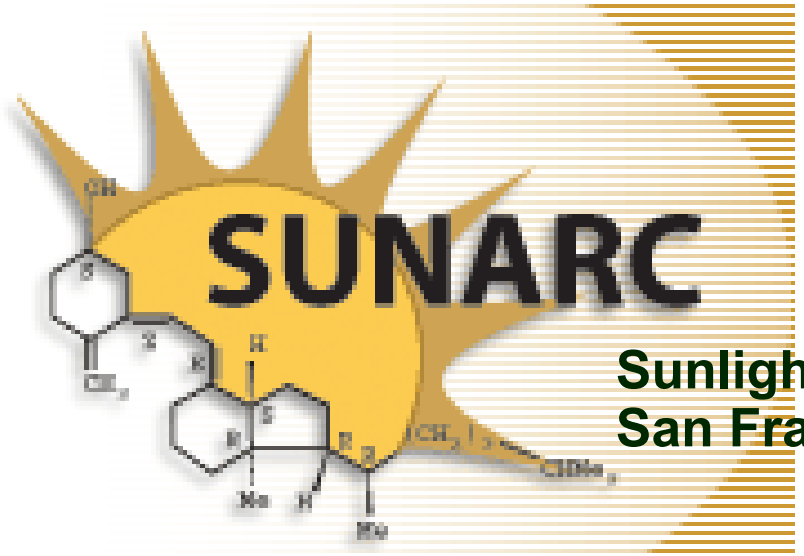
The Impact of Improving Vitamin D Levels – Health & Financial Outcomes

Vitamin D – Experts' Forum

London, April 7, 2011

by **William B. Grant, Ph.D.**



Sunlight, Nutrition, and Health Research Center
San Francisco, California, **www.sunarc.org**

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Disclosure

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- UV Foundation (McLean, Virginia) www.uvfoundation.org
- Sunlight Research Forum (Veldhoven)
- Bio-Tech-Pharmacal (www.Bio-Tech-Pharm.com) (Fayetteville, AR)
- The Vitamin D Council

  www.vitaminDCouncil.org

Outline

- Vitamin D – Types of evidence for benefits
- Major vitamin D-sensitive diseases for Europe
- Effect of vitamin D for these diseases
  - Cardiovascular disease, cancers, respiratory diseases, respiratory infections, diabetes mellitus, tuberculosis, Alzheimer's disease, falls, Parkinson's disease, meningitis, multiple sclerosis
- Reductions in mortality rates for Europe if 25(OH)D levels were raised from 54 nmol/l to 105 nmol/l

Types of Epidemiological Studies

- There are four basic types of epidemiological studies used to identify and quantify links between risk-modifying factors and disease:
  - Nested case control – a defined population followed for years after blood draw; (accuracy decreases with time since draw)
  - Case-control – blood draw at time of diagnosis;
  - Cross-sectional – survey of a large population;
  - Ecological – populations are defined geographically; both disease outcome and risk-modifying factors are averaged by region.

Randomized Controlled Trials (RCTs)

- Some are given an agent, others placebo, people followed for some time, outcomes beneficial and adverse noted.
- RCTs are essential for pharmaceutical drugs.
- In my opinion, RCTs are not essential for vitamin D since 90% of vitamin D comes from solar UVB and vitamin D is a naturally occurring compound that the body is adapted to having.
- Many RCTs used too little vitamin D (400 IU/day) to produce any effects; effects are seen for 800-2000 IU/day. Also, compliance may be poor, and vitamin D from solar UVB or other oral intake interferes.

Scientific Analysis

- In my analysis, I base my estimates on a combination of ecological and observational studies, augmented by an understanding of mechanisms, and RCTs when available.
- This is not the approach taken by the Institute of Medicine on November 30, 2010, which found a beneficial effect only for bones.
- However, since the primary source of vitamin D is solar UVB irradiance, and vitamin D is not a drug, it is justifiable scientifically.

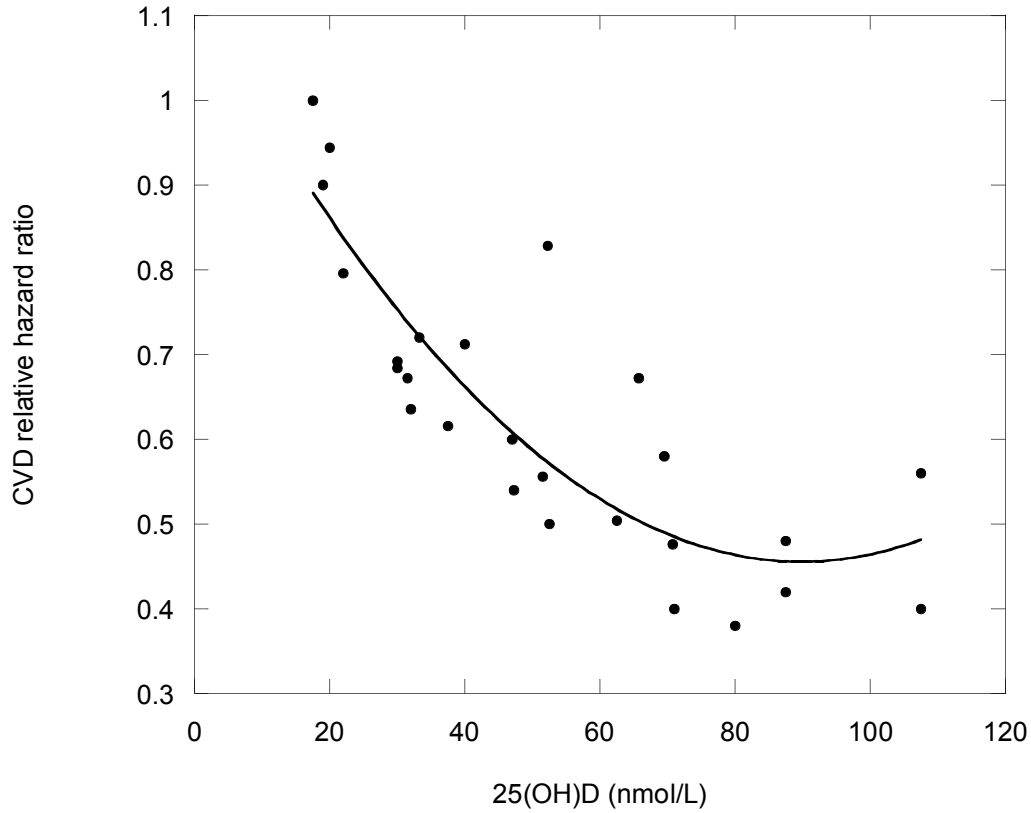
Basis for 54 nmol/l as the Mean Serum 25(OH)D Level in Europe

- The mean 25(OH)D level was 54 nmol/l (95% CI: 52-57 nmol/l). Women had borderline significantly higher 25(OH)D levels than men, and Caucasians had higher levels than non-Caucasians.
- There was a significant decline with latitude for Caucasians (-0.69 +/- 0.30 nmol/l per degree, p = 0.02), but not for non-Caucasians (0.03 +/- 0.39 nmol/l per degree, p = 0.14).
- After adjustment for age, gender, and ethnicity, no overall correlation was present between 25(OH)D and latitude (-0.29 +/- 0.24 nmol/l per degree, p = 0.23).
- Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, *et al.* Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009;20:133-140.

Vitamin D and Cardiovascular Disease

- Several recent observational studies found that those with lower serum 25(OH)D had higher risk of cardiovascular disease incidence or mortality rate.
- The hazard or odds ratios were as high as a factor of two or more for <25 nmol/l vs. >75 nmol/l.
- CVD rates are higher in winter, even in warm climates, supporting a role for UVB/vitamin D.
- No randomized controlled trials have reported reduced risk of CVD yet.

CVD Risk vs. Serum 25(OH)D Level



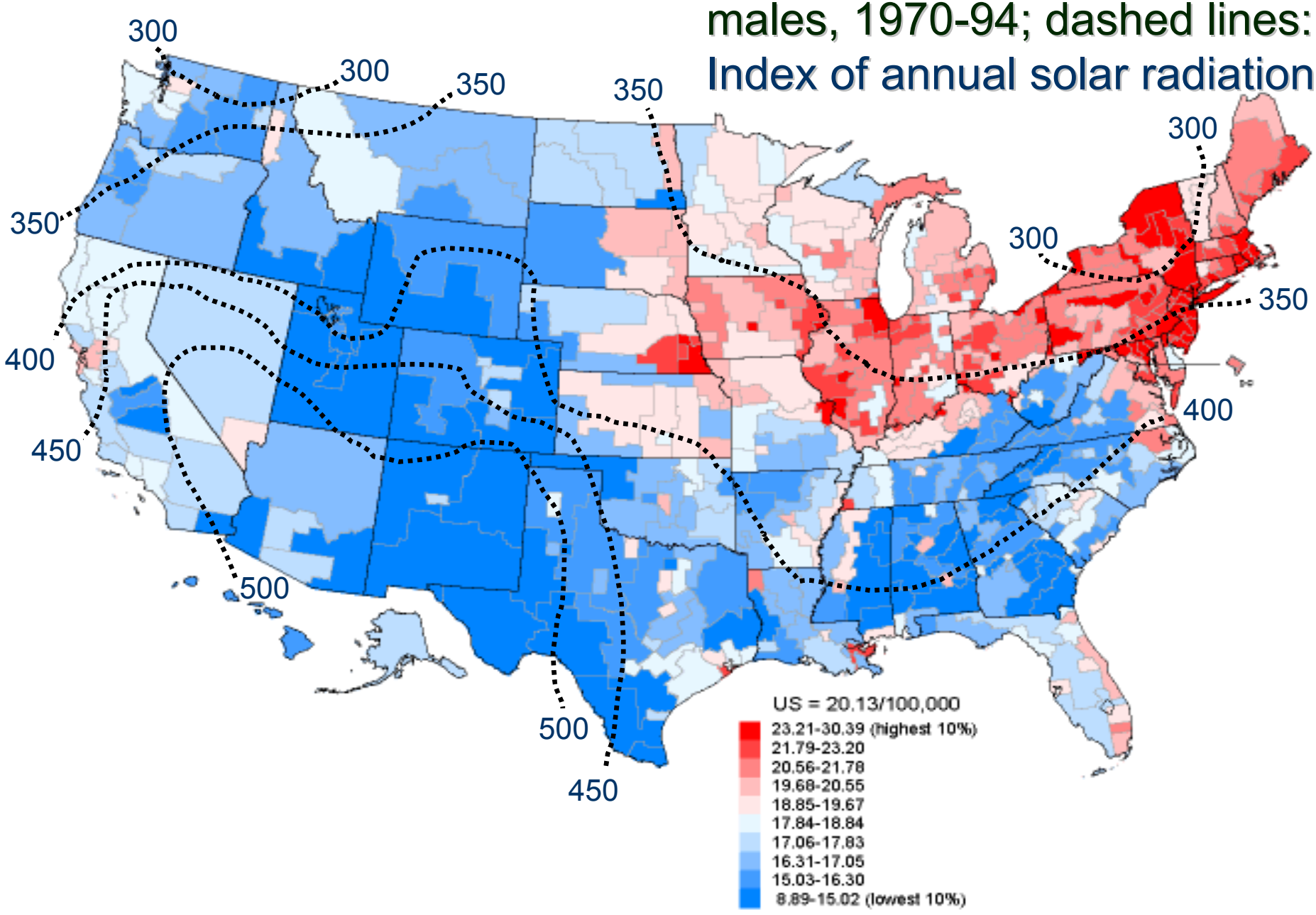
The effect is nonlinear, with more rapid change at lower 25(OH)D levels

Reduction of 40% in increasing from 54 to 105 nmol/l

Ecological Studies of UVB, Vitamin D, Cancer

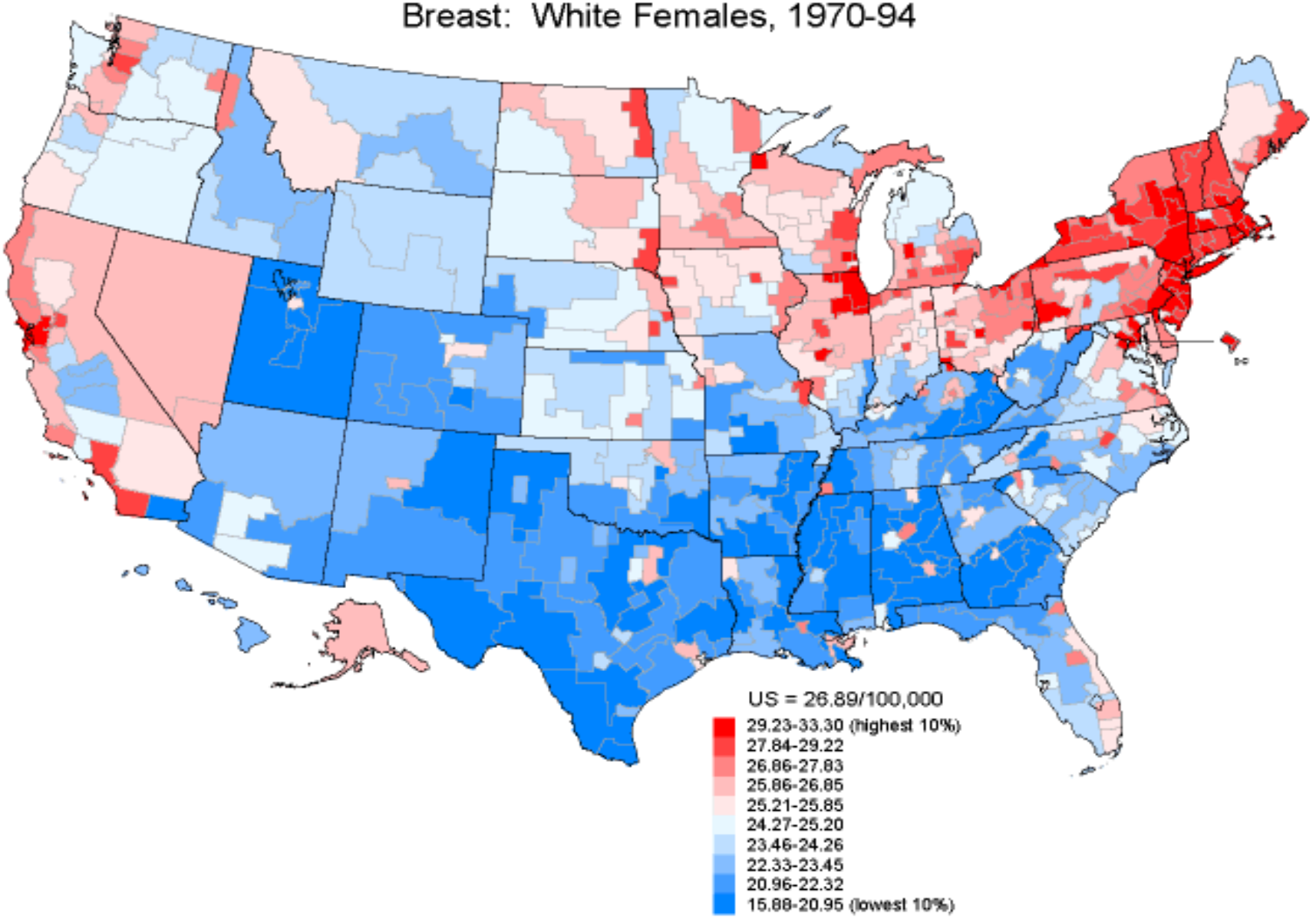
- The first epidemiological study hypothesizing that solar UVB, through production of vitamin D, reduced the risk of cancer was published in 1980.
- The brothers Cedric Garland and Frank Garland, then at Johns Hopkins School of Public Health, looked at the map of colon cancer mortality rates in the U.S. and saw a link to solar radiation.

Colon cancer mortality rates, males, 1970-94; dashed lines: Index of annual solar radiation

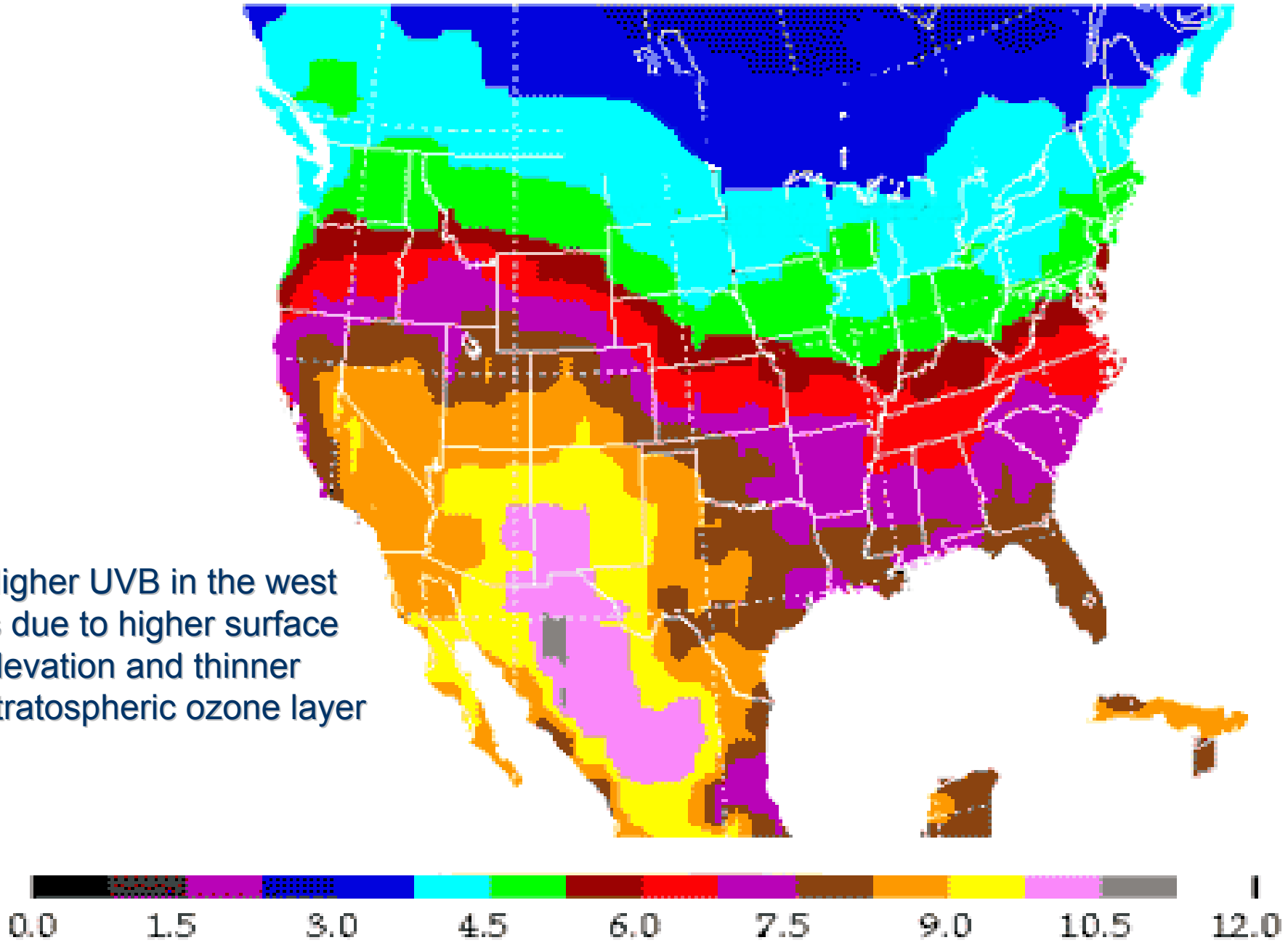


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)

Breast: White Females, 1970-94



DNA SPECTRAL EXPOSURE (kJ/m²) FOR JULY 1992



Higher UVB in the west is due to higher surface elevation and thinner stratospheric ozone layer

19 Vitamin D-Sensitive Cancers

- Vitamin D-sensitive cancers with moderate-to-strong support from several ecological studies after accounting for other factors:
  - Gastrointestinal: colon, esophageal, gallbladder, gastric, pancreatic, rectal
  - Urinary: bladder, kidney; Male: prostate
  - Female: breast, cervical, endometrial, ovarian, vulvar
  - Blood: Hodgkin's and non-Hodgkin's lymphoma, leukemia
  - Miscellaneous: brain, lung, melanoma

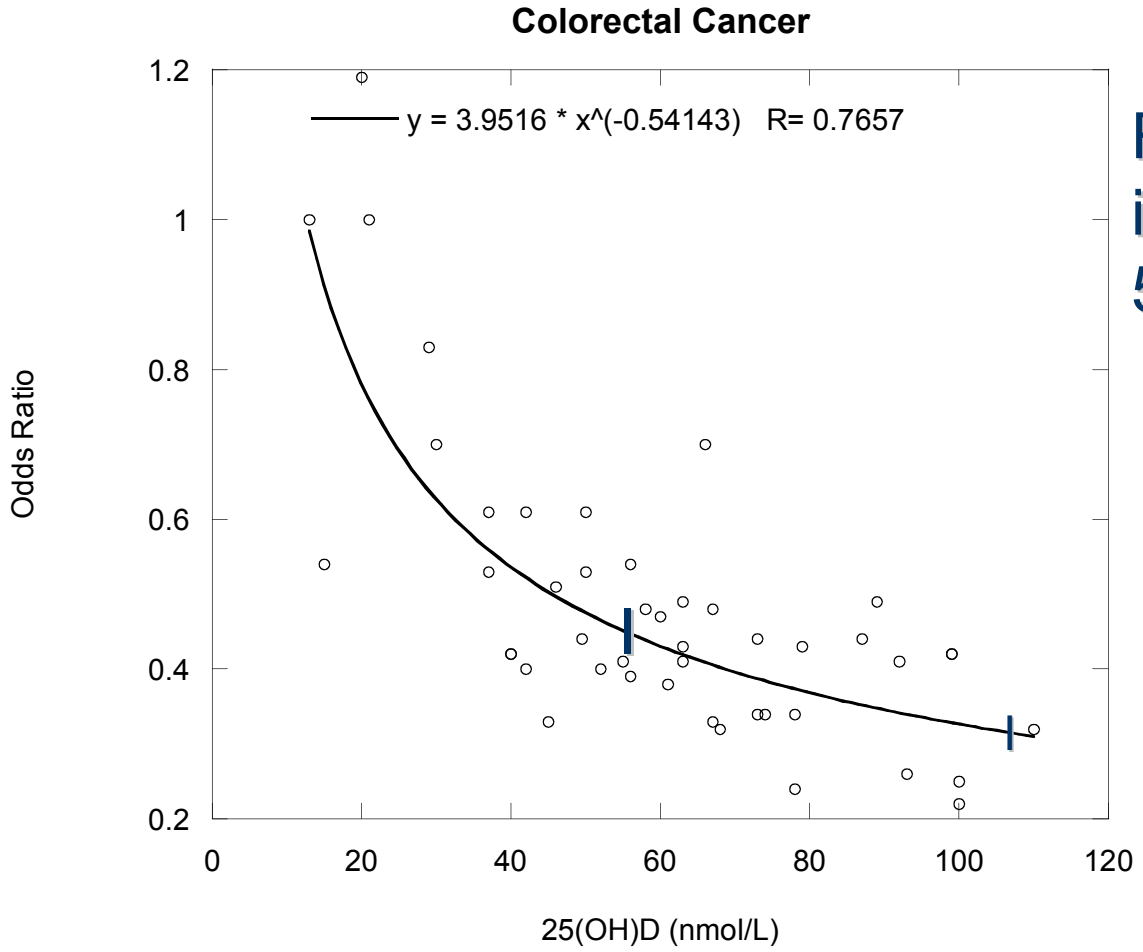
Why Ecological Studies Are Powerful

- Cancers generally take 15-40 years to progress from initiation to detection or death.
- Vitamin D has effects at many stages of cancer, initiation, angiogenesis, and metastasis.
- If serum 25(OH)D levels drop when tumors are ready for angiogenesis, they can grow rapidly.
- Thus, integrated serum 25(OH)D levels over long periods of time are important in reducing the risk of cancer incidence and death.

Observational Studies of Breast and Colorectal Cancer vs. Serum 25(OH)D

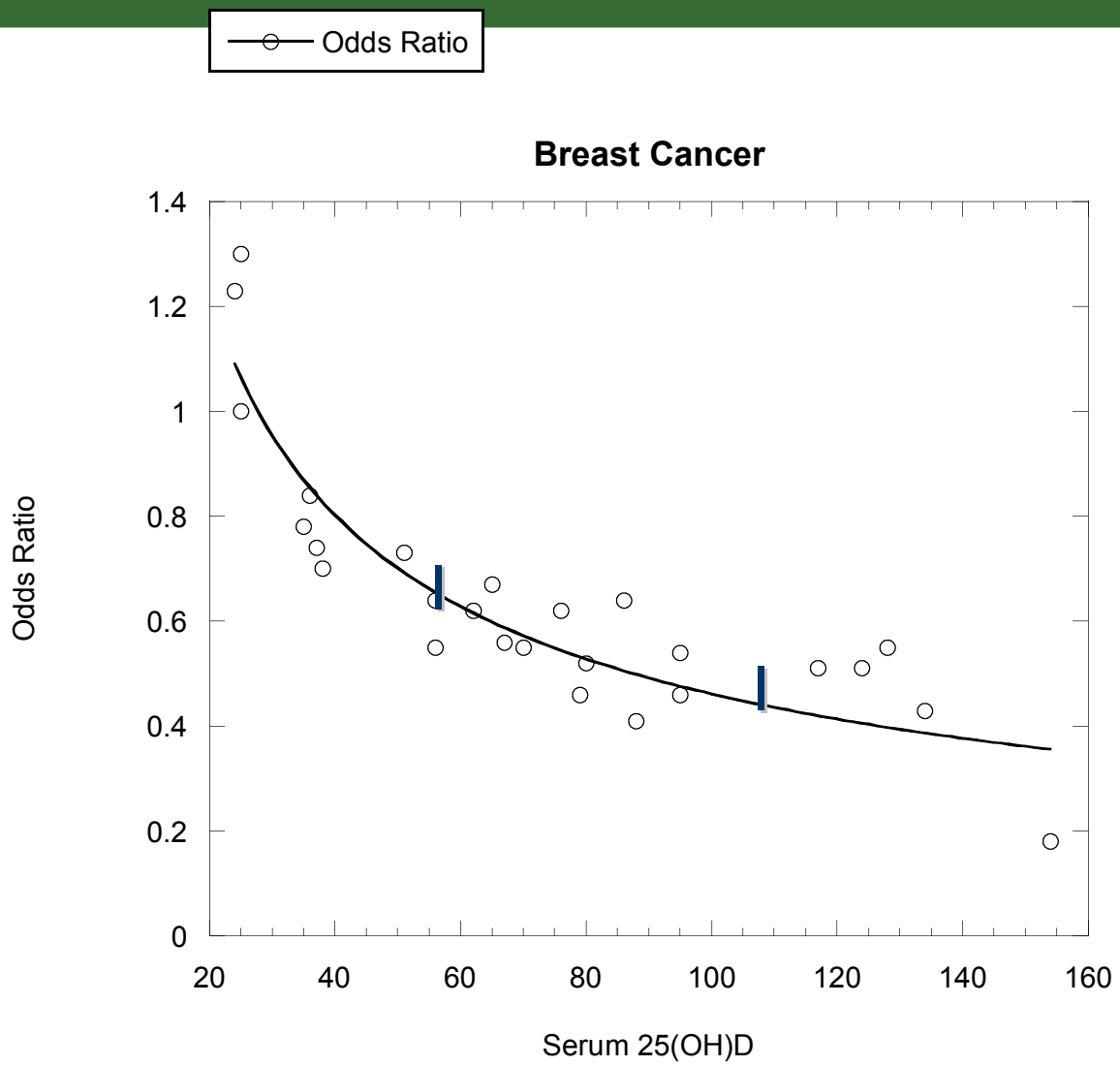
- Observational studies provide useful data for determining the serum 25(OH)D level-cancer incidence rate relation for breast and colorectal cancer
- For breast cancer, serum 25(OH)D levels are useful out to 3 years
- For colorectal cancer, serum 25(OH)D levels are useful out to 12 years

Colorectal Cancer Incidence Rate vs. Serum 25(OH)D Level – Meta-Analysis



Reduction of 30% in increasing from 54 to 105 nmol/l

Meta-Analysis of Breast Cancer Risk with Respect to Diagnostic Serum 25(OH)D



Reduction of 35% in increasing from 54 to 105 nmol/l

Vitamin D and Cancer, Conclusion

- One RCT found a large reduction in incidence rate for 1100 IU/day vitamin D3 and 1450 mg/day calcium.
- Those with higher serum 25(OH)D at time of diagnosis have an increased all-cause survival rate.
- Vitamin D seems worthwhile to add to the treatment for those diagnosed with several types of cancer.
- 2373 papers with vitamin D and cancer in the title or abstract are listed at www.pubmed.gov (March 28, 2011)

Respiratory Diseases

- The most important non-infectious respiratory disease is chronic obstructive pulmonary disease.
- Observational studies have found inverse correlations between lung function and serum 25(OH)D levels.
- A prospective study based on lung function 5 years after blood draw did not find an association [Kunisaki et al., Eur Respir J. 2011]. However, the long lag time means the 25(OH)D level may not be correct.
- I assume a 10% reduction in mortality rates for 105 nmol/l vs. 54 nmol/l.

Respiratory Infections

- The most important respiratory infections are influenza and pneumonia.
- Influenza is most common in winter, when it is cold, the absolute humidity is low, and vitamin D levels are low.
- Bacterial pneumonia can develop after influenza.
  - Cytokines from the immune response to influenza lead to damage of lung epithelial cells, permitting bacterial invasion.

Bacterial Infectious Diseases – Vitamin D-Induced Cathelicidin

- 1,25-dihydroxyvitamin D induces production of human cathelicidin, LL-37, a polypetide with modest antimicrobial and potent antiendotoxin activities.
- There is strong evidence that cathelicidin can fight bacterial infections: dental caries, pneumonia, sepsis, tuberculosis and possibly meningitis.

Viral Infections – T-helper Cells

- The effect of vitamin D for viral infections appears to be mediated through modification of the cytokine production by the innate immune system.
- Switch from Th1/Th17 response to the Th2/ Treg profile.
- This reduces production of proinflammatory cytokines IL-6, IL-10, IL-17, and TNF-alpha.
- Cathelicidin may also play a role.

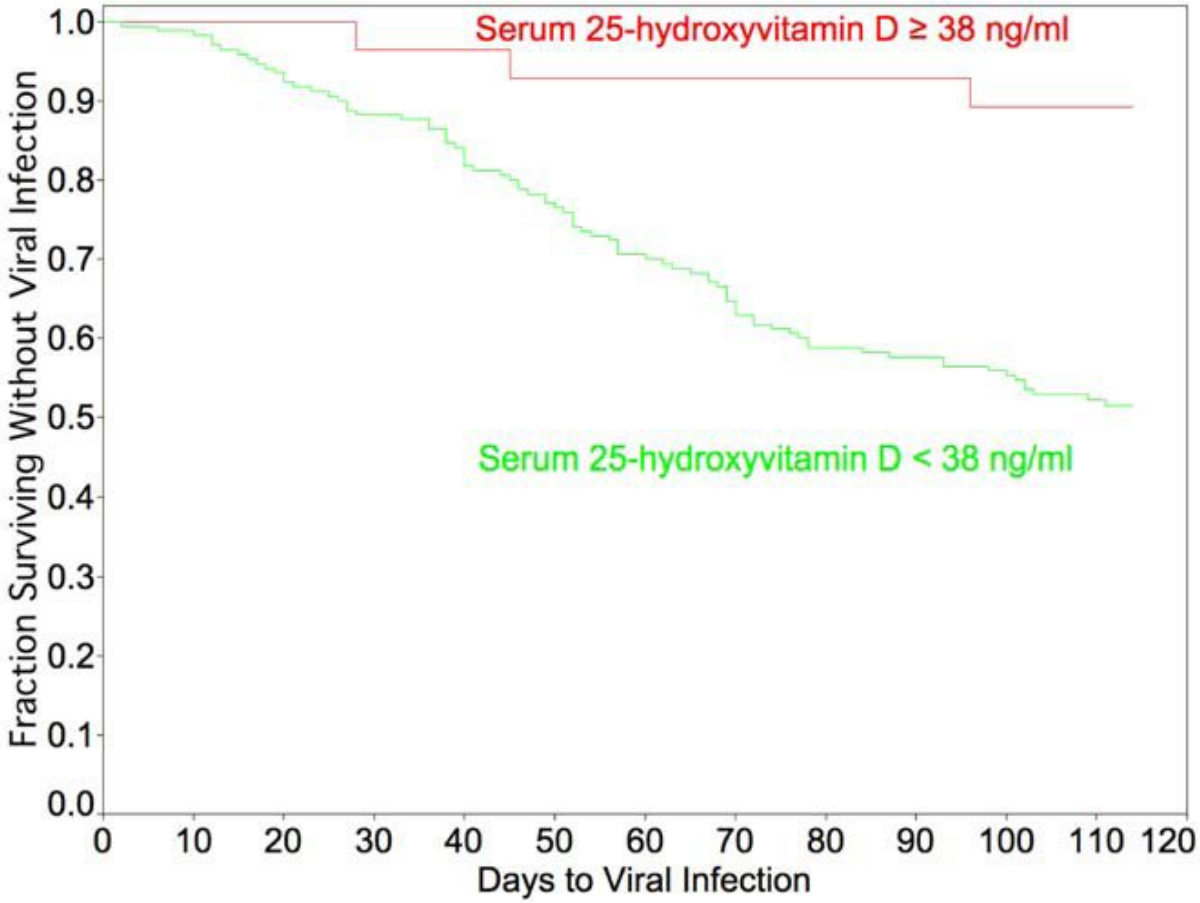
Epidemic Influenza

- Edgar Hope-Simpson [1981] pointed out that influenza outbreaks were inversely correlated with solar UV.
- John Cannell, M.D., et al. hypothesized that epidemic influenza is seasonal in part due to seasonal variations of solar UVB and vitamin D.

Hope-Simpson RE. The role of season in the epidemiology of influenza. J Hyg (Lond). 1981 Feb;86(1):35-47.

Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. Epidemiol Infect. 2006 Dec;134(6):1129-40.

95 nmol/l Reduces Risk of Acute Viral Respiratory Infection



Sabetta JR, et al. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One. 2010 Jun 14;5(6):e11088.

“Swine flu” and Vitamin D

- There is strong evidence that the recent “Swine flu” type A/H1N1 influenza virus was vitamin D sensitive:
  - Is seasonal, with peak rates in winter.
  - Pregnant women in the U.S. have a 4X increased risk of hospitalization from swine flu.
  - Australian Aborigines have a 6X increased risk of complications from swine flu.
  - Those with metabolic diseases have higher risk.
  - All of these groups are known to have lower serum 25(OH)D than the general population.

Type 2 Diabetes Mellitus

- Vitamin D and calcium have been found inversely correlated with incidence and prevalence of type 2 diabetes mellitus.

Pittas, Diabetes Care. 2006 Mar;29(3):650-6

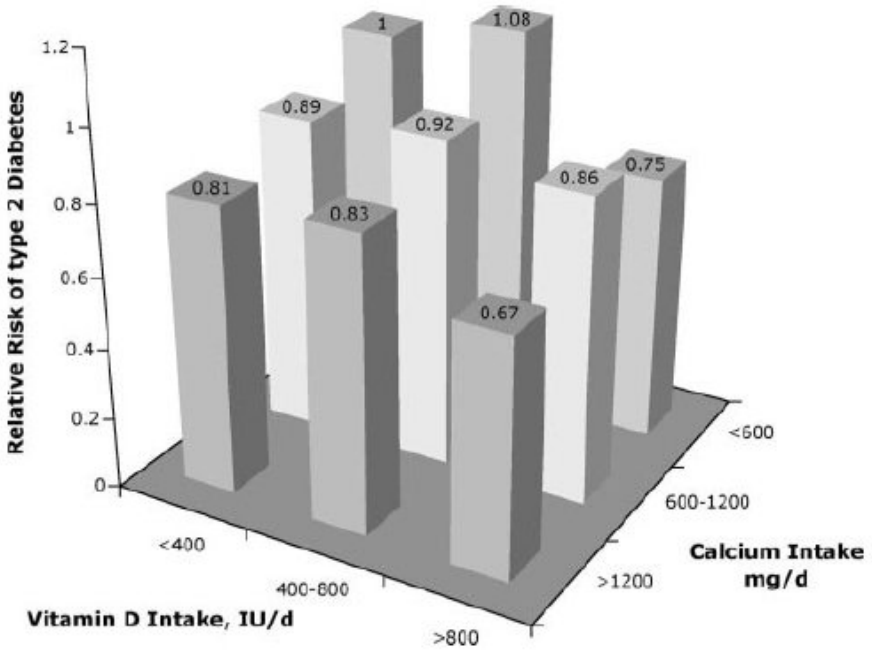


FIG. 1. Adjusted relative risk of incident type 2 DM in the Nurses Health Study by calcium and vitamin D intake (52).

Alzheimer's Disease (AD)

- There is mounting evidence that low 25(OH)D levels are a risk factor for AD.
- Comorbid diseases for AD are generally vitamin D sensitive.
  - cardiovascular diseases, cognitive impairment, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease [Grant, JAD, 2009]
- Serum 25(OH)D levels have been found to affect the progression of cognitive impairment, a precursor to AD.

Tuberculosis (TB)

- TB mortality rates are highest in Africa and the Western Pacific regions. Studies from these regions generally report that those who develop TB have lower serum 25(OH)D levels than those of control subjects.
- A study in Vietnam found that “The prevalence of vitamin D insufficiency was 35.4% in men with TB and 19.5% in controls (*P* = 0.01). In women, there were no significant differences in serum 25(OH)D and serum (parathyroid hormone) levels between TB patients and controls” (Ho-Pham *et al.*, BMC Infect Dis. 2010).
- Unfortunately, treating TB with vitamin D doesn’t always work.

Falls and Fractures

- The classical function of vitamin D is to regulate calcium absorption and metabolism.
- Falls and fractures are linked to musculoskeletal effects.
- RCTs indicate about a 20% reduction in falls and fractures for those taking >800 IU/d vitamin D3 compared to those taking <400 IU/d.

Parkinson's Disease

- There is mounting evidence that low serum 25(OH)D levels are a risk factor for Parkinson's disease.
- A study in Denmark found the following:
  - Relying on trade grouping codes, we estimated ORs for study subjects with moderate, frequent and maximal outdoor work compared with exclusive indoor work of 0.90 (95% CI 0.78 to 1.02), 0.86 (95% CI 0.75 to 0.99) and 0.72 (95% CI 0.63 to 0.82), respectively, for Parkinson's disease. Reduced risks were also found for Parkinson's disease among outdoor workers based on study subjects' job titles. [Kenborg et al., Occup Environ Med. 2011].

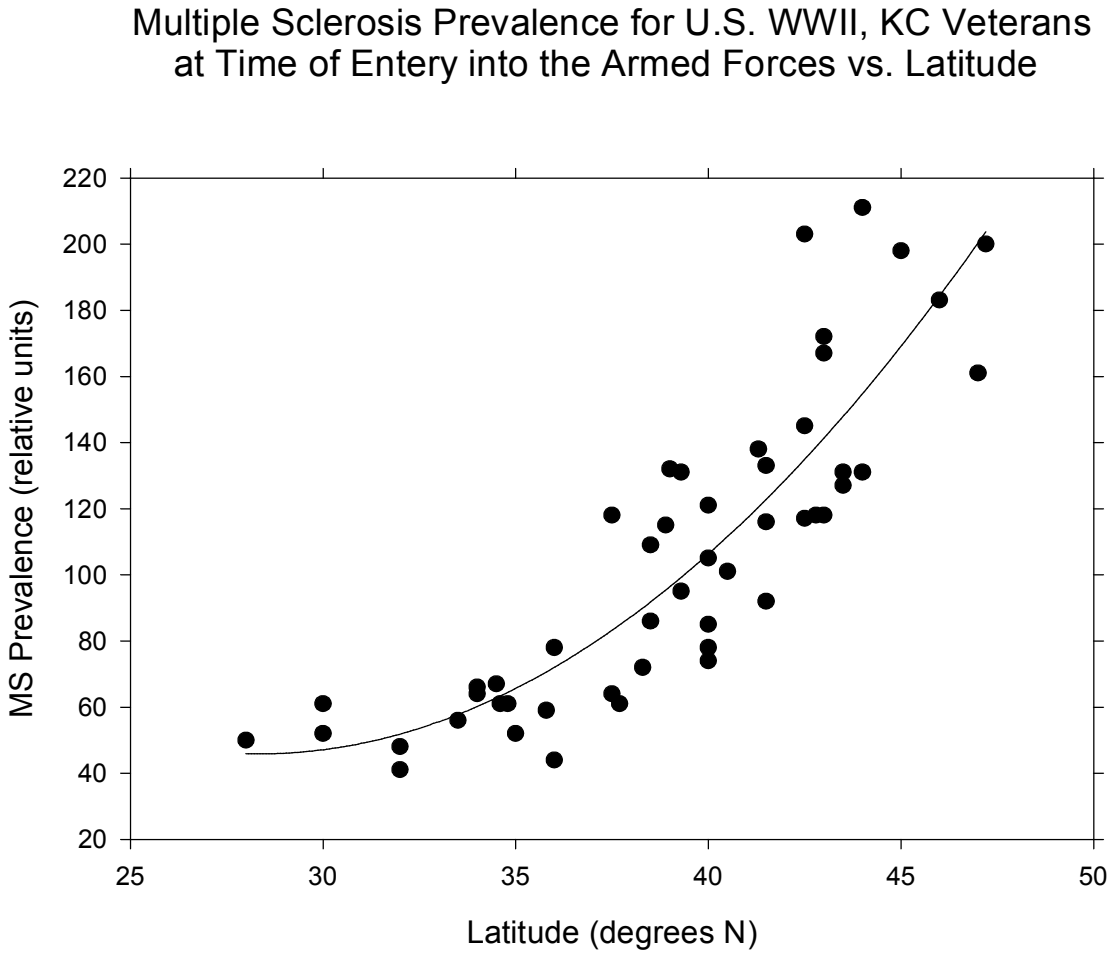
Meningitis

- The best evidence for a solar UV effect is the seasonality of meningococcal disease (MD) infection. Studies in many countries found that meningococcal disease and/or meningitis incidence rates peak in winter, often overlapping with influenza epidemic, sometimes with respiratory syncytial virus (RSV) activity.
- Mortality rates in African-Americans were 1.45 and 3.32 times higher than mortality rates in whites and Asians/Pacific Islanders, respectively. Mortality caused by meningococcal disease rose in winter months and declined during the summer. [Sharip, Pediatr Infect Dis J 2006]

Multiple Sclerosis (MS)

- MS prevalence increases with latitude in Australia, Europe, and North America.
- MS incidence is higher in spring.
- Epstein-Barr virus is an important risk factor.
- Vitamin D reduces the risk of MS [Munger et al., 2006]

Multiple Sclerosis Prevalence vs. Latitude, in the United States



Latitude is an index of wintertime UVB doses

Wallin et al., 2004; Grant and Holick, 2005; Grant, 2008

Estimate of Mortality Rate Reduction for Europe for 105 nmol/l vs. 54 nmol/l

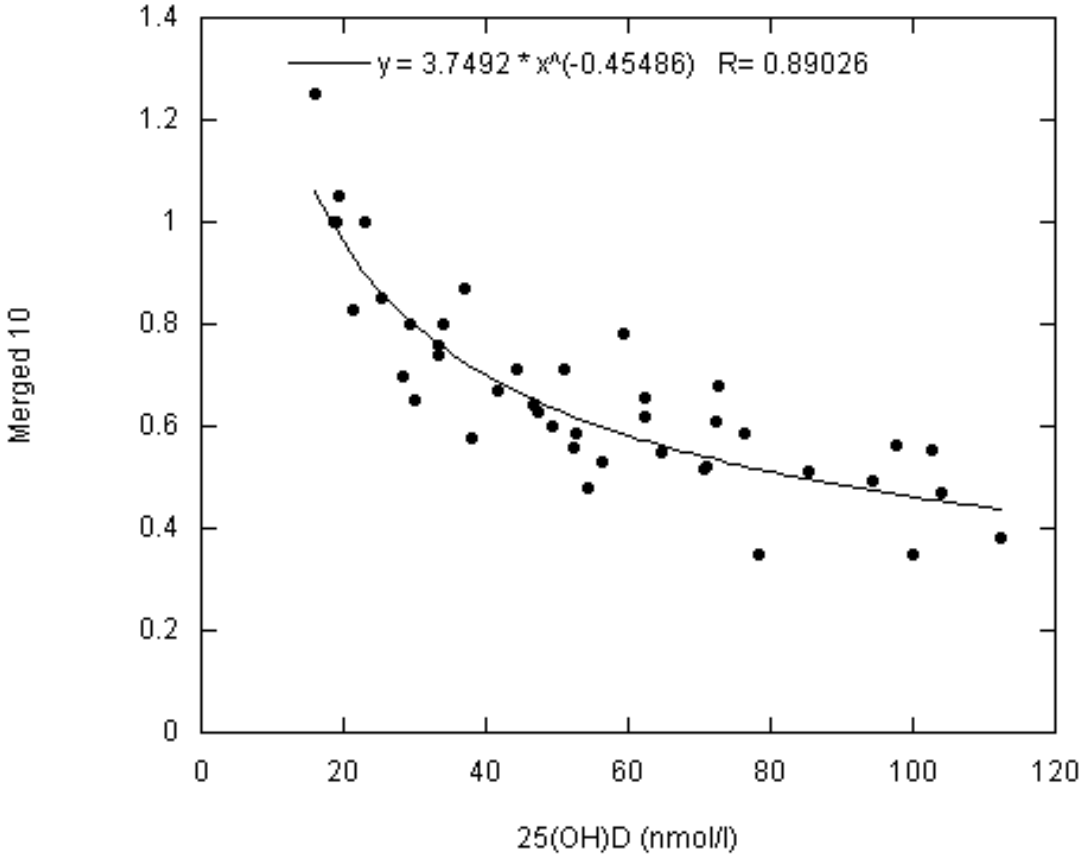
Disease	Deaths/yr (x1000)	Vitamin D (%)	Reduced (x1000)
Cardiovascular diseases	4.767	25	1,192
Malignant neoplasms	1,862	25	491
Respiratory diseases	374	10	37
Respiratory infections	244	30	73
Diabetes mellitus	399	25	100
Alzheimer's disease	137	15	21
Tuberculosis	78	40	31

Estimate of Mortality Rate Reduction for Europe for 105 nmol/l vs. 54 nmol/l (2)

Disease	Deaths/yr (x1000)	Vitamin D (%)	Reduced (x1000)
Falls, fractures	79	25	20
Parkinson's	29	15	4
Meningitis	11	30	3
Multiple scler	8	60	5
Total, Vitamin D	7,744	26	1,977
Total, All causes	9,493	21	1,977

All-Cause Mortality Rate vs. 25(OH)D

Based on my meta-analysis of observational studies of those over the age of 45 years at time of enrollment.



The all-cause mortality rate drops by 26% in going from 54 nmol/l to 105 nmol/l;
This is greater than my estimate (21%), but was based on older people.

Implications of This Analysis

- All-cause mortality rate decreases by 21%
  - Life expectancy increases by 2 years
  - Healthy life expectancy increases by about the same amount
- Direct costs for health care may drop by 10%.
- Indirect costs for health care may also drop by about 10%.
- Increasing serum 25(OH)D levels at the population level appears to be the most cost-effective way to reduce disease rates.

100+ Vitamin D Sensitive Diseases

- I have a project for John Cannell to produce documents on the health benefits of sunlight and vitamin D for approximately 100 types of disease.
- Most of the diseases have increased risk for lower UVB doses or serum 25(OH)D levels.
- Some of the diseases have low serum 25(OH)D levels as a consequence of the disease and/or its treatment.
- The documents are due to go online at www.vitamindcouncil.org by mid-May.

List of Vitamin D-Sensitive Diseases A-E

Acute lower respiratory infection
Alzheimer's disease
Amyotrophic lateral sclerosis
Anaphylaxis
Anemia
Ankylosing spondylitis
Anxiety
Asthma
Athersclerosis
Autism
Bacterial vaginosis
Biliary cirrhosis, primary (PBC)
Birth defects
Bones – fractures
Bones - osteopenia
Bones – osteoporosis
Bones – Paget's disease?
Bones – rickets
Brain injury, traumatic
Bronchitis
Cancer – 20 types (Bladder, breast, cervical, colorectal, endometrial, esophageal, gallbladder, gastric, Hodgkin's lymphoma, leukemia, lung, melanoma, multiple myeloma, non-Hodgkin's lymphoma, ovarian, pancreatic, prostate, renal, vulvar)
Cardiovascular disease
Celiac disease
Cerebrovascular disease
Chronic kidney disease
Chronic liver disease
Chronic, non-specific muscle pain
Cognitive impairment
Common cold
Epstein-Barr virus
Congestive heart failure
Chronic obstructive pulmonary disease
Coronary heart disease
Craniotabes
Cystic fibrosis
Dental caries
Depression
Diabetes, type 1
Diabetes, type 2,
Epilepsy

List of Vitamin D-Sensitive Diseases F-V

Fertility, regular menses
Fibromyalgia
Hashimoto's thyroiditis (HT)
Headache
Hearing loss
Hepatitis
HIV/AIDS
Hypercalcemia
Hyperparathyroidism
Hypertension
Inflammatory bowel disease
Influenza, type A
Insulin resistance
Ischemic cardiac arrhythmias
Kidney stones
Lupus
Macular degeneration
Meningitis
Metabolic disease
Mononucleosis
Multiple sclerosis
Muscle strength
Osteoarthritis
Pancreatis
Parkinson’s disease
Pelvic floor status
Periodontal disease
Peripheral artery disease
Pneumonia
Polycystic ovary syndrome
Post herpetic neuralgia
Preeclampsia
Premature birth and low birth weight
Psoriatic arthritis
Renal failure
Renal osteodystrophy
Rheumatoid arthritis
Respiratory syncytial virus
Schizophrenia
Sepsis/septicemia
Sickle cell disease
Systemic sclerosis
Tonsillitis
Tuberculosis
Thrombosis
Uterine leiomyomas (fibroids)
Vascular dementia
Vitiligo vulgaris

Institute of Medicine's Vitamin D Recommendations

- The Institute of Medicine concluded that evidence for beneficial effects of vitamin D is limited to bones, that 600 IU/day suffices for most people, 800 IU/day for those over 71 years of age, and 50 nmol/l is adequate.
- They were constrained by the federal sponsors in the evidence they could consider to only RCTs and nested case-control studies.
- Their report has been critiqued by many including Bischoff-Ferrari, Gillie, Grant, Heaney, Holick, and Willett in at least 28 journal letters, editorials, and papers to date.

Additional Resources

- http://www.grassrootshealth.net/
- http://www.healthresearchforum.org.uk/
- http://www.pubmed.gov
- http://www.sunarc.org/
- http://www.vitamindcouncil.org/

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