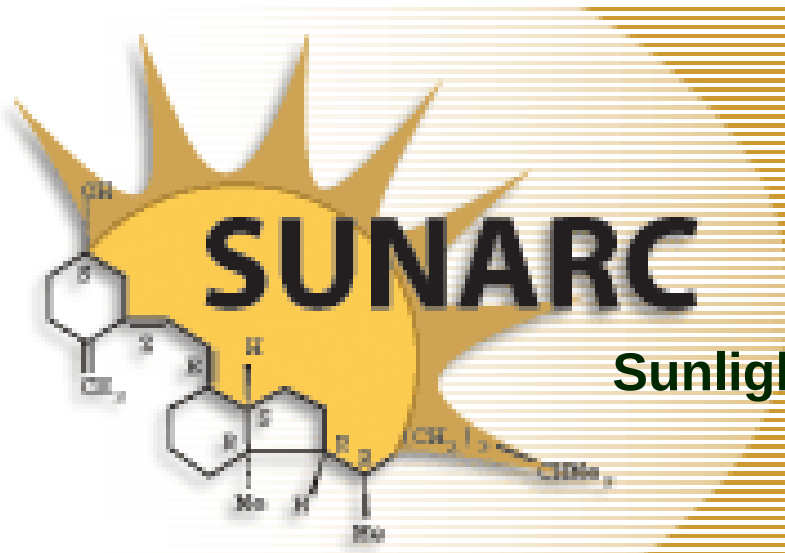


Reducing the Burden of Disease Through Adequate Intake of Vitamin D3

A presentation at
University of California, San Diego
April 9, 2008

by William B. Grant, Ph.D.



Sunlight, Nutrition, and Health Research Center
San Francisco, California

www.sunarc.org

Disclosure



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www.uvfoundation.org
- ★ The Vitamin D Society (Canada)
www.vitamindsociety.org
- ★ The European Sunlight Association
www.europeansunlight.eu



Learning Objectives

- ★ **Learn the vitamin D-sensitive diseases**
 - ★ **Bones, Cancers**
 - ★ **Infectious diseases, Autoimmune diseases**
 - ★ **Metabolic diseases, Congestive heart failure and muscles**
- ★ **Quantify potential benefits of solving vitamin D deficiency**
 - ★ **Disease incidence and mortality rate risk reductions**
 - ★ **Economic burden reductions**



Definitions

- ★ **Vitamin D₃ (cholecalciferol) is made in the skin from 7-dehydrocholesterol from ultraviolet-B (UVB) and a thermal process.**
- ★ **Solar UVB extends from 290-315 nm
UVA extends from 315-400 nm**
- ★ **Vitamin D₃ is converted in the liver to 25-hydroxyvitamin D₃ (calcidiol).**
- ★ **Calcidiol is converted in the kidney and other organs to 1,25-dihydroxyvitamin D₃ (calcitriol).**

Scientific Evidence



- ★ **Types of evidence used to link risk-modifying factors to disease outcomes:**
 - ★ **Ecological studies: populations, diseases and risks delimited geographically**
 - ★ **Observational studies: case-control, cohort studies**
 - ★ **Meta-analyses of several observational studies**
 - ★ **Randomized controlled trials**
 - ★ **Laboratory studies can identify mechanisms**

Proof of Causality in Biological Systems



- ★ **A. B. Hill laid down the criteria for establishing causality in a biological system:**
 - ★ **Strength of association**
 - ★ **Repeated finding in many diverse populations**
 - ★ **Linear dose-response relation**
 - ★ **Mechanisms understood**
 - ★ **Ruling out confounding factors**
 - ★ **Experimental verification**
 - ★ **Analogy**

Bones and Fracture Risk Reduction



- ★ Vitamin D increases the absorption of calcium.
- ★ Vitamin D regulates parathyroid hormone (PTH) levels and serum calcium levels. If calcidiol levels are low and PTH levels are high, calcium will be taken from the bones, and may end up in the arterial walls.
- ★ Vitamin D supplementation improves neuromuscular or neuroprotective function.¹

¹Dhesi JK, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing. 2004 Nov;33(6):589-95.



Bones – Meta-analysis

- ★ A vitamin D dose of 700 to 800 IU/d reduced the relative risk (RR) of hip fracture by 26% (pooled RR, 0.74; 95% CI: 0.61-0.88) and any nonvertebral fracture by 23% vs calcium or placebo.
- ★ No significant benefit was observed for RCTs with 400 IU/d vitamin D.

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. JAMA. 2005 May 11;293(18):2257-64.

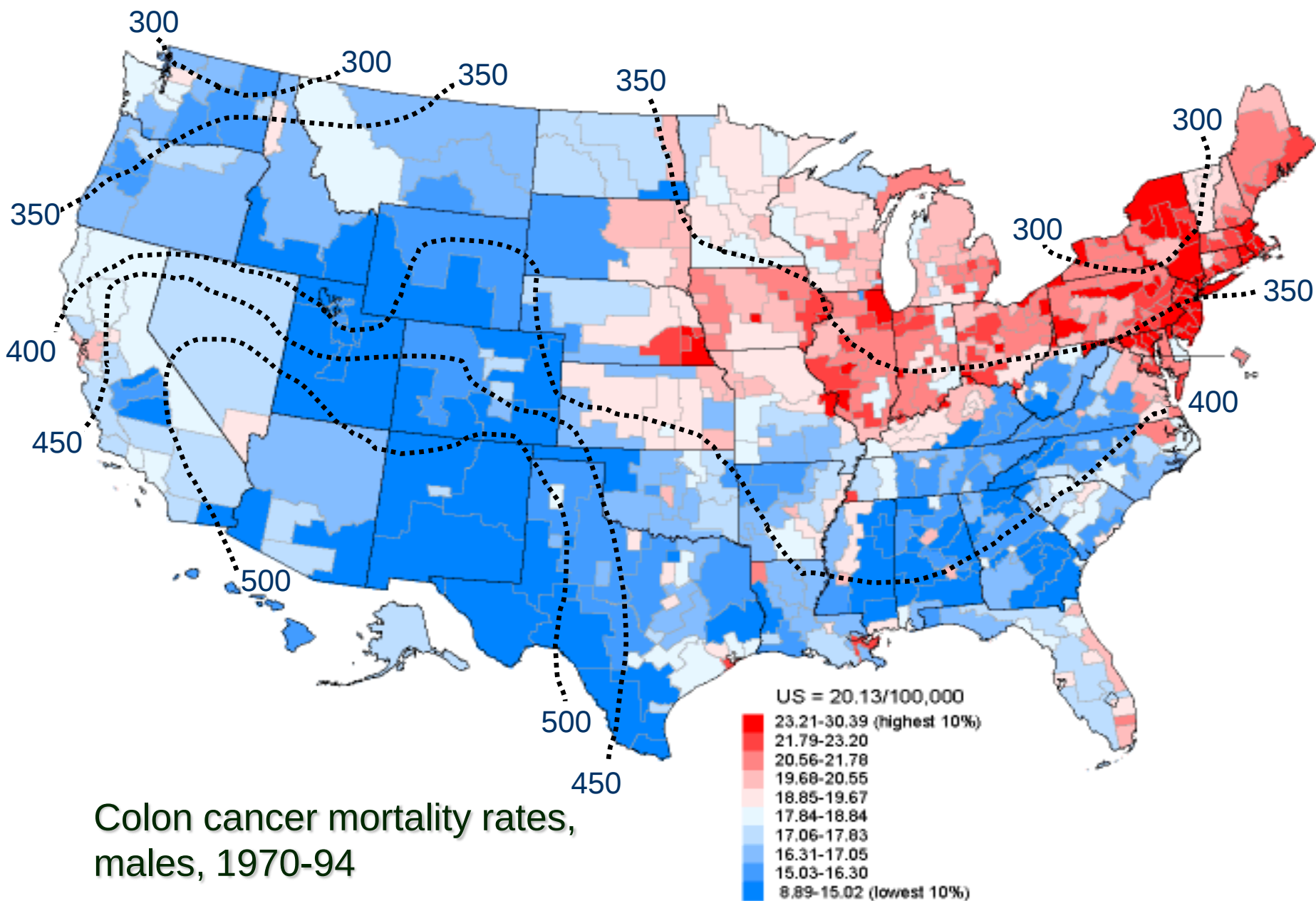
Studies of UVB and Cancer



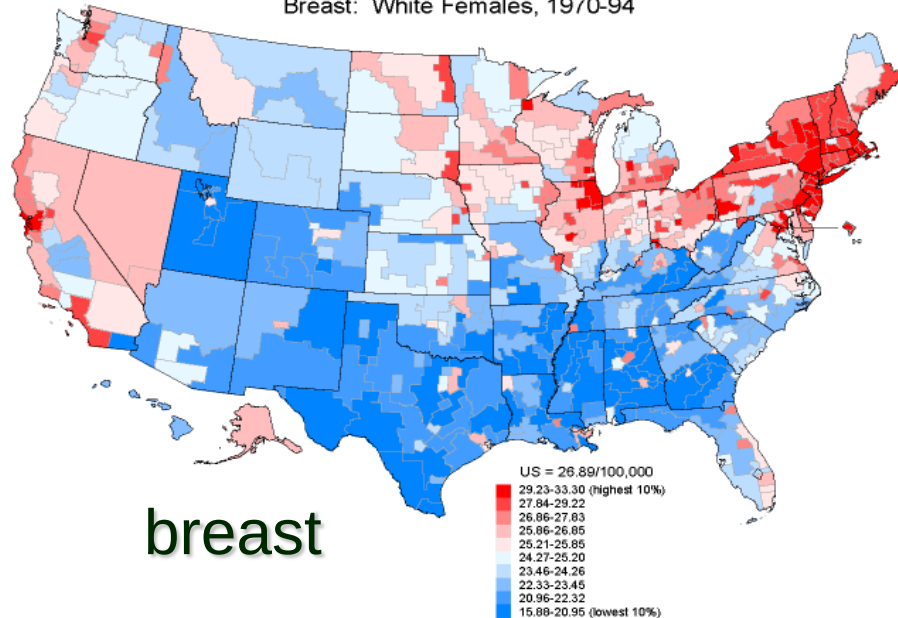
Ecological Studies of UVB and Cancer Incidence and Mortality

- ★ Cedric and Frank Garland made the first ecological study of cancer and solar UVB in 1980.
- ★ They saw that colon cancer rates were lowest in the sunniest part of the country.
- ★ They hypothesized that vitamin D was likely the agent.

Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol.* 1980 Sep;9(3):227-31.

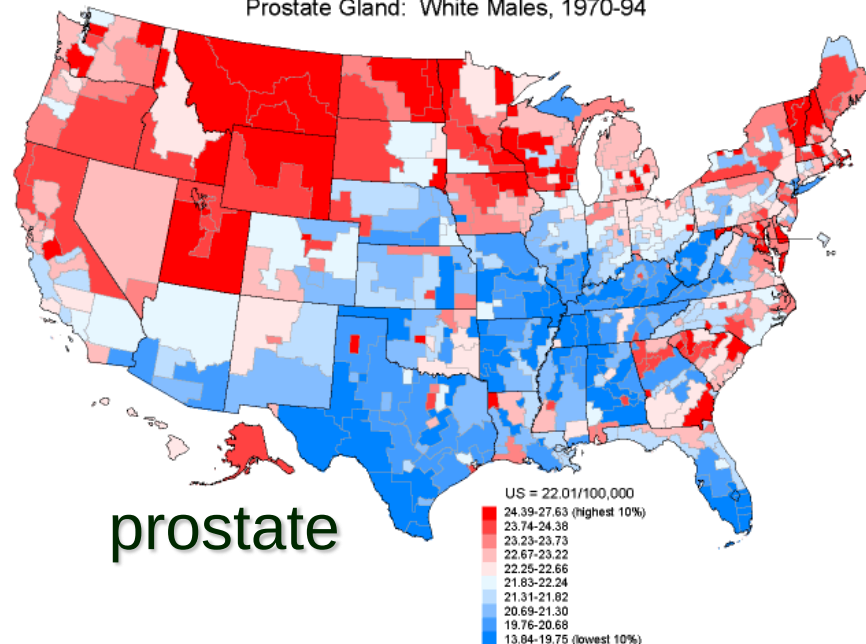


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Breast: White Females, 1970-94



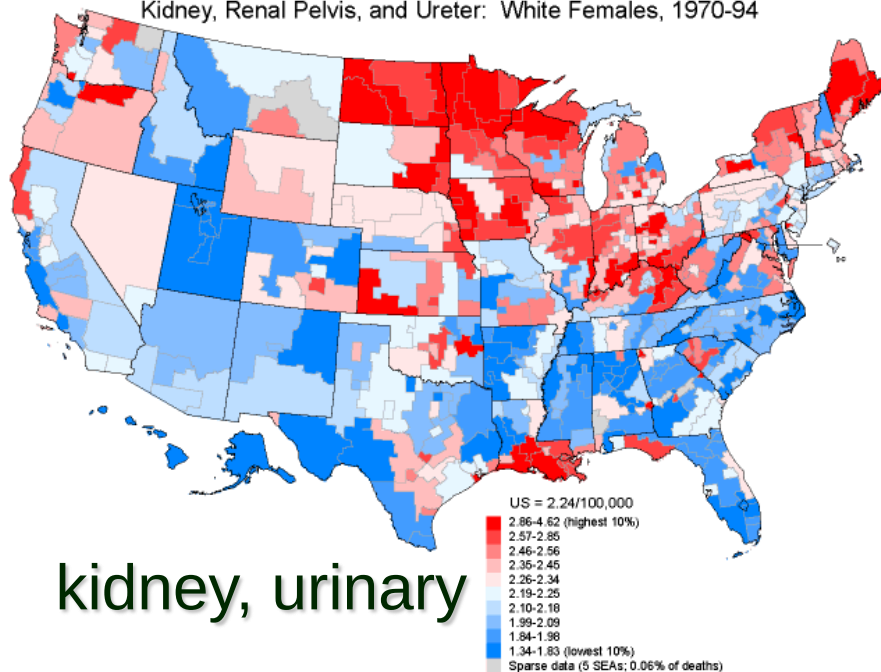
breast

Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Prostate Gland: White Males, 1970-94



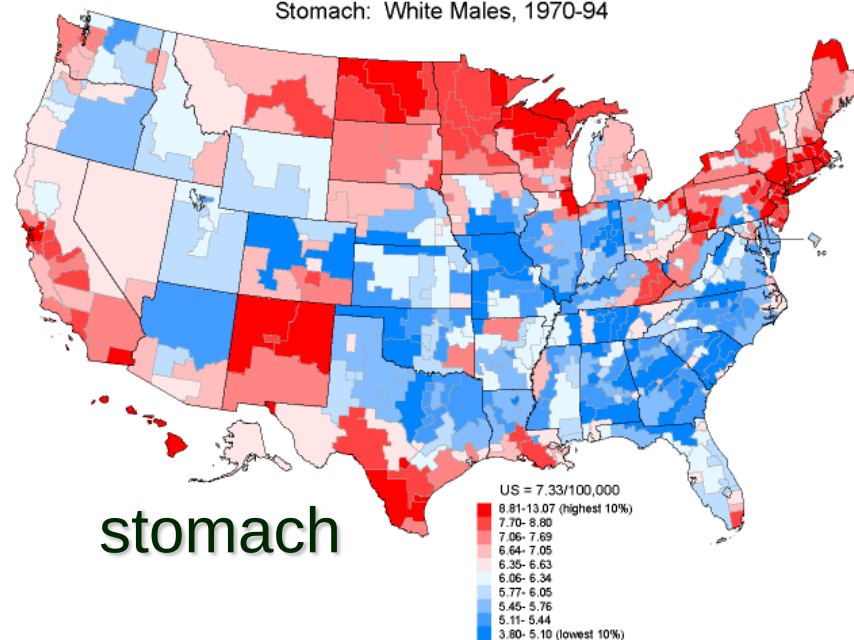
prostate

Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Kidney, Renal Pelvis, and Ureter: White Females, 1970-94



kidney, urinary

Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Stomach: White Males, 1970-94



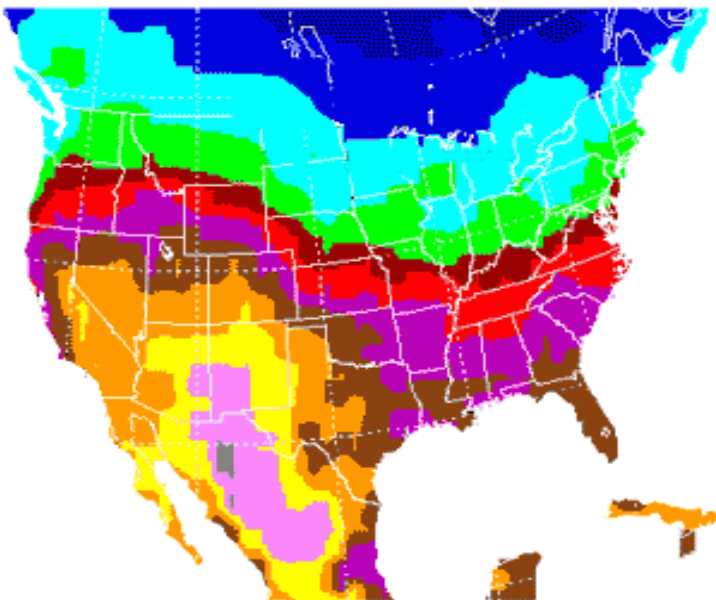
stomach

Cancer Risk Modifying Factors



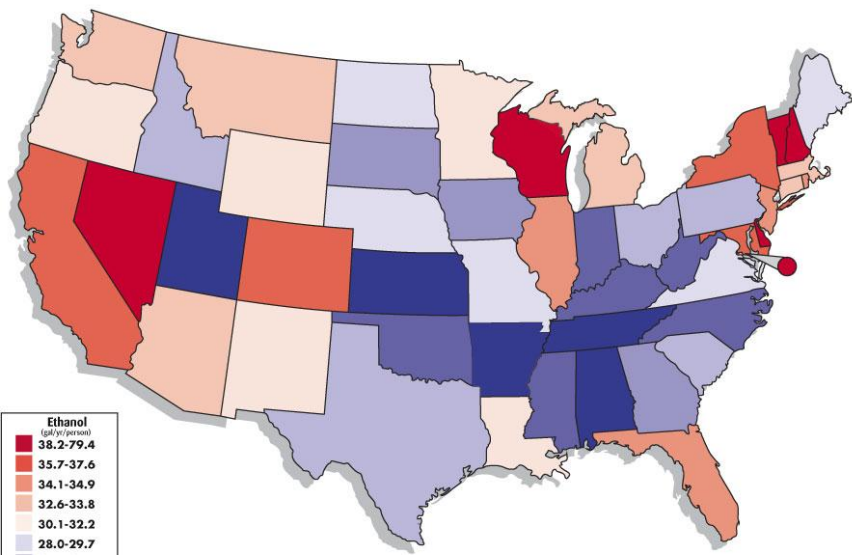
- ★ There are a number of factors that modify the risk of cancer.
- ★ They can often be included in studies by means of indices.
- ★ Examples include air pollution, diet, smoking, alcohol consumption, ethnic heritage, and urban/rural residence.

DNA SPECTRAL EXPOSURE (kJ/m²) FOR JULY 1992



0.0 1.5 3.0 4.5 6.0 7.5 9.0 10.5 12.0

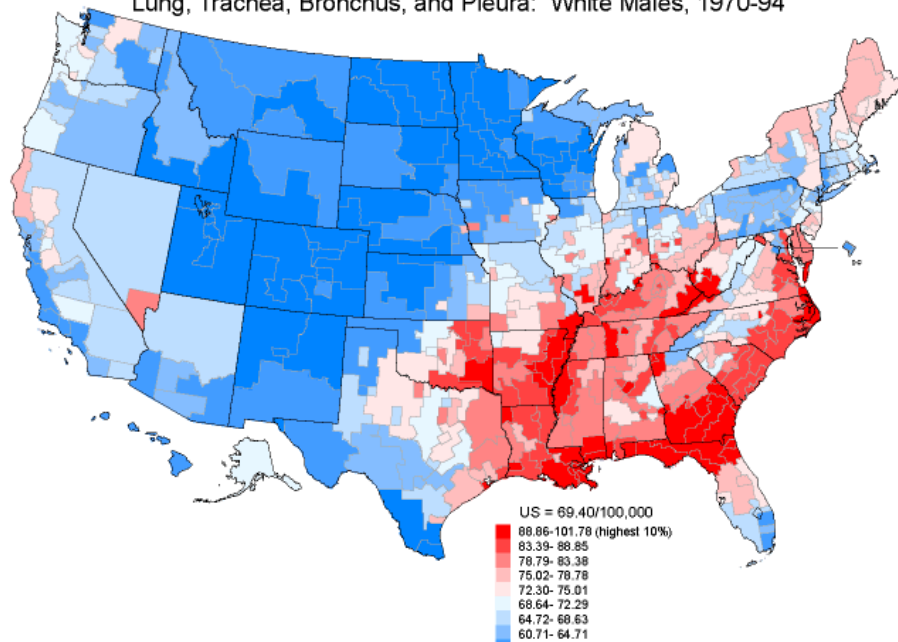
AICNONOI: Adult Per Capita Consumption 1970



Ethanol
(g/yr/person)

38.2-79.4
35.7-37.6
34.1-34.9
32.6-33.8
30.1-32.2
28.0-29.7
25.5-27.4
22.4-24.6
20.1-22.2
17.1-19.5

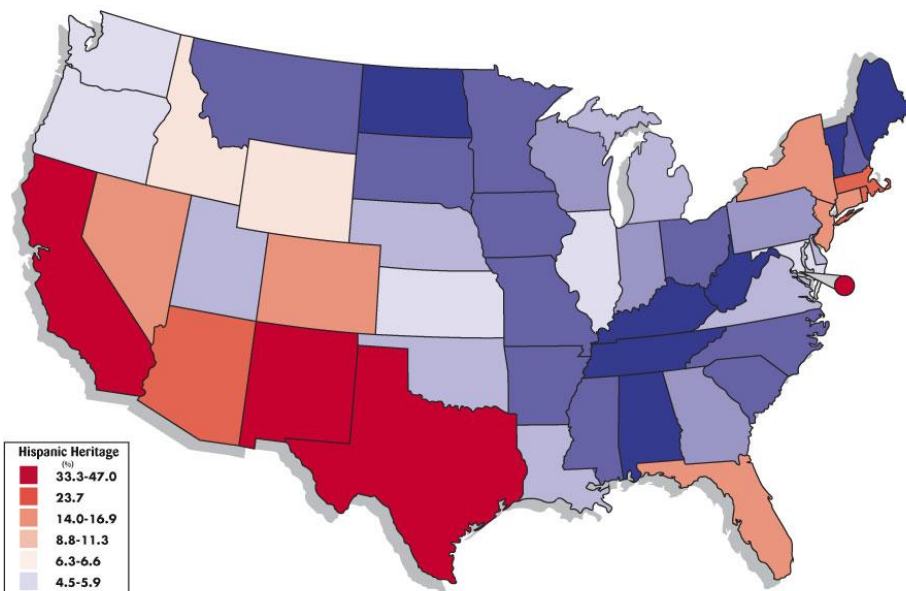
Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Lung, Trachea, Bronchus, and Pleura: White Males, 1970-94



US = 69.40/100,000

88.86-101.78 (highest 10%)
83.39-88.85
78.79-83.38
75.02-78.78
72.30-75.01
68.64-72.29
64.72-68.63
60.71-64.71

Fractions of White Americans with Hispanic Heritage, 1995



Hispanic Heritage
(%)

33.3-47.0
23.7
14.0-16.9
8.8-11.3
6.3-6.6
4.5-5.9
3.0-3.9
2.3-2.9
1.1-1.9
0.6-1.0

15 Vitamin D-Sensitive Cancers



- ★ **Vitamin D-sensitive cancers with strong support after accounting for other factors:**
 - ★ **Gastrointestinal:** Colon, esophageal, gallbladder, gastric, pancreatic, rectal, small intestinal
 - ★ **Urogenital:** Bladder, kidney, prostate
 - ★ **Female:** Breast, endometrial, ovarian
 - ★ **Blood:** Hodgkin's lymphoma, non-Hodgkin's lymphoma

U.S. Vitamin D-Sensitive Cancer Deaths



★ Digestive system	118,000
★ Breast	41,000
★ Genital system	51,000
★ Urinary system	27,000
★ Lymphoma	20,000
★ Total	257,000 (46% of all cancer deaths in the U.S. in 2007)

Jemal A, et al. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66.

Randomized Controlled Trial



Recent prospective study of vitamin D₃ and calcium and cancer risk post-menopausal women in Nebraska¹

- ★ 1100 IU of vitamin D₃ and/or 1400 mg of calcium per day, or a placebo.**
- ★ Serum calcidiol levels rose from 71.8 nmol/L (28.7 ng/mL) to 96.0 nmol/L (38.4 ng/mL)**
- ★ The all-cancer incidence for women over the age of 55 years at time of enrollment was reduced by 77% between the ends of the first and fourth years of the study.**

1. 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 Jun; 85(6): 1586-91.

Seasonal Survival in Norway



Cancer Survival with Respect to Season of Diagnosis in Norway¹ (mortality rate relative risk in southeast Norway vs. midwest winter for 36 months)

- ★ Prostate cancer: 0.76 (0.73-0.79)***
- ★ Breast cancer: 0.75 (0.72-0.79)***
- ★ Colon cancer: 0.79 (0.76-0.82)***
- ★ Hodgkin's lymphoma: 0.85 (0.74-0.98)**

*** indicates statistically significant result**

1. Porojnicu AC, Dahlback A, Moan J. Sun exposure and cancer survival in Norway: changes in the risk of death with season of diagnosis and latitude. Adv Exp Med Biol. 2008;624:43-54.

Vitamin D, Cancer Survival: Implications



- ★ These findings strongly suggest that for many types of cancer, vitamin D is more important in the latter stages than in the earlier stages.
- ★ The mechanisms likely to be involved later are reduction in angiogenesis and metastasis.
- ★ However, other mechanisms are also involved in reducing cancer incidence, such as controlling cell differentiation and apoptosis and improving immune system function.

Vitamin D and Cancer Disparities

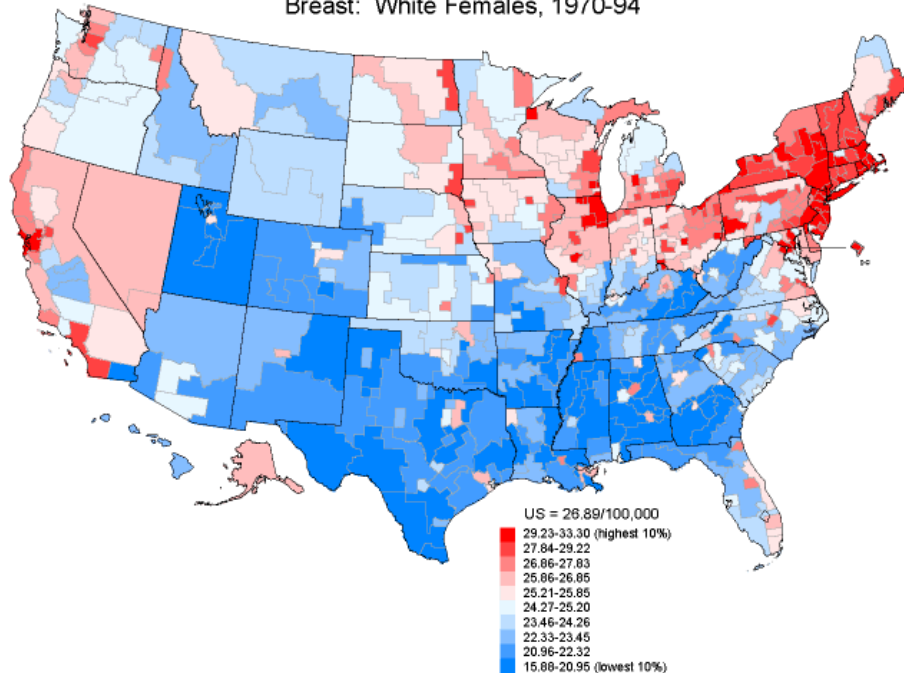


- ★ **Two papers reported that differences in solar UVB and vitamin D can explain a good part of the cancer disparities between black and white Americans**
 - ★ **Ecological study: Solar UVB was inversely correlated with mortality rates for breast, colon, esophageal, gastric and rectal cancers.**
[Grant, J National Med Assoc, 2006]
 - ★ **Cohort study: Black men were at higher risk of total cancer incidence [relative risk (RR), 1.32; (95% CI), 1.08-1.61; P = 0.007] and mortality (RR, 1.89; 95% CI, 1.40-2.56; P < 0.0001), especially digestive system cancer mortality.** [Giovannucci, Cancer Epidemiol Biomarkers Prevent, 2006]

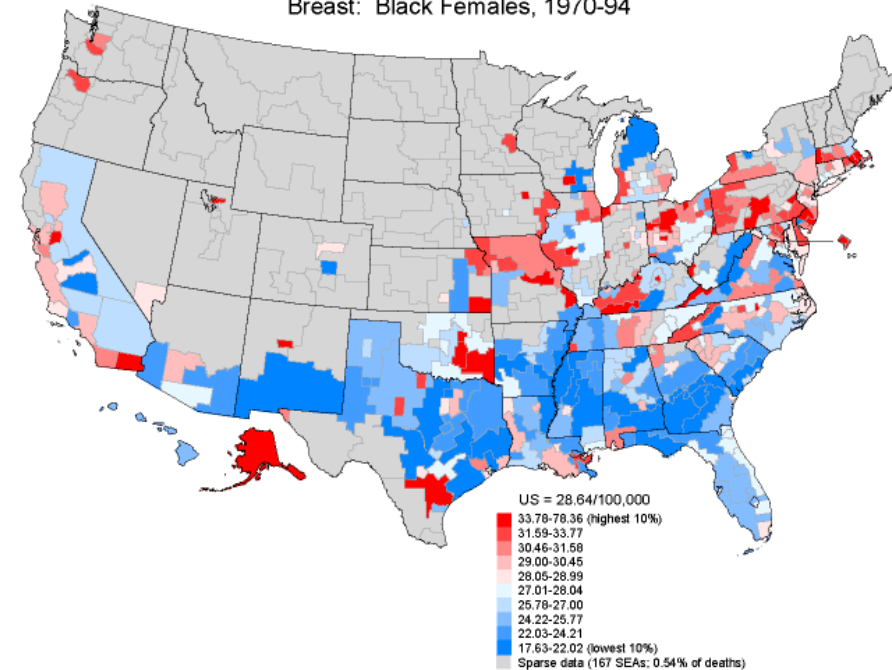
Breast Cancer, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Breast: White Females, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Breast: Black Females, 1970-94



Vitamin D Explains Much of the Breast Cancer Disparity



- ★ **Black American women have a mortality rate 25% higher than white women in state-by-state comparisons.** [Atlas of Cancer Mortality Rates, NCI]
- ★ **This corresponds to a summertime serum calcidiol difference of 20 ng/mL.**
[Lappe et al., 2006; Garland et al., 2007]
- ★ **Black women have 18 ng/mL lower calcidiol levels in Boston in summer than white women.** [Harris and Dawson-Hughes, 1998]

Racial Disparities in Cancer



- ★ **Black Americans have higher mortality rates for most types of cancer than white Americans, even for same stage at discovery and level of treatment. Those cancers are primarily vitamin D-sensitive and/or smoking related.**
- ★ **Black Americans could reduce many cancer rates by 20-40% with adequate vitamin D3 intake.**



Infectious Diseases

- ★ **Calcitriol induces production of human cathelicidin, LL-37, a polypeptide with modest antimicrobial and potent antiendotoxin activities.¹**
- ★ **There is strong evidence that LL-37 can fight bacterial infections.**
- ★ **There is weaker but growing evidence that LL-37 can fight viral infections.**

¹Mookherjee N, Rehaume LM, Hancock RE. Cathelicidins and functional analogues as antisepsis molecules. Expert Opin Ther Targets. 2007 Aug;11(8):993-1004.



Tuberculosis

- ★ **Dr. Auguste Rollier treated those with TB using heliotherapy at Leysin, Switzerland, from 1903 to the early 1940s with excellent results.**
- ★ **Dark-skinned Asian immigrants have the highest TB rates in England.**
- ★ **There is strong evidence that LL-37 reduces the risk of tuberculosis.¹**

¹Liu PT, Stenger S, Tang DH, Modlin RL. Cutting Edge: Vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol. 2007 Aug 15;179(4):2060-3.



Periodontal Disease (PD)

- ★ Serum calcidiol is inversely correlated with prevalence of PD.¹
- ★ Darker-skinned individuals are at higher risk for PD in Brazil and the United States.
- ★ Smoking is a risk factor for PD and lower calcidiol.
- ★ PD is associated with risk of metabolic diseases, for which low calcidiol is a risk factor.²

¹Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr. 2004 Jul;80(1):108-13.

²Dörfer CE, Becher H, Ziegler CM, Kaiser C, Lutz R, Jörss D, Lichy C, Buggle F, Bültmann S, Preusch M, Grau AJ. The association of gingivitis and periodontitis with ischemic stroke. J Clin Periodontol. 2004 May;31(5):396-401.



Epidemic Influenza

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

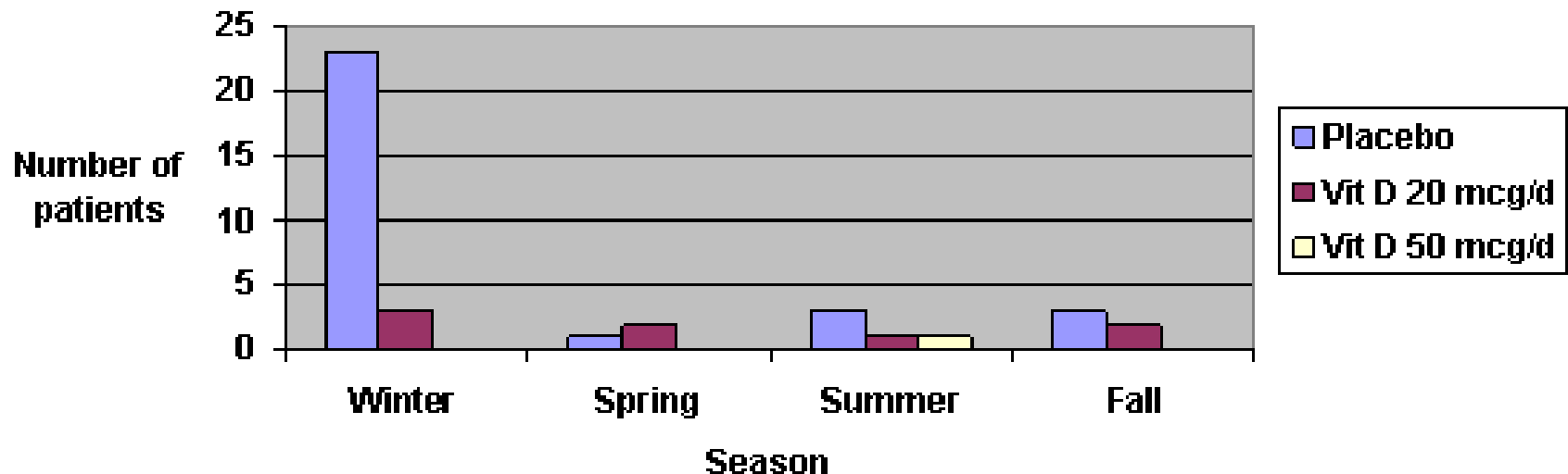
Hope-Simpson RE. The role of season in the epidemiology of influenza. J Hyg (Lond). 1981 Feb;86(1):35-47.

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.



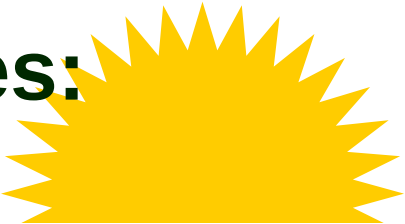
Cold and Flu Prevention

Results of a prospective double blind vitamin D supplementation study involving 208 African-American post-menopausal women living in or near Mineola, NY. The vertical scale refers to cases of common cold or flu.



Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. Epidemiol Infect. 2007 Oct;135(7):1095-6; author reply 1097-8.

Vitamin D and Infectious Diseases: Summary of Evidence of Benefit



★ Bacterial diseases

- ★ Pneumonia**
- ★ Porphyromonas gingivalis (periodontal disease)**
- ★ Septicemia**
- ★ Tuberculosis**

★ Viral diseases, respiratory system

- ★ Influenza (seasonal)**
- ★ Respiratory syncytial virus (bronchitis)**
- ★ Rhinovirus (common cold)**



Autoimmune Diseases

- ★ **The strongest evidence for a beneficial effect of vitamin D in reducing the risk of autoimmune diseases is for multiple sclerosis (MS) and type 1 diabetes mellitus.**
- ★ **For MS, the evidence points to the direct and indirect regulation of T cell development and function by vitamin D and cytokine expression.**

Cantorna MT, Mahon BD. D-hormone and the immune system. J Rheumatol Suppl. 2005 Sep;76:11-20.

Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol. 2006 Sep;92(1):60-4.

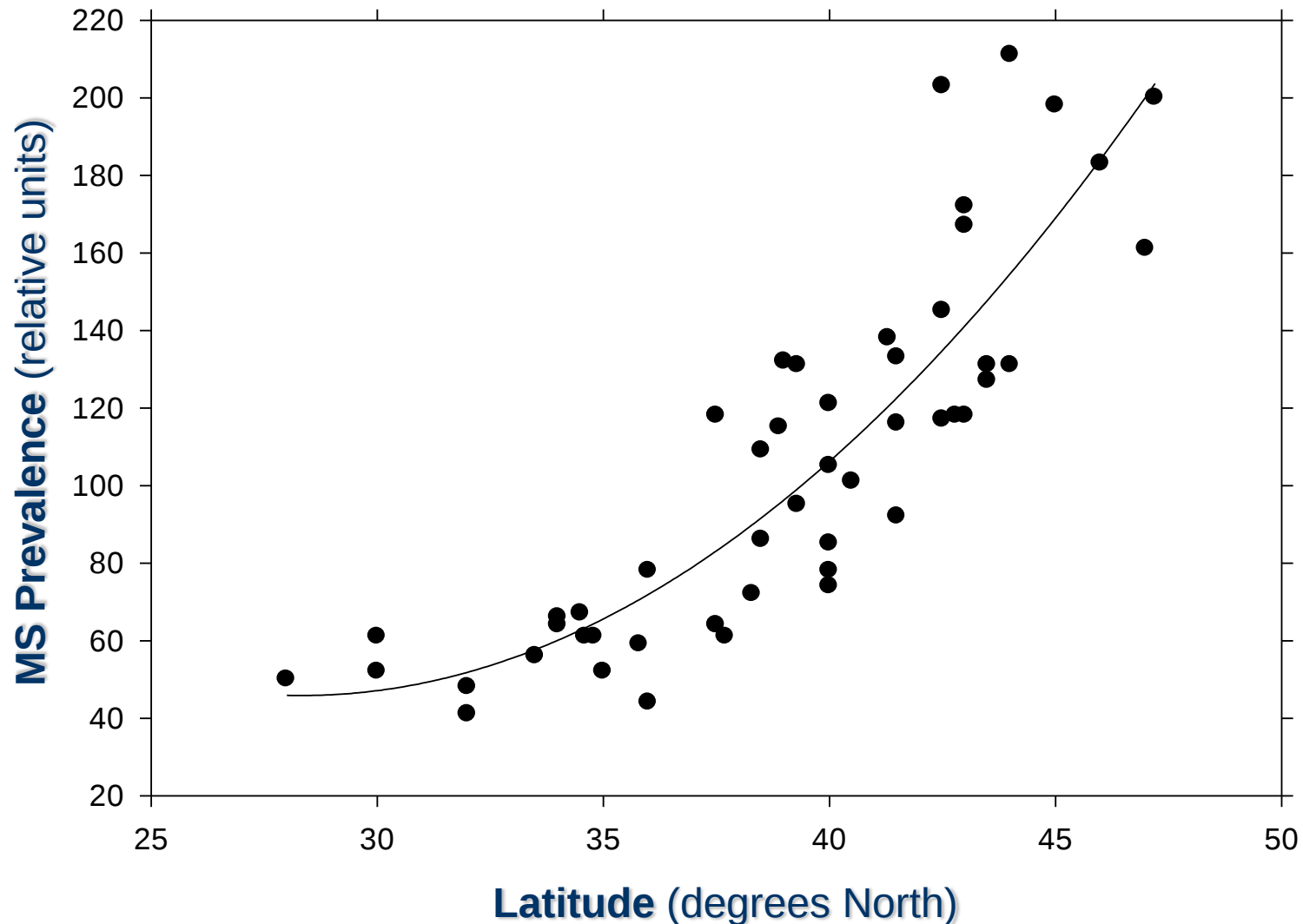


Autoimmune Diseases

- ★ **However, vitamin D might also act through reducing the risk of viral infections, such as Epstein Barr virus and mononucleosis in the case of MS.¹**
- ★ **Evidence includes benefits of vitamin D in childhood and geographical variation of cases.**

¹Grant WB. Hypothesis-Ultraviolet-B Irradiance and Vitamin D Reduce the Risk of Viral Infections and thus Their Sequelae, Including Autoimmune Diseases and some Cancers. Photochem Photobiol. 2008 Mar-Apr;84(2):356-65.

Multiple Sclerosis Prevalence for US WWII KC Veterans at Time of Entry into the Armed Forces Versus Latitude



Vitamin D and Multiple Sclerosis



- ★ A nested case-control study among more than 7 million US military personnel.¹
- ★ The OR for the highest quintile, corresponding to calcidiol levels higher than 99.1 nmol/L, was 0.38 (95% CI, 0.19-0.75; P = 0.006).
- ★ The inverse relation with multiple sclerosis risk was particularly strong for calcidiol levels measured before age 20 years.

¹Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. JAMA. 2006 Dec 20;296(23):2832-8.



Metabolic Diseases

- ★ **Metabolic diseases include cardiovascular diseases, coronary heart disease, type 2 diabetes, hypertension, stroke, etc.**
- ★ **There is growing observational evidence that vitamin D reduces the risk of metabolic diseases.**
- ★ **However, randomized controlled trials have not been reported yet.**

Metabolic Disease Parameters



- ★ The adjusted prevalence of hypertension (odds ratio [OR], 1.30), diabetes mellitus (OR, 1.98), obesity (OR, 2.29), and high serum triglyceride levels (OR, 1.47) was significantly higher in the first than in the fourth quartile of serum calcidiol levels ($P < .001$ for all).

Martins D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007 Jun 11;167(11):1159-65.



Hypertension

- ★ **During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma calcidiol levels were <15 ng/mL (i.e., vitamin D deficiency) compared with those whose levels were ≥ 30 ng/mL was 6.13 (95% CI: 1.00 to 37.8).**
- ★ **Among women, the same comparison yielded a relative risk of 2.67 (95% CI: 1.05 to 6.79).**

Forman JP, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension*. 2007 May;49(5):1063-9.

Coronary Heart Disease



- ★ There was a graded increase in cardiovascular risk across categories of calcidiol, with multivariable-adjusted hazard ratios of 1.53 (95% CI: 1.00 to 2.36) for levels 10 to < 15 ng/mL and 1.80 (95% CI: 1.05 to 3.08) for levels < 10 ng/mL (P for linear trend=0.01).

Wang TJ, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008 Jan 29;117(4):503-11.

CHD – Vitamin D Mechanisms



- ★ **Reduces blood pressure.**
- ★ **Reduces risk of infection.**
- ★ **Increases insulin sensitivity.**
- ★ **Reduces circulating osteoprotegerin (a cytokine) levels¹**

¹Gannagé-Yared MH, Azoury M, Mansour I, Baddoura R, Halaby G, Naaman R. Effects of a short-term calcium and vitamin D treatment on serum cytokines, bone markers, insulin and lipid concentrations in healthy post-menopausal women. J Endocrinol Invest. 2003 Aug;26(8):748-53.



Type 2 Diabetes Mellitus

- ★ **Adjusting for sex, age, BMI, leisure activity, and quarter of year, ethnicity-specific odds ratios (ORs) for diabetes (fasting glucose ≥ 7.0 mmol/l) varied inversely across quartiles of calcidiol in a dose-dependent pattern (OR 0.25 [95% CI: 0.11-0.60] for non-Hispanic whites and 0.17 [0.08-0.37] for Mexican Americans) in the highest calcidiol quartile compared with the lowest.**
- ★ **This inverse association was not observed in non-Hispanic blacks.**

Scragg R, Sowers M, Bell C; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2004 Dec;27(12):2813-8.

Vitamin D, Diabetes, Mechanisms



- ★ **The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, and a direct action on pancreatic beta-cell function.**

Palomer X, González-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes Obes Metab.* 2008 Mar;10(3):185-97.

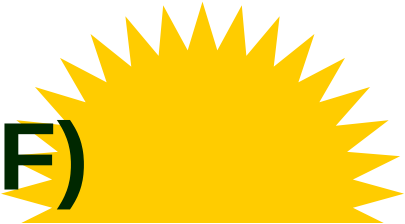


Muscles

- ★ **150 primary care outpatients with persistent, nonspecific musculoskeletal pain syndromes refractory to standard therapies.**
- ★ **Of all patients, 93% (140/ 150) had deficient levels of calcidiol (mean, 12.08 ng/mL; 95% CI, 11.18-12.99 ng/mL).**

Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc. 2003 Dec;78(12):1463-70.

Congestive Heart Failure (CHF)



- ★ CHF results when the heart is no longer able to maintain adequate circulation of blood.**
- ★ The heart is a muscle.**
- ★ Risk increases rapidly with increasing age among the elderly.**
- ★ Those over the age of 60 years produce vitamin D with about one-fourth the efficiency of those under the age of 20 years.**



CHF, Calcitriol, Mortality

- ★ **METHODS AND RESULTS:** We collected blood samples in 383 end-stage CHF patients who were on a waiting list for cardiac transplantation. In electively listed patients (n=325), 31% had deficient calcitriol levels (<43 pmol/l) compared to 47% in urgently/high urgently listed patients (n=58; $P<0.001$).
- ★ **Cox regression analysis:** patients in the highest calcitriol tertile had a hazard ratio of 0.506 (95% CI 0.334-0.767) compared with patients in the lowest tertile ($P=0.005$).

Zittermann A, Schleithoff SS, Götting C, Dronow O, Fuchs U, Kuhn J, Kleesiek K, Tenderich G, Koerfer R. Poor outcome in end-stage heart failure patients with low circulating calcitriol levels. Eur J Heart Fail. 2008 Mar;10(3):321-7.

Mortality Rate Data, U.S., 2003



- ★ Data are available by sex, race, age for leading causes of death.
- ★ The leading causes of death are tabulated in the following tables.
- ★ Most of the diseases tabulated are vitamin D sensitive.
- ★ The black/white racial disparities are much higher for those aged 55-64 years than 65+ years.

Heron MP, Smith BL. Deaths: leading causes for 2003. Natl Vital Stat Rep. 2007 Mar 15;55(10):1-92.

Mortality Rates, Males 55-64 Years

Disease	Black	White	Black/White
Cancer	597	385	1.55
Heart	589	312	1.89
Stroke	114	32	3.56
Diabetes	98	38	2.58
Nephritis	53		
Lower respir	52	50	1.04
HIV	51		
Liver	41	31	1.32
Septicemia	39	12	3.25

Mortality Rates, Females 55-64 Years

Disease	Black	White	Black/White
Cancer	388	309	1.26
Heart	311	127	2.45
Diabetes	79	25	3.16
Stroke	73	26	2.81
Nephritis	37	9	4.11
Lower respir.	33	<9	>3.67
Septicemia	28	11	2.55
Hypertension	21	<9	>2.33
Flu, pneum.	14	9	1.56

Vitamin D and Mortality Rates



We examined the risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation on any health condition. The study parameters:

- ★ 18 independent randomized controlled trials**
- ★ including 57,311 participants**
- ★ A total of 4777 deaths from any cause occurred**
- ★ Mean daily vitamin D dose was 528 IU, 5.7 year average.**
- ★ The summary relative risk for mortality from any cause was 0.93 (95% CI: 0.87-0.99).**

Autier P. Gandini S. Arch Intern Med. 2007 Sep 10;167(16):1730-7.

Death Reductions with Vitamin D: Estimate for the U.S. for 2001



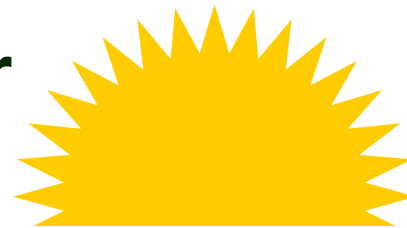
Disease	Deaths (x1000)	Vitamin D Reduction %	Deaths Reduction
CVD	923	20	185
Cancer	559	20	112
Diabetes	77	15	12
Lower respir.	60	25	15
Septicemia	31	25	8
Hip fractures	14	25	4
TB	1	25	0.3
Total, vit. D	1665	20	336
Total, all	2401	14 (8-20)	336

Reduction in Economic Burden



Disease	Cost (\$billion)	Vit. D Reduction	Cost Savings
Fractures	25	0.25	6
Cancers	219	0.20	44
Influenza	87	0.20	17
Other respir.	40	0.20	8
Septicemia	25	0.25	6
MS	11	0.30	3
CVD	432	0.20	86
Diabetes	146	0.15	22
CHF	33	0.20	7
Totals	1018	0.20	199

Value of 1% Reduction in Cancer Deaths



- ★ **We develop an economic framework for valuing improvements to health and life expectancy, based on individuals' willingness to pay. Over the 20th century, cumulative gains in life expectancy were worth over \$1.2 million per person for both men and women. Reduced mortality from heart disease alone has increased the value of life by about \$1.5 trillion per year since 1970. Even a modest 1 percent reduction in cancer mortality would be worth nearly \$500 billion.**

Murphy KM, Topel RH. National Bureau of Economic Research Working Paper No. 11405. June 2005.



Conclusion

- ★ There is enough evidence now to conclude that vitamin D intake or production at the rate of 2000-4000 IU/day, leading to serum calcidiol levels of greater than 40 ng/mL (100 nmol/L) can significantly reduce the burden of both chronic and infectious diseases.
- ★ Those with darker skin should take higher vitamin D supplementation.

Ode to Sunshine, 1913



- ★ **Sunshine is a marvelous health-giving and healing power in the world. While sunshine is death to disease-producing agencies, it is life and health to all natural forms of life.**
- ★ **Sit in the sun, recline in the sun, walk on the sunny side of the street, avoid parasols, and ever recognize the sun as a friend and not an enemy, a promoter of health, and a destroyer of disease.**

Frederick M. Rossiter, M.D. The Practical Guide to Health. Pacific Press Pub. Assoc., Mountain View, CA. 1913:193-5.

Learning Objectives of Presentation, 1



- ★ **List vitamin D-sensitive diseases**
 - ★ **Falls and fractures**
 - ★ **Cancers: digestive, female, urogenital, lymphomas**
 - ★ **Infectious diseases, bacterial and viral**
 - ★ **Autoimmune diseases: multiple sclerosis, type 1 diabetes**
 - ★ **Metabolic diseases: CHD, type 2 diabetes, etc.**
 - ★ **Congestive heart failure**

Learning Objectives of Presentation, 2



- ★ Quantify the potential benefits of vitamin D**
 - ★ Reduction of disease risks by about 15-25%**
 - ★ Reduction of mortality rate by about 14% (8-20%)**
 - ★ Reduction in economic burden by \$199 billion/year**

Appendix



- ★ The following slides provide additional information regarding the topics discussed in this presentation.



Additional Resources

- ★ <http://www.sunarc.org/>
- ★ <http://www.vitamindcouncil.org/>
- ★ <http://www.healthresearchforum.org.uk/>
- ★ <http://www.pubmed.gov>
 - ★ At this site you may search over 17 million entries from the world's health literature dating back to about 1960. Enter key words, authors, and/or dates, then click on the authors' names to see the abstract.



Additional Definitions

- ★ Odds ratio: a measure of treatment effect that compares the probability of a type of outcome in the treatment group with the outcome of a control group.
- ★ Risk ratio: Ratio of the risk of disease or death among the exposed segment of the population to the risk among the unexposed.
- ★ 95% confidence interval: the range which includes 95% of the results.



My Assumptions

- ★ I am a physicist by education and an atmospheric scientist by profession.
- ★ Thus, I accept the findings of well-conducted scientific studies.
- ★ Randomized controlled trials are most appropriate for pharmaceutical drugs, which, by definition, have not been part of the human experience. They can also be used to confirm ecological and observational studies providing sufficient vitamin D is employed.
- ★ Since solar UVB and vitamin D have coexisted with mankind since the beginning, we have plenty of evidence regarding their roles in health and disease.

Cancer Risk-Modifying Factors



In multi-factorial ecological studies of cancer mortality rates in the United States, we found:

- ★ UVB: inverse for 14 types of cancer¹
- ★ Air pollution (PAH with black carbon): 13 types²
- ★ Smoking: risk for 10 types¹
- ★ Alcohol: risk for 9 types¹
- ★ Latitude: minor risk for 5 types³
- ★ Hispanic heritage: risk for 3 types¹
- ★ Latitude: primary risk for 1 type (prostate) and important for 1 type (Hodgkin's lymphoma)³

1. Grant and Garland, Anticancer Research, 2006;

2. Grant, in review;

3. Grant, Photochem Photobiol. 2008

Harvard Cohort Study, Vitamin D, Cancer



Harvard cohort study on vitamin D and cancer

- ★ Edward Giovannucci developed a vitamin D index based on vitamin D from oral intake and UVB production, and controlled for other factors.
- ★ Significant inverse correlations with vitamin D were found for colon, esophageal, oral, pancreatic, and rectal cancer and leukemia.
- ★ Insignificant inverse correlations were found for bladder, gastric, lung, prostate, and renal cancer.
- ★ He estimated that male cancer deaths could be reduced by 29% for 1500 IU of vitamin D₃/day.

Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006 Apr 5;98(7):451-9.

Vitamin D and Cancer Survival



★ An ecological study in the United States found that solar UVB was more highly correlated with survival rates than incidence rates for:

★ Males

- ★ Bladder: 1.24 vs. 1.13 (Relative Risk, north vs. south)
- ★ Colon: 1.27 vs. 1.11
- ★ Esophageal: 1.36 vs. 1.27
- ★ Rectal: 1.53 vs. 1.27

★ Females

- ★ Breast: 1.15 vs. 1.06
- ★ Non-Hodgkin's lymphoma: 1.15 vs. 1.09

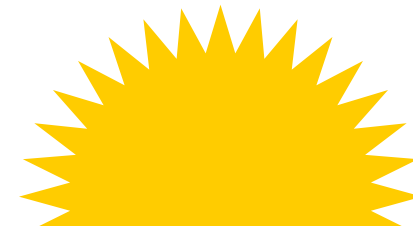
Cancer and Early Life UVB Irradiance



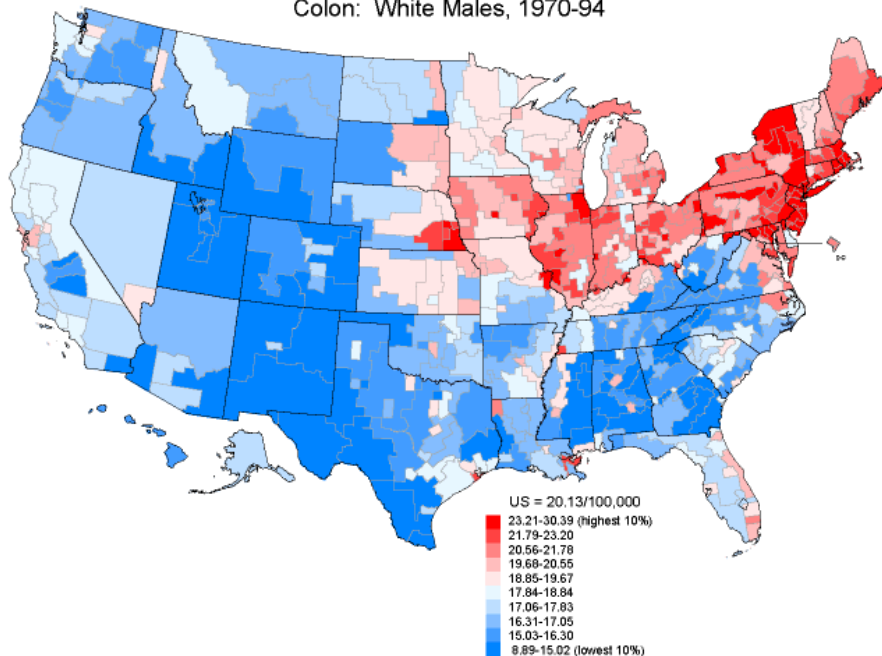
- ★ Prostate cancer is one for which early life UVB irradiance seems to be an important risk reduction factor [John et al., CEBP, 2007].
- ★ Also, wintertime UVB seems to be much more important than summertime UVB [Colli and Grant, Urology, 2008].
- ★ My hypothesis is that viral (and bacterial?) infections early in life are important risk factors, and that vitamin D, through production of human cathelicidin, reduces the risk of prostate cancer much later in life [Grant, 2008].

Grant WB. Hypothesis-Ultraviolet-B Irradiance and Vitamin D Reduce the Risk of Viral Infections and thus Their Sequelae, Including Autoimmune Diseases and some Cancers. Photochem Photobiol. 2008 Mar-Apr;84(2):356-65.

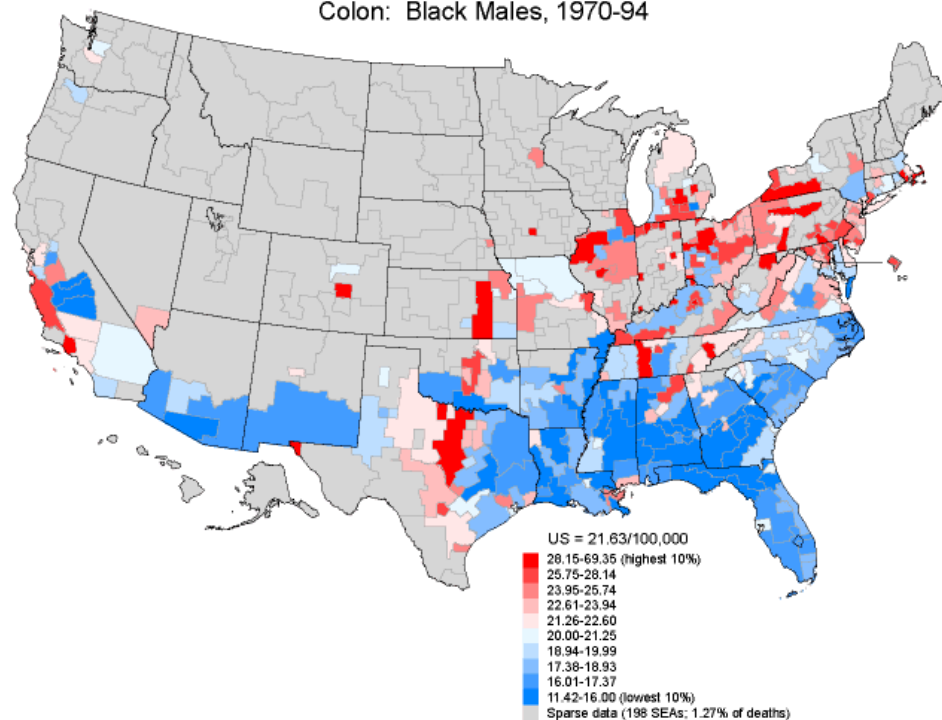
Colon Cancer, Males, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Colon: White Males, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Colon: Black Males, 1970-94



Vitamin D Explains Much of the Disparity for Colon Cancer



- ★ Black males have 25-30% higher colon cancer mortality rates for a state-by-state comparison [Atlas of Cancer Mortality Rates, NCI]
- ★ This translates to 15 ng/mL in summer [Gorham et al., 2007]
- ★ Black women have 18 ng/mL lower calcidiol levels in Boston in summer than white women [Harris and Dawson-Hughes, 1998]



Septicemia

Septicemia (infectious blood disease caused by bacterial infections) has these epidemiological features in the United States:

- ★ Highest in the Northeast, lowest in the Southwest.
- ★ Highest in winter, lowest in fall.
- ★ Higher in black Americans than white Americans.
- ★ Rapid increase with advancing age.
- ★ Comorbid diseases are vitamin D sensitive.

These features are explained by the epidemiological features of solar UVB, vitamin D, and LL-37

[Mookherjee et al., 2007; Grant, Alt Med Rev, submitted].

Respiratory Syncytical Virus



Yusuf et al. [2007] showed that solar UVB modulates the incidence of respiratory syncytical virus (RSV) (bronchitis) in a latitudinally-consistent manner.

Yorita et al., *Pediatr Infect Dis J* [2008] reported that infant incidence rates of RSV were directly related to skin pigment. This is further evidence for UVB/vitamin D [Grant, *Pediatr Infect Dis J*, in press]

Other important factors associated with increased number of cases were temperature and relative humidity.

- ★ Low temperature impairs white blood cells from getting to the surface.
- ★ Low relative humidity makes exhaled viruses smaller and have a longer life time.

Hypertension - Mechanisms



- ★ Vitamin D is a potent endocrine suppressor of renin biosynthesis to regulate the renin-angiotensin system (RAS).
- ★ The renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure, volume and electrolyte homeostasis.

Li YC, et al. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol. 2004 May;89-90:387-92.

Type 1 Diabetes Risk Factors



- ★ Viral childhood diseases (OR 4.29; 95%CI: 1.57-11.74) and bottle feeding (OR 1.83; 95%CI: 1.08-3.09) were directly correlated to type 1 diabetes; an inverse correlation was found for vitamin D administration during lactation (0-14 years) (OR 0.31; 95%CI: 0.11-0.86) and for history of scarlet fever in both sexes and age groups (OR 0.19; 95%CI: 0.08-0.46).

Tenconi MT, et al. Major childhood infectious diseases and other determinants associated with type 1 diabetes: a case-control study. Acta Diabetol. 2007 Mar;44(1):14-9.

Type 1 Diabetes Mellitus



- ★ Meta-analysis of data from the case control studies showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI: 0.60 to 0.84).

Zipitis CS, Akobeng AK. Vitamin D Supplementation in Early Childhood and Risk of Type 1 Diabetes: a Systematic Review and Meta-analysis. Arch Dis Child. 2008 Mar 13; [Epub ahead of print]



CHF Risk Mechanisms

- ★ The clinical syndrome congestive heart failure (CHF) has its origins rooted in a salt-avid state mediated largely by effector hormones of the renin-angiotensin-aldosterone system (RAAS). In addition, a systemic illness accompanies chronic RAAS activation. Its features include: the presence of oxidative stress in diverse tissues coupled with a reduction in activity of endogenous oxidoreductases; a proinflammatory phenotype with activated immune cells and increased circulating levels of proinflammatory cytokines; and a catabolic state with loss of soft tissues and bone that eventuates in a wasting syndrome termed cardiac cachexia.



Lost Minerals and CHF

- ★ Less well appreciated is the importance of a dyshomeostasis of various minerals, including Ca^{2+} , Mg^{2+} , Zn, and Se, and their impact on the systemic and progressive nature of CHF. A convergence of multiple factors, some hormonal (e.g., aldosteronism, secondary hyperparathyroidism, hypovitaminosis D), others pharmacologic (e.g., loop diuretics, angiotensin-converting enzyme inhibitors), predispose to the heightened excretion of these minerals in urine and feces while parathyroid hormone promotes intracellular Ca^{2+} overloading in diverse tissues. The importance of these macro- and micronutrients to the appearance of oxidative stress, compromised antioxidant defenses, an immunostimulatory state and tissue wasting needs to be critically addressed.

Newman KP, et al. The importance of lost minerals in heart failure. Cardiovasc Hematol Agents Med Chem. 2007 Oct;5(4):295-9.

CHF and African Americans



- ★ An emerging body of evidence suggests secondary hyperparathyroidism (SHPT) may be an important covariant of congestive heart failure (CHF), especially in African-Americans (AA) where hypovitaminosis D is prevalent. In addition to the role of hypovitaminosis D in contributing to SHPT is the increased urinary and fecal losses of macronutrients $\text{Ca}(2+)$ and $\text{Mg}(2+)$ associated with the aldosteronism of CHF and their heightened urinary losses with furosemide treatment of CHF. Thus, a precarious $\text{Ca}(2+)$ balance seen with reduced serum $25(\text{OH})\text{D}$ is further compromised when AA develop CHF with circulating RAAS activation and are then treated with a loop diuretic.

Bhattacharya SK, et al. Macro- and micronutrients in African-Americans with heart failure. Heart Fail Rev. 2006 Mar;11(1):45-55.

Oral Infections, Metabolic Disease Risk



- ★ Oral conditions such as gingivitis and chronic periodontitis are found worldwide and are among the most prevalent microbial diseases of mankind. The cause of these common inflammatory conditions is the complex microbiota found as dental plaque, a complex microbial biofilm. Similarly, recognition of the threats posed by periodontal diseases to individuals with chronic diseases such as diabetes, respiratory diseases and osteoporosis is relatively recent. A number of hypotheses have been postulated, including direct infection and cross-reactivity or molecular mimicry between bacterial antigens and self-antigens.

Oral Infections, Metabolic Disease Risk



- ★ With respect to the latter, cross-reactive antibodies and T-cells between self heat-shock proteins (HSPs) and *Porphyromonas gingivalis* GroEL have been demonstrated in the peripheral blood of patients with atherosclerosis as well as in the atherosclerotic plaques themselves. In addition, *P. gingivalis* infection has been shown to enhance the development and progression of atherosclerosis in apoE-deficient mice. From these data, it is clear that oral infection may represent a significant risk-factor for systemic diseases, and hence the control of oral disease is essential in the prevention and management of these systemic conditions.



CHD and Periodontitis

- ★ OBJECTIVE: We analyzed the association of coronary heart disease (CHD) and serology of periodontitis in a random sample (n=1163) of men (aged 45 to 74 years) by determining serum IgG-antibodies to *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*.
- ★ METHODS AND RESULTS: In the dentate population, CHD was more common among subjects seropositive for *P. gingivalis* compared with those seronegative (14.0% and 9.7%, $P=0.029$). When adjusted for age and several CHD risk factors, the subjects with a high combined antibody response had an odds ratio of 1.5 (95% CI, 0.95 to 2.50, $P=0.077$) for prevalent CHD. In a linear regression model, the combined antibody response was directly associated with prevalent CHD ($P=0.046$) and inversely with serum HDL cholesterol concentration ($P=0.050$).

Infections, Metabolic Diseases, References



- ★ Pussinen PJ, et al. Antibodies to periodontal pathogens are associated with coronary heart disease. *Arterioscler Thromb Vasc Biol.* 2003 Jul 1;23(7):1250-4.
- ★ Seymour GJ, et al. Relationship between periodontal infections and systemic disease. *Clin Microbiol Infect.* 2007 Oct;13 Suppl 4:3-10.
- ★ Yamazaki K, et al. Relationship of periodontal infection to serum antibody levels to periodontopathic bacteria and inflammatory markers in periodontitis patients with coronary heart disease. *Clin Exp Immunol.* 2007 Sep;149(3):445-52.

Vitamin D, PTH, Muscles



- ★ In men and women aged 65 yr and older, participants of the Longitudinal Aging Study Amsterdam, grip strength (n = 1008) and appendicular skeletal muscle mass (n = 331) were measured in 1995-1996 and after a 3-yr follow-up. Sarcopenia was defined as the lowest sex-specific 15th percentile of the cohort. After adjustment for confounding factors, persons with low (<25 nmol/liter) baseline 25-OHD levels were 2.57 (95% CI: 1.40-4.70, based on grip strength) times more likely to experience sarcopenia, compared with those with high (>50 nmol/liter) levels. High PTH levels (≥ 4.0 pmol/liter) were associated with an increased risk of sarcopenia, compared with low PTH (<3.0 pmol/liter): OR = 1.71 (1.07-2.73) based on grip strength, OR = 2.35 (1.05-5.28) based on muscle mass.

Visser M, et al. J Clin Endocrinol Metab. 2003 Dec;88(12):5766-72.

The prevalence of hypovitaminosis D and secondary hyperparathyroidism in obese Black Americans.

★ Clin Endocrinol (Oxf). 2006 May;64(5):523-9. _ Links

★ [Yanoff LB](#), [Parikh SJ](#), [Spitalnik A](#), [Denkinger B](#), [Sebring NG](#), [Slaughter P](#), [McHugh T](#), [Remaley AT](#), [Yanovski JA](#).

★ CONTEXT: Both obesity (body mass index, BMI ≥ 30 kg/m²) and Black race are associated with a higher risk of vitamin D deficiency and secondary hyperparathyroidism. We hypothesized the risk of hypovitaminosis D would therefore be extraordinarily high in obese Black adults.

★ OBJECTIVE: To study the effects of race and adiposity on 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (iPTH).

★ DESIGN, SETTING AND PARTICIPANTS: Cross-sectional study of 379 Black and White adults from the Washington D.C. area. BMI ranged from 19.9 to 58.2 kg/m². MAIN OUTCOME MEASURES: Prevalence of hypovitaminosis D [25(OH)D < 37.5 nmol/l] and secondary hyperparathyroidism [25(OH)D < 37.5 nmol/l with iPTH > 4.2 pmol/l].

★ RESULTS: Obese Black subjects had lower mean 25(OH)D, 40.3 (SD, 20.3) nmol/l, compared with obese Whites, 64.5 (29.7), $P < 0.001$, nonobese Blacks, 53.3 (26.0), $P = 0.0025$ and nonobese Whites, 78.0 (33.5), $P < 0.001$. The prevalence of hypovitaminosis D increased with increasing BMI, and was greater ($P < 0.001$) in Blacks than Whites within all BMI categories examined. Among subjects with BMI ≥ 35 kg/m², 59% of Blacks vs 18% of Whites had hypovitaminosis D (odds ratio 6.5, 95% confidence interval 3.0-14.2). iPTH was negatively correlated with 25(OH)D ($r = -0.31$, $P < 0.0001$), suggesting those with hypovitaminosis D had clinically important vitamin D deficiency with secondary hyperparathyroidism. For secondary hyperparathyroidism 35.2% of Blacks met the criteria, compared to 9.7% of Whites (OR 3.6, CI 1.5-98.8).

★ CONCLUSIONS: Obese Black Americans are at particularly high risk for vitamin D deficiency and secondary hyperparathyroidism. Physicians should consider routinely supplementing such patients with vitamin D or screening them for hypovitaminosis D.

Mortality Rates, Males 65+ Years



Disease	Black	White	Black/White
Heart	1896	1726	1.10
Cancer	1662	1363	1.22
Stroke	430	341	1.26
Diabetes	266	150	1.77
Lower respir.	265	373	0.71
Nephritis	195	106	1.84
Flu, pneum.	169	167	1.01
Septicemia	146	<73	>2.00
Hypertension	98	<73	>1.34

Mortality Rates, Females 65+ Years

Disease	Black	White	Black/White
Heart	1625	1537	1.06
Cancer	963	932	1.03
Stroke	454	430	1.06
Diabetes	384	129	2.98
Nephritis	168	84	2.00
Lower respir	131	307	0.43
Septicemia	130	71	1.83
Flu, pneumo	125	168	0.74
Hypertension	109	<70	>1.56