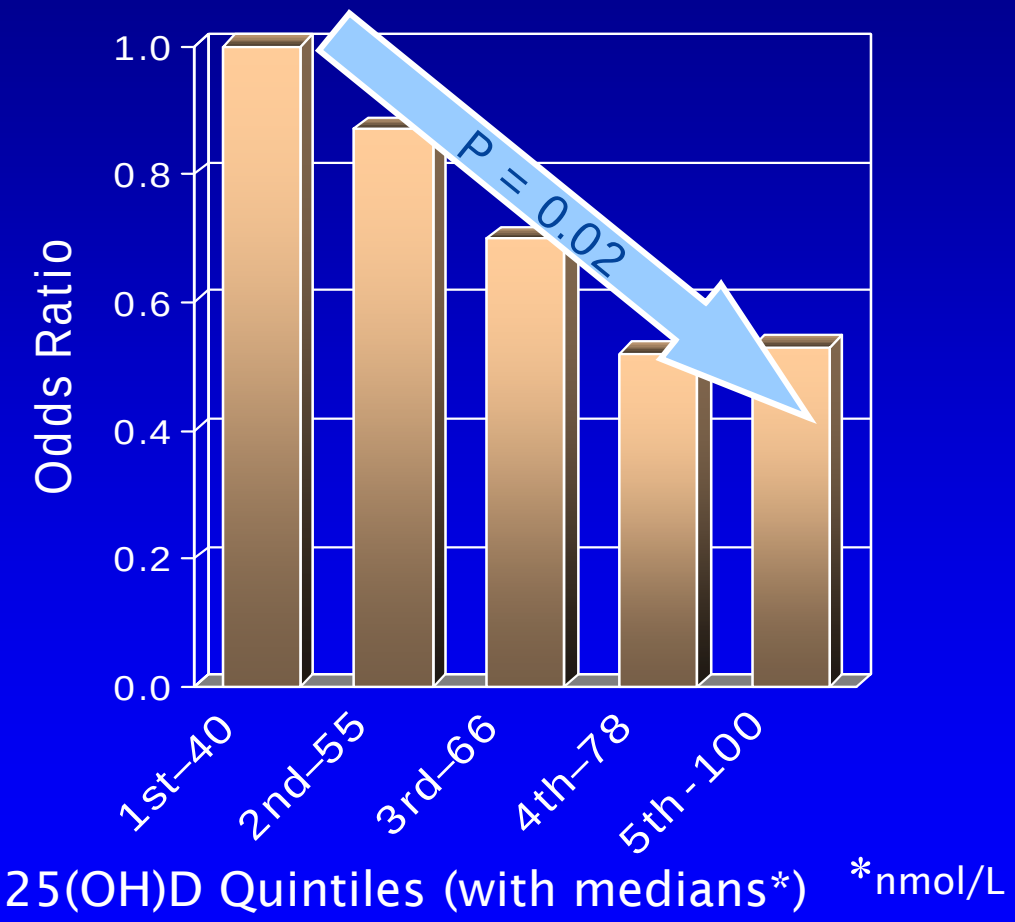


Abbas et al., 2007

COLORECTAL CANCER

- Nurses' Health Study
- ages 46–78
- nested case-control study
- 193 incident cases

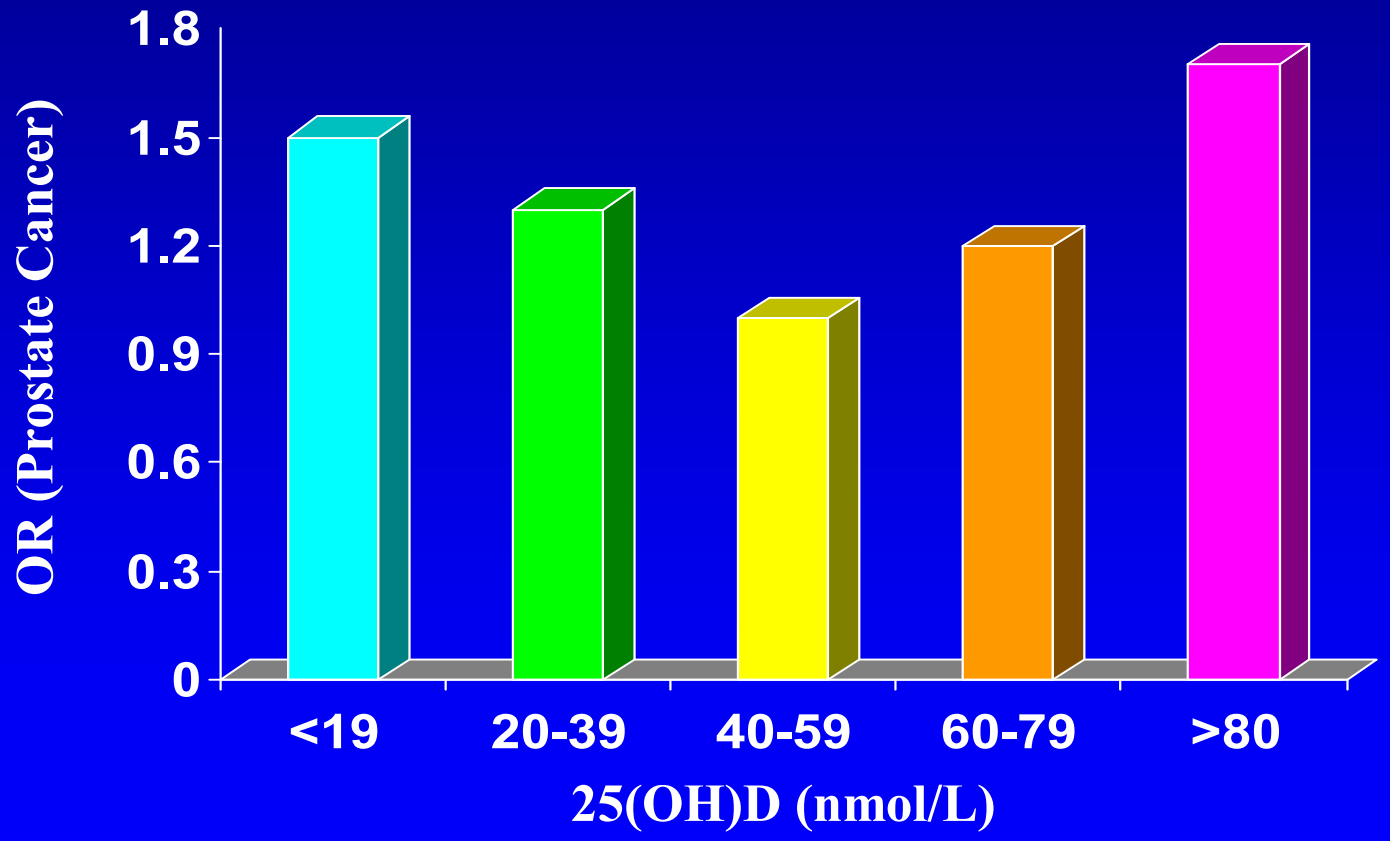
Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08



- The preponderance of evidence from ecological, cohort, and case control studies supports an anticancer effect of vitamin D.
- However, there were studies that did not find the effect.
- A few studies showed an increased risk of cancer with higher serum 25OHD levels.

Risk of Prostate Cancer by Quintile of 25(OH)D Example of the U-shaped Curve

Nested Case-Control Study in Nordic Men (622 cases and 1451 controls)



Tuohimaa et al. Int J Cancer 108: 104-108, 2004

Randomized Clinical Trials

Women's Health Initiative (WHI)

36,282 women randomly assigned to 400 IU vitamin D3/d and 1000 mg calcium/d or placebo for both

Primary outcome – fracture; secondary outcome colorectal and breast cancer

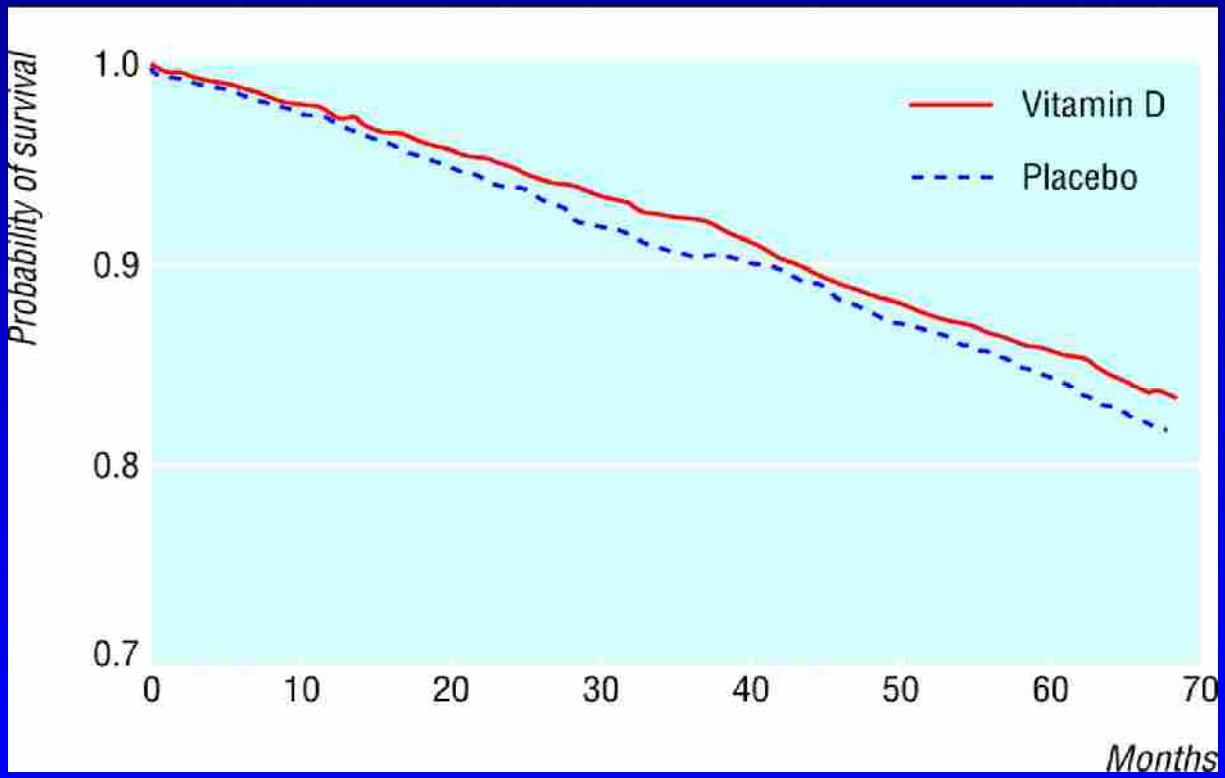
No effect of vitamin D intervention on cancer incidence

- Vitamin D_3 dose – 400 IU
- Poor treatment adherence
- 15% of placebo subjects crossed into the active group by taking their own supplements
- 58% of subjects were assigned to hormone replacement therapy in the study

WHI did find a highly significant inverse association between baseline 25OHD and incident colon cancer. Risk for lowest quartile was 2.5 times greater than highest quartile.

Cumulative survival according to treatment with vitamin D (n=1345) or placebo (n=1341)

- 2686 British men and women
- RCT
- Vit D3 100,000 IU q 4 mos/5 yrs (~800 IU/d)
- Vit D3 had no effect on overall survival or cancer survival



Trivedi et al 2003

Randomized Trial of Vitamin D3 & Calcium Supplementation and All-type Cancer

Specific Aims

- Primary : to determine the anti-fracture efficacy of supplementation with calcium or calcium and vitamin D in a population of older women.
- Secondary: to determine the efficacy of supplementation in reducing incident cancer risk of all types.

Lappe et al. Am J Clin Nutr 2007

Funded by the National Institute of Aging

Randomized Trial of Vitamin D3 & Calcium Supplementation and All-type Cancer

Random sample of the population

N = 1179 post-menopausal women

Ages 55- 89

Randomized, double-blind, placebo-controlled

Four yrs duration

Three groups

1. Calcium 1400-1500 mg/d
2. Vitamin D3 1100 IU/d plus calcium
3. Placebo for both

Lappe et al. Am J Clin Nutr 2007

Target Population

- Healthy women in a nine-county rural Nebraska area
- At least four years postmenopausal
- 55 years of age and older
- Any ethnic background
- Living independently

Population-Based Study

- In human clinical studies, we want to make inferences from the sample about the population from which the sample is derived.
- Convenience samples are more likely to have unknown biases that render the sample different than the population.
- Probability sampling is the best way to obtain a sample that is representative of the population.
- Simple random sampling is the easiest form of probability sampling; each individual has an equal probability of being selected for the sample.

Simple Random Sampling

Midwest Survey and Research (MSR), a market research firm:

- used a complete list of telephone numbers for target area
- randomly selected numbers from all households with listed telephone numbers and called them to do an initial telephone screen.
- continued calling until 1179 women were selected who met the inclusion and exclusion criteria and were willing to participate in this four year study.
- reported 96,301 dialings and 27,713 persons contacted.

Exclusion Criteria

- History of cancer except

  a) superficial basal or squamous cell carcinoma of the skin

  b) other malignancies treated curatively more than 10 years ago
- History of chronic kidney disease or renal calculi
- Diagnosis of Paget's metabolic bone disease

Measurements

Annually

- Serum 25OHD (RIA –IDS, Fountain Hills AZ) Our lab participates in the international quality assessment by DEQAS.
- A sample of each lot of vitamin D3 was analyzed at the beginning and end of each year to assure potency.

Semiannually

- Supplement compliance
- Review of medical status & meds.
  Cancer cases were validated by medical records.

Baseline and end of study

- Dietary assessment

Adherence

- Mean adherence (defined as ≥ 80% of assigned doses)
  86% for vitamin D
- 74% for calcium.

Of the 1179 women enrolled, 1024 (86.8%) completed the study.

Subject Characteristics by Treatment Group

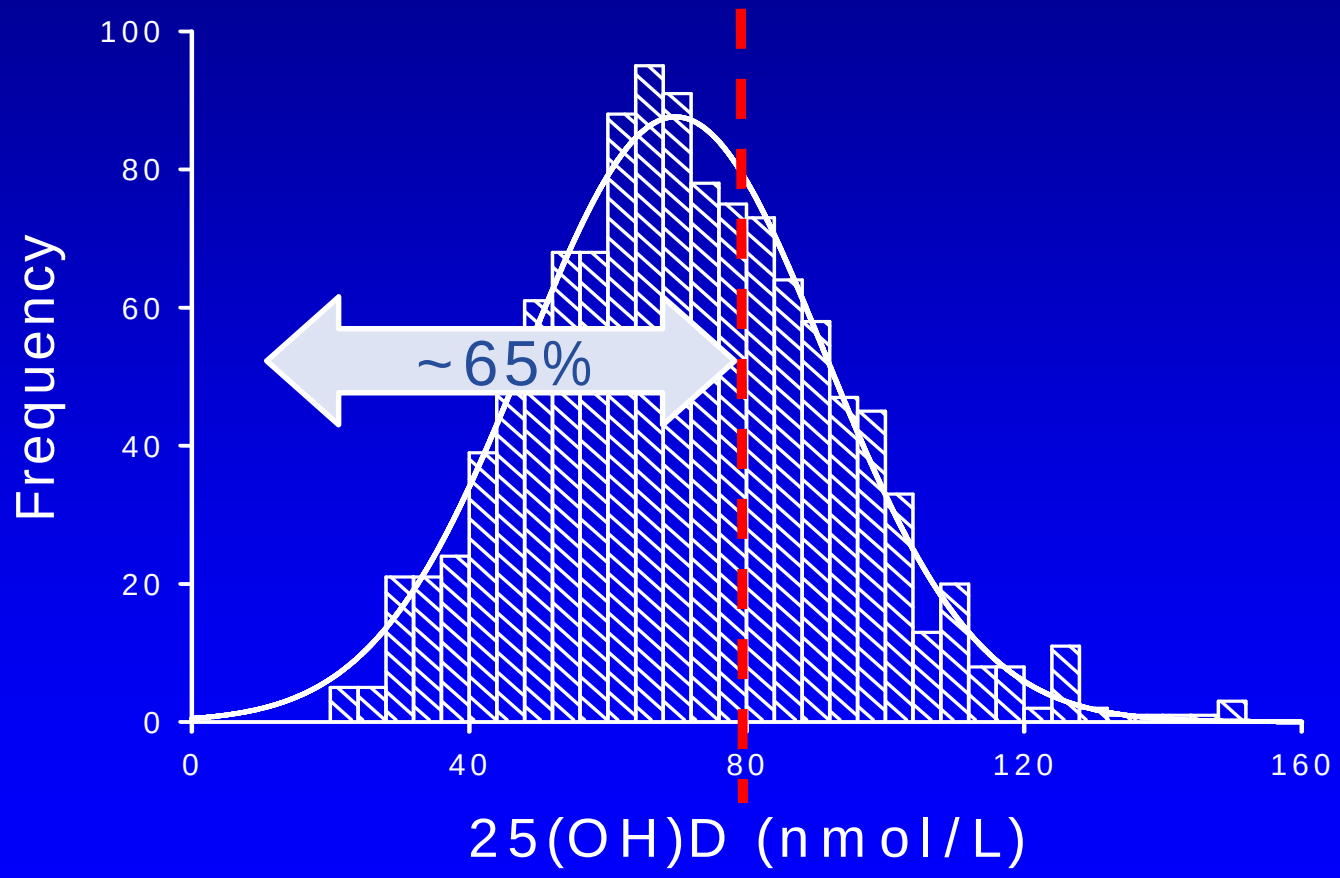
Variable	Placebo N=288	Calcium N=445	Calcium/D N=446
Age (yrs)	66.1±6.8	66.5±7.2	67.3±7.7
Height (m)	1.63±0.06	1.63±0.06	1.62±0.06
Weight (kg)	76.2±14.7	77.7±16.0	75.8±15.0
Body mass index ($wt/ht^{2)}$	28.8±5.5	29.4±5.9	28.8±5.5
Diet calcium intake (mg/d)	699±415	692±388	662±397
Total calcium intake (mg/d)	1062±588	1058±597	1020±559

Baseline and 12-month Serum 25OHD (nmol/L - ng/mL)

	Baseline (mean ± S.D)	12 months (mean ± S.D)	Change (mean ± S.D)
Placebo	72.1 ± 20.7 28.8 ± 8.3	71.1 ± 19.8 28.4 ± 7.9	-0.23 ±14.7 -0.09 ± 5.9
Calcium only	71.6 ± 20.5 28.6 ± 8.2	71.0 ± 20.3 28.4 ± 8.1	-0.74 ±13.0 -0.30 ± 5.2
Calcium plus D	71.8 ± 20.0 28.7 ± 8.0	96.0 ± 21.4 38.4 ± 8.6	+23.9 ± 17.8 9.6 ± 7.1

25(OH)D in Older Women in Nebraska at Baseline

- women aged 55 & older
- latitude 41º N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU



Lappe et al., JACN 2006

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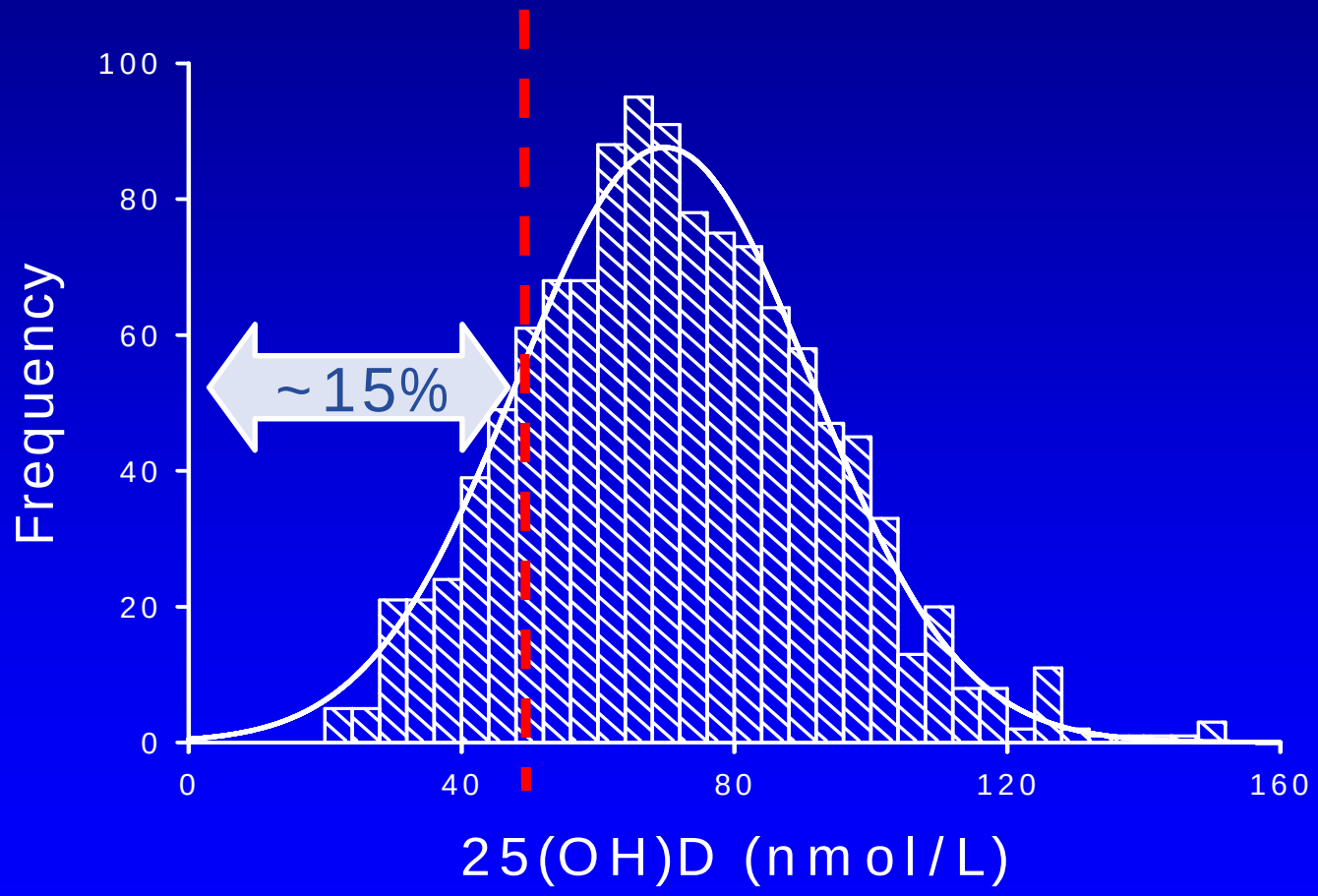


Lappe et al., JACN 2006

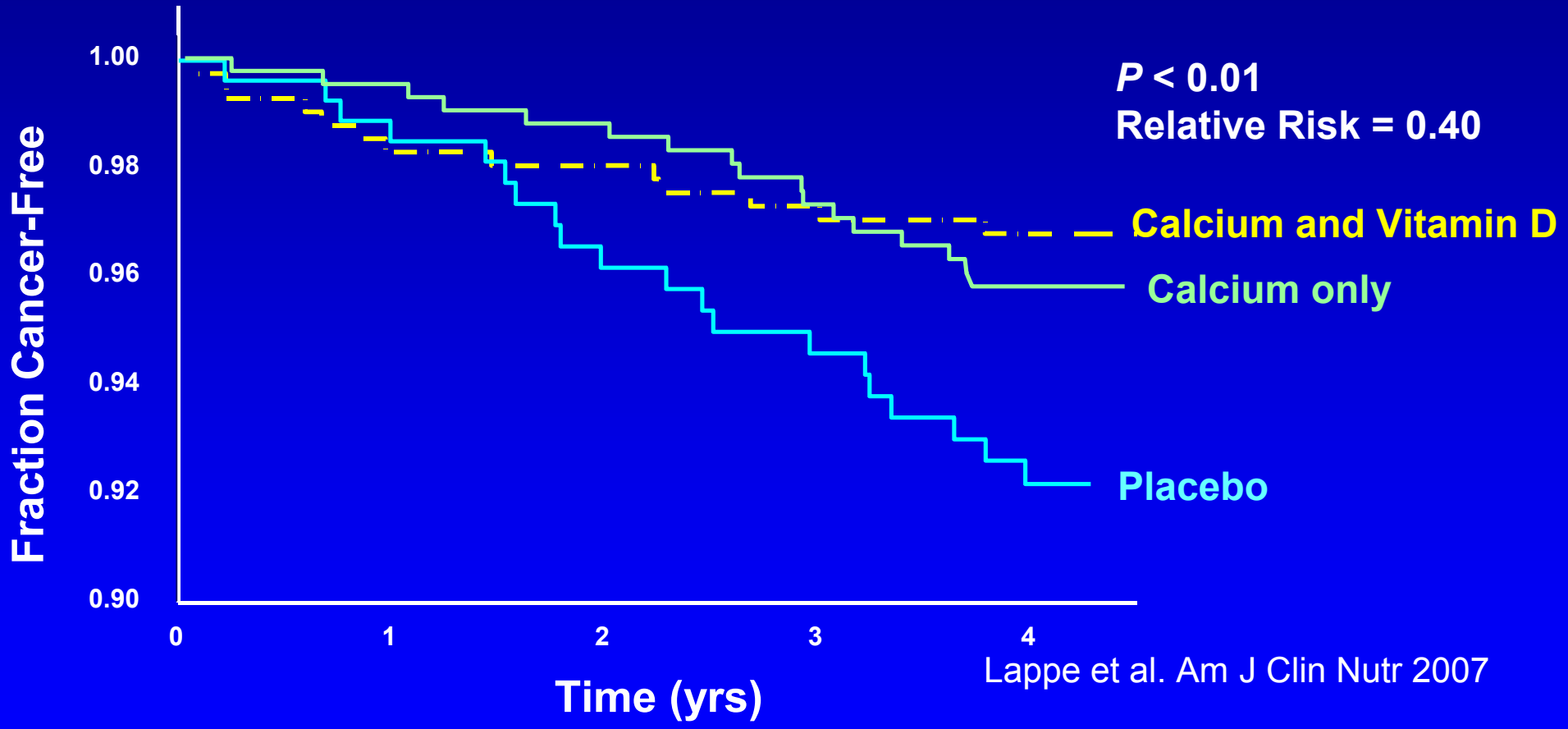
Cancer Occurrence

Over the 4 years of study 50 women were diagnosed with cancer, 13 in the first year and 37 thereafter.

Number of Cancers by Site and Treatment Group

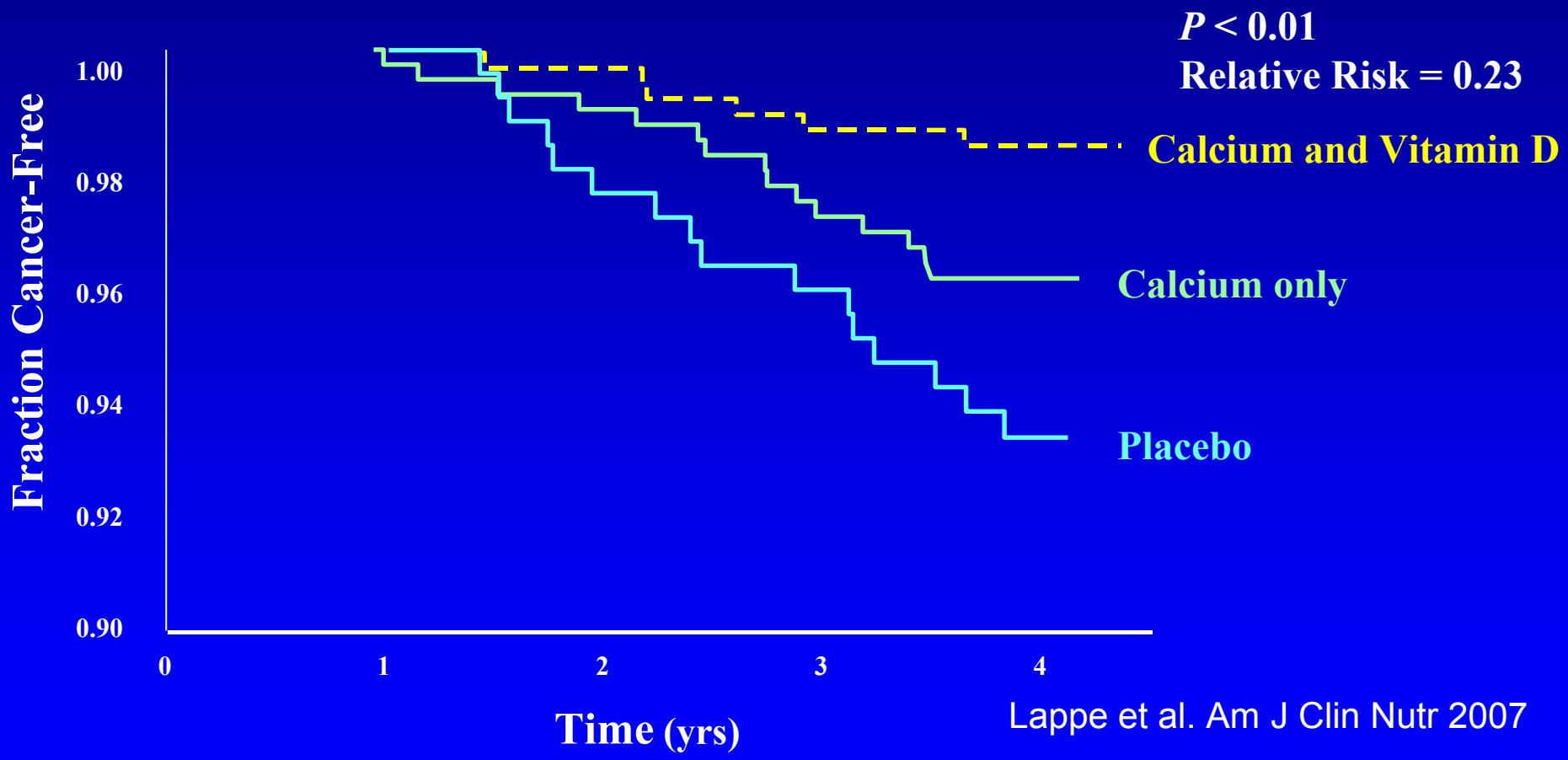
Anatomical Site	Placebo n = 288	Calcium n = 445	Vitamin D plus Calcium n = 446
Breast	8	6	5
Colon	2	0	1
Lung	3	3	1
Lymph/Leukemia/Myeloma	4	4	2
Uterus	0	2	1
Other	3	2	3
Total	20 (6.9%)	17 (3.8%)	13 (2.9%)

Kaplan-Meier survival curves (i.e., free of cancer) for the 3 treatment groups in the entire cohort of 1,179 women.



Lappe et al. Am J Clin Nutr 2007

Kaplan-Meier survival curves for the 3 treatment groups in the cohort of women free of cancer at 1 year of intervention (n = 1,085).



Lappe et al. Am J Clin Nutr 2007

Results (cont)

Logistic regression models were developed to explore determinants of cancer incidence.

- 12-month 25OHD ($P < 0.002$)
- Baseline 25OHD ($P < 0.03$)

- Treatment and 12 month 25OHD level - only 25OHD was a significant predictor ($R^2 = 0.037$; $P < 0.05$)

- Treatment and baseline 25OHD - both were significant predictors ($R^2 = 0.055$; $P < 0.05$).

- Neither age or BMI was a significant predictor.

Study Limitations/Strengths

- Primary outcome was antifracture efficacy
- Small sample size compared to many cancer studies

+ Population-based study with few exclusion criteria
+ Rigorous design (double-blind, randomized, placebo-control)
+ High adherence to supplement regimen
+ Low dropout rate

Our study is the first to report the effects of vitamin D status on all-cancer incidence.

It is also the first randomized clinical trial that used a vitamin D intervention sufficient to raise serum 25OHD to optimum levels and that targeted a cancer outcome.

World Health Organization
International Agency for Research on Cancer

"The statistical analysis of the Nebraska trial was not correct.

- For instance, subjects that received (Ca only) had a decrease in cancer risk of similar magnitude to subjects receiving (Ca + D). Thus a correct intent to *threat* analysis comparing the (Ca + D) group with (Ca only pooled with placebo) shows no significant decrease in cancer risk.
- In contrast, an intent to *threat* analysis of (Ca + D pooled with Ca only) versus placebo shows a significant reduced cancer risk due to calcium supplements.
- The methodology and statistical analysis of this trial have been much criticised (Sood *et al.,*2007; Bolland *et al.,*2007; Ojha *et al.,*2007; Shabas *et al.,*2008). For instance, the cancer incidence was unusually high in the placebo group, a bias that undermined the trial's findings (Shabas *et al.,*2008). In conclusion, the design of the Nebraska trial was biased, and its results were negative for vitamin D."

Vitamin D and Cancer. IARC Working Group Reports Vol.5, Lyon, 25 November 2008.

Summary

- A variety of research designs, other than randomized clinical trials, provide evidence that vitamin D decreases risk of cancer.
- One randomized controlled trial with all-type cancer as a secondary outcome reported a 60% reduction in cancer incidence in older women.
- However, many members of the scientific community, including the International Agency for Research on Cancer, find the data lacking support for a causative effect.
- In addition, there are concerns about safety of consistently “high” levels of 25(OH)D over a long period of time.
- Two randomized trials, funded by the NIH, are currently in progress - designed to run 4 and 7 years, respectively.

Vitamin D: The Sunshine Vitamin