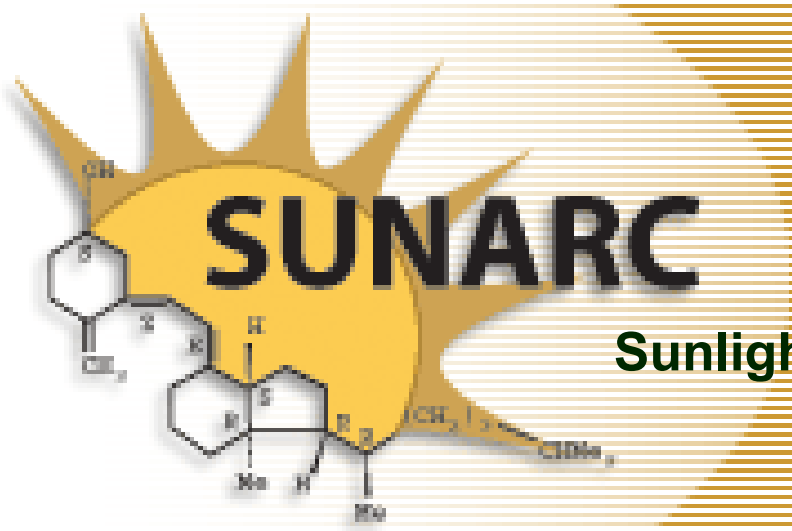


# The Evidence that Ultraviolet-B and Vitamin D Reduce the Risk of Cancer

A presentation in London

On May 18, 2011

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



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

[www.sunarc.org](http://www.sunarc.org)

# Disclosure



I am pleased to acknowledge funding from these organizations:

- ★ UV Foundation (McLean, Virginia)  
[www.uvfoundation.org](http://www.uvfoundation.org)
- ★ Sunlight Research Forum (Veldhoven)
- ★ Bio-Tech-Pharmaceutical (www.Bio-Tech-Pharm.com)  
(Fayetteville, AR)
- ★ The Vitamin D Council  
[www.vitaminDCouncil.org](http://www.vitaminDCouncil.org)

# Outline



- ★ Vitamin D – mechanisms for preventing cancer
- ★ Types of evidence for benefits with findings
  - ★ Ecological studies
  - ★ Observational studies
- ★ Prostate cancer - genetics
- ★ Hill's criteria for causality
- ★ General benefits of increasing 25(OH)D levels
- ★ 100 vitamin D-sensitive health conditions

# Mechanisms Whereby Vitamin D May Reduce the Risk of Cancer



- ★ Regulation of cell growth, differentiation, apoptosis and a wide range of cellular mechanisms central to the initiation of cancer.
- ★ Enhances calcium absorption and metabolism.
- ★ Maintains epithelial layer integrity & reduces risk of disjunction, protecting organs from cancer.
- ★ Reduces risk of angiogenesis, required for tumours >1-3 mm.
- ★ Reduces cancer metastasis (spreading).

# Types of Epidemiological Studies



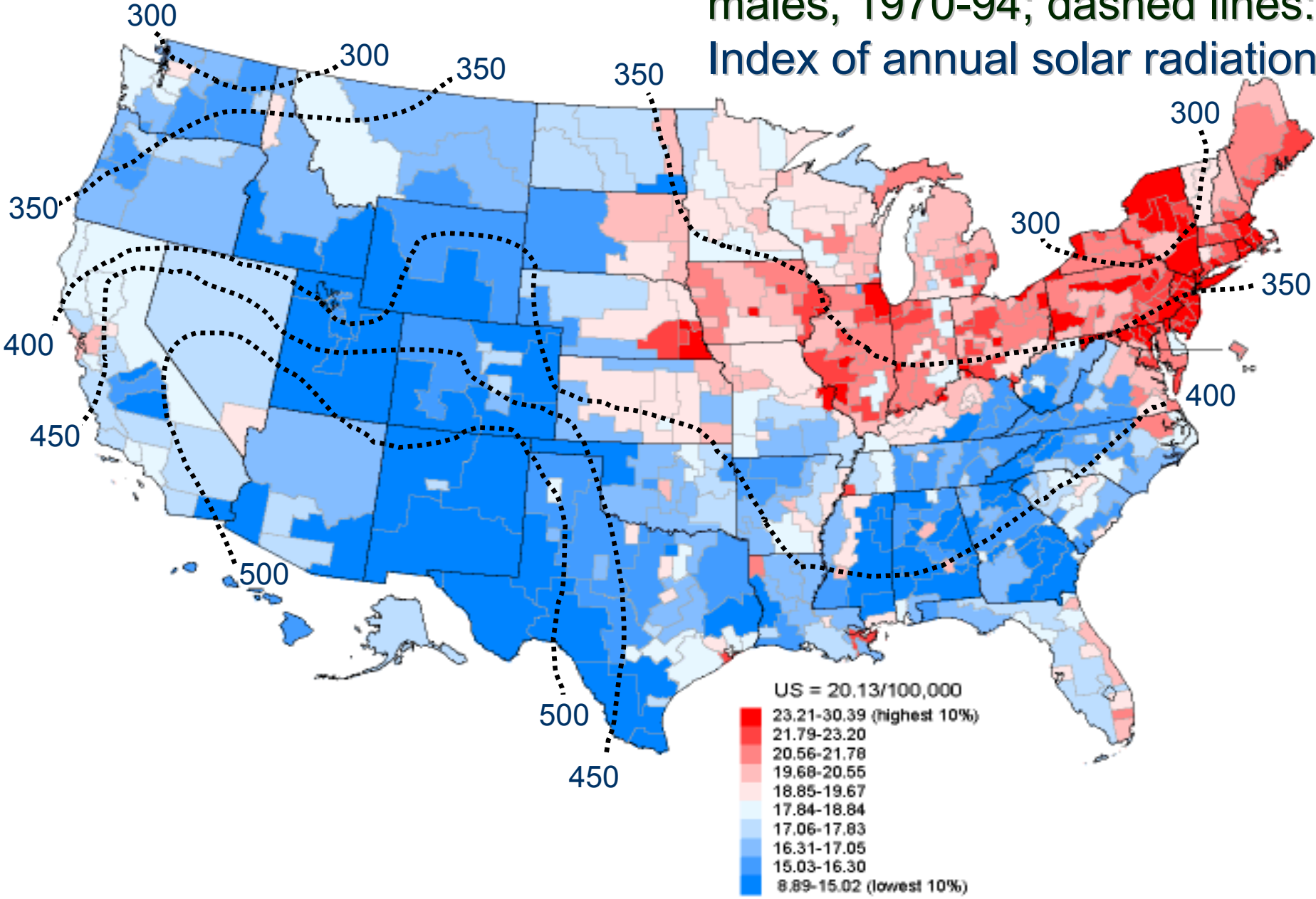
- ★ There are four basic types of epidemiological studies used to identify and quantify links between risk-modifying factors and disease. The first three are called “observational” studies.
  - ★ Nested case control – a defined population followed for years after blood draw; (accuracy decreases with 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.

# Ecological Studies of UVB, Vitamin D, Cancer

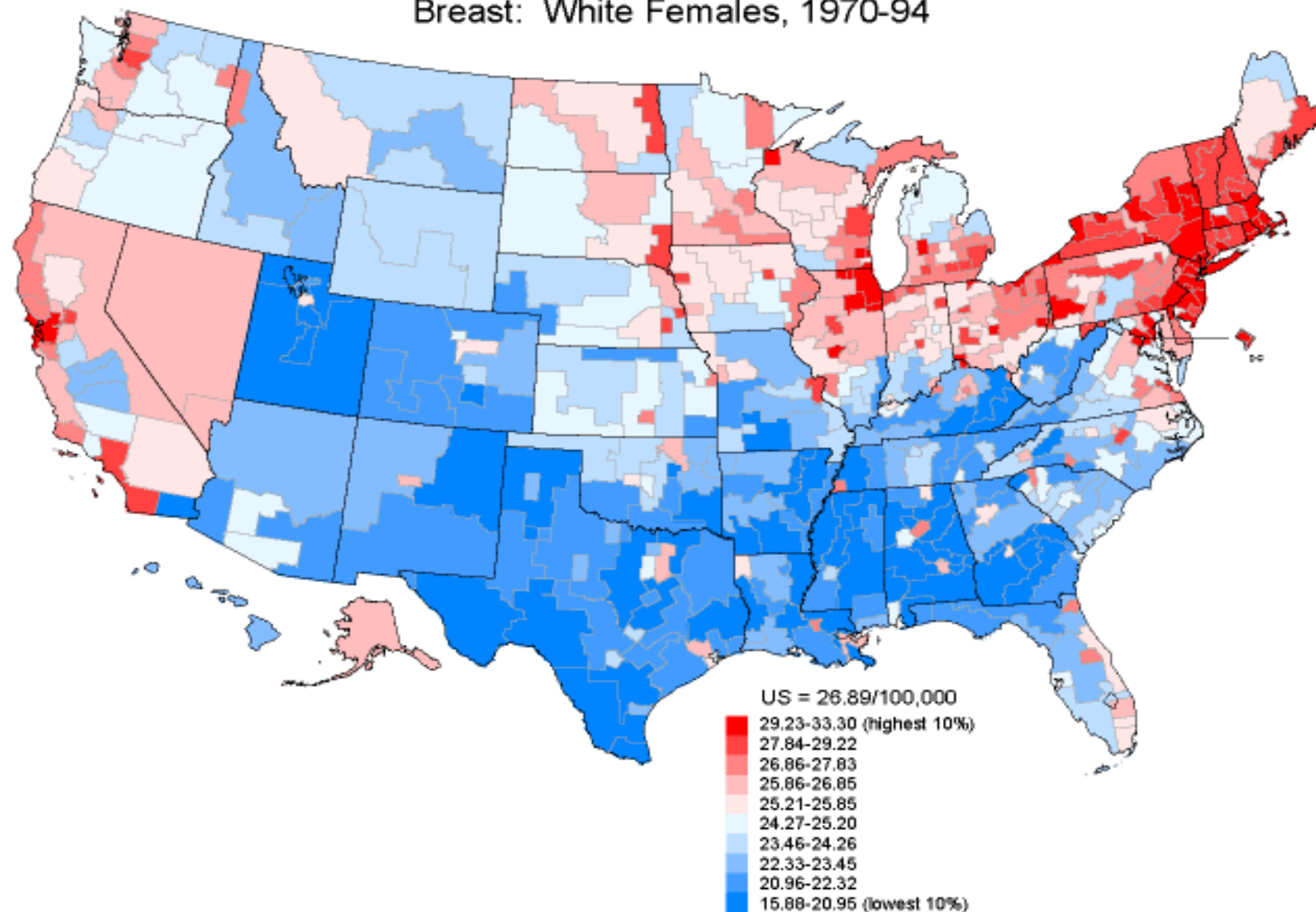


- ★ The first epidemiological study hypothesizing that solar UVB, through production of vitamin D, reduced the risk of cancer was an ecological study, published in 1980.
- ★ The brothers Cedric Garland and Frank Garland, beginning students at Johns Hopkins School of Public Health in 1974, looked at the map of colon cancer mortality rates in the U.S. and saw a link to solar radiation.
- ★ They hypothesized that vitamin D production was the mechanism.

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

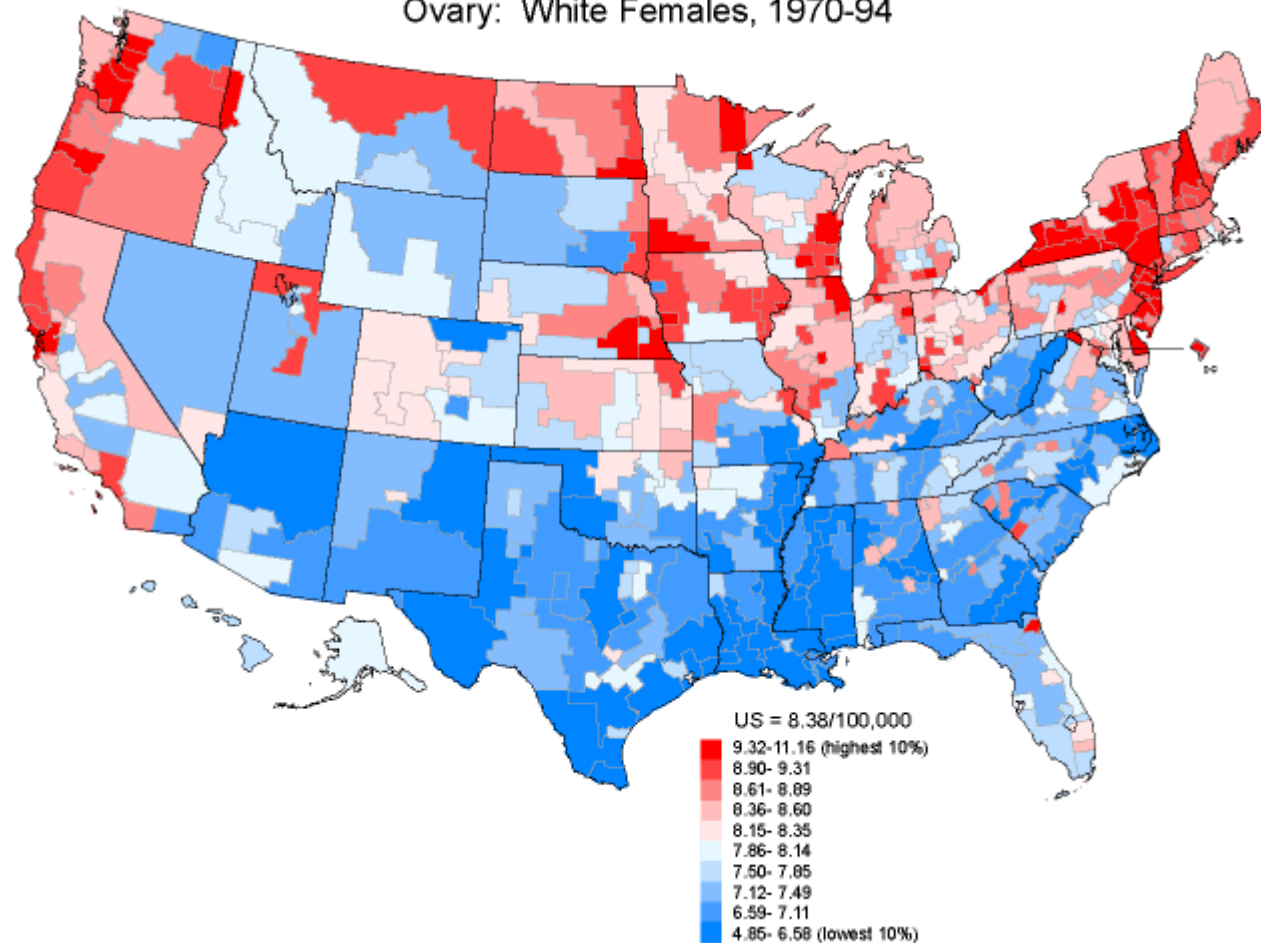




# Ovarian Cancer, 1970-94

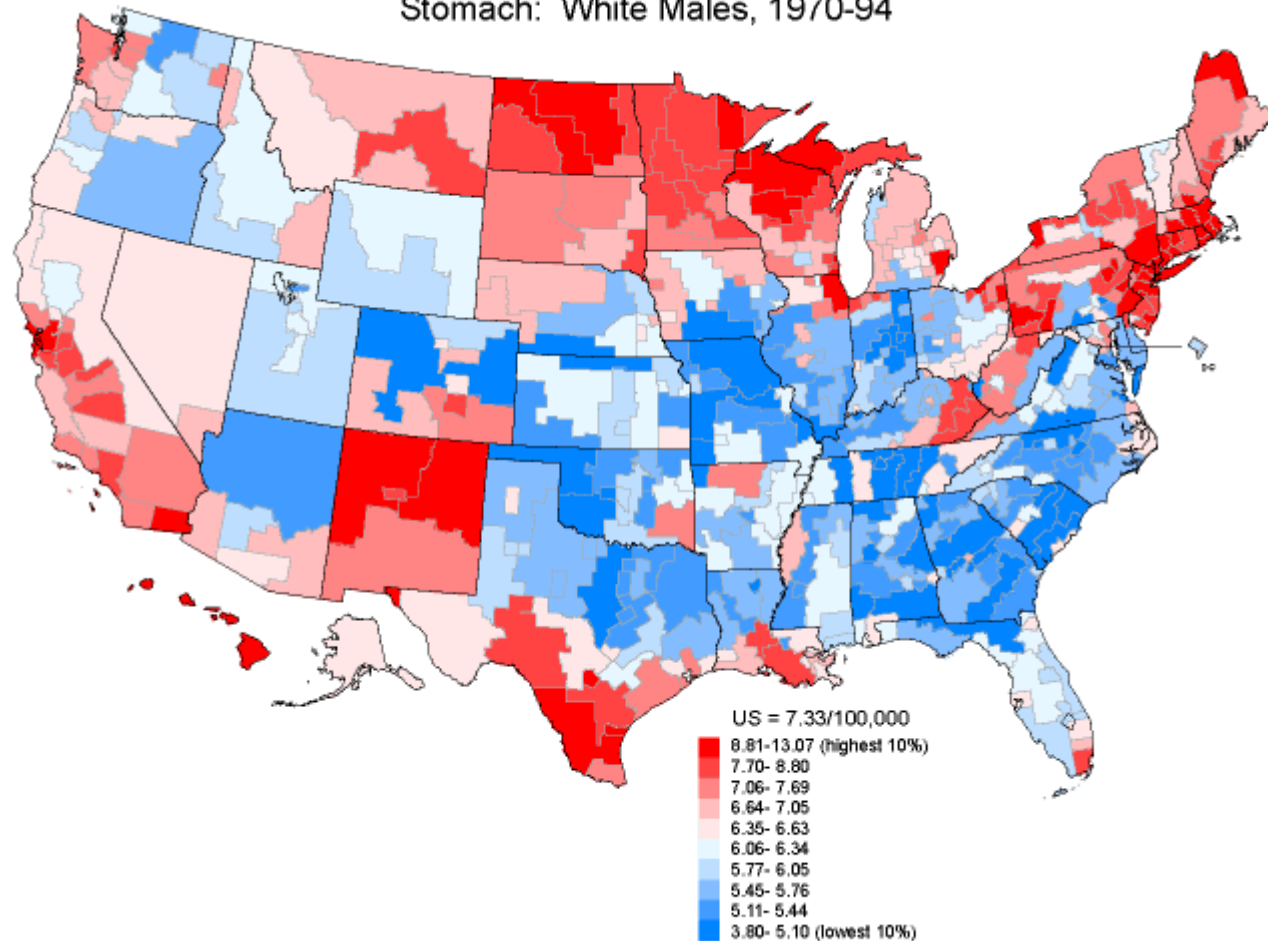


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Ovary: White Females, 1970-94



# Gastric Cancer, Males, 1970-94

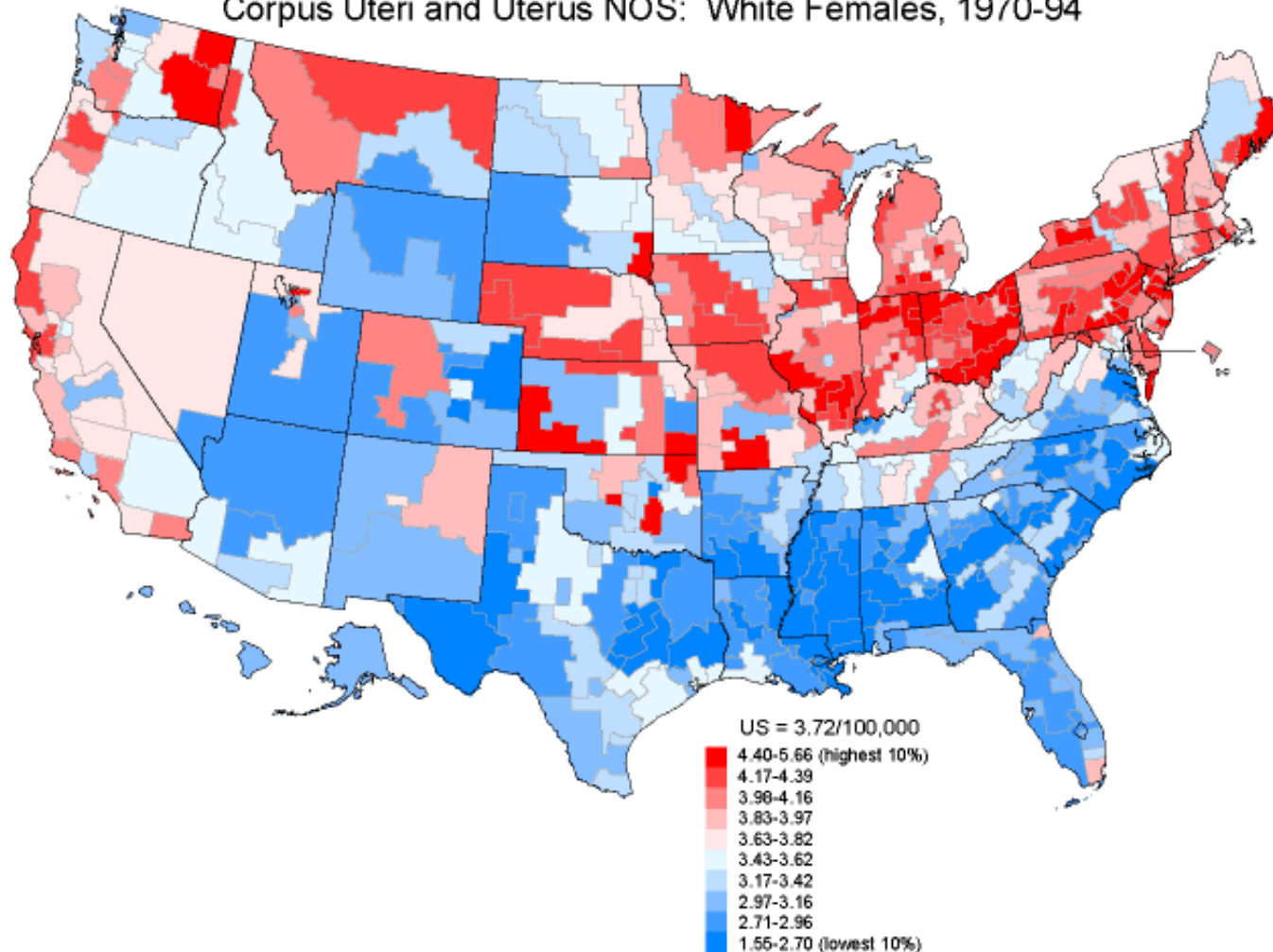
Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Stomach: White Males, 1970-94



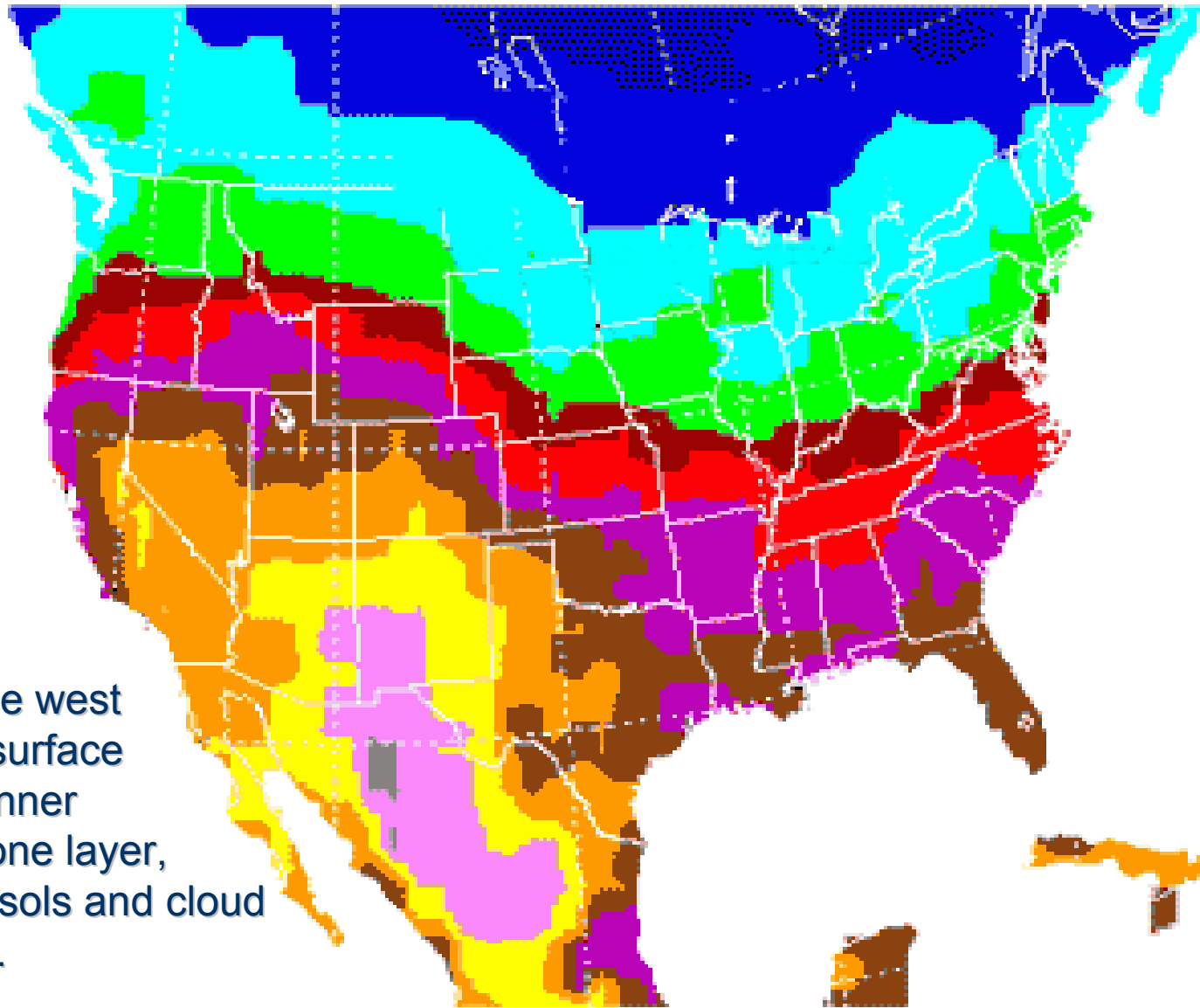
# Corpus Uteri (Endometrial) Cancer, White Females, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Corpus Uteri and Uterus NOS: White Females, 1970-94



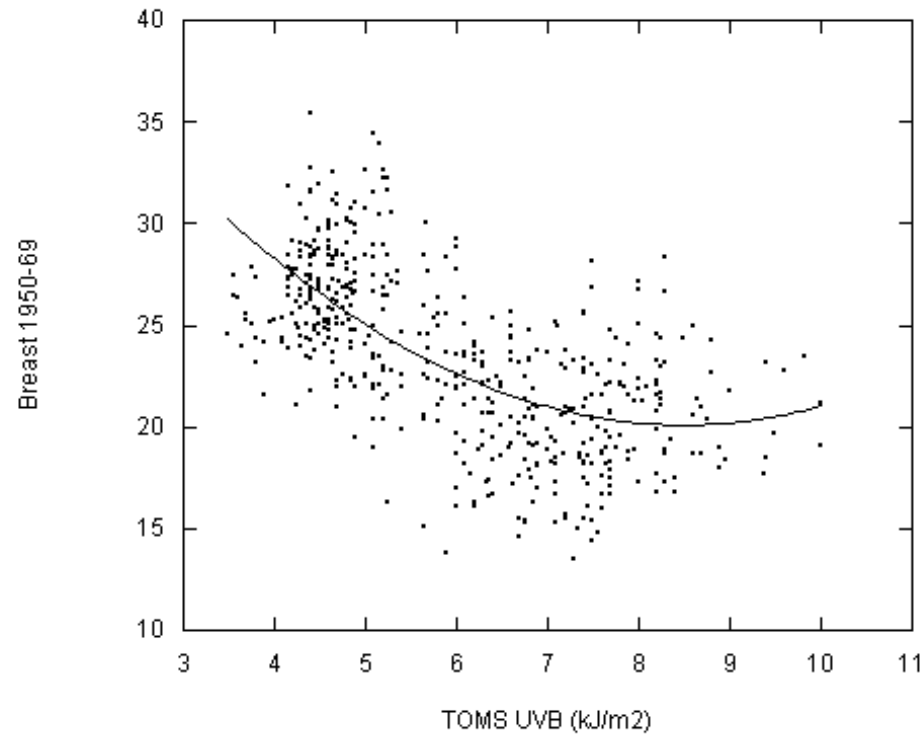
# DNA SPECTRAL EXPOSURE (kJ/m<sup>2</sup>) FOR JULY 1992



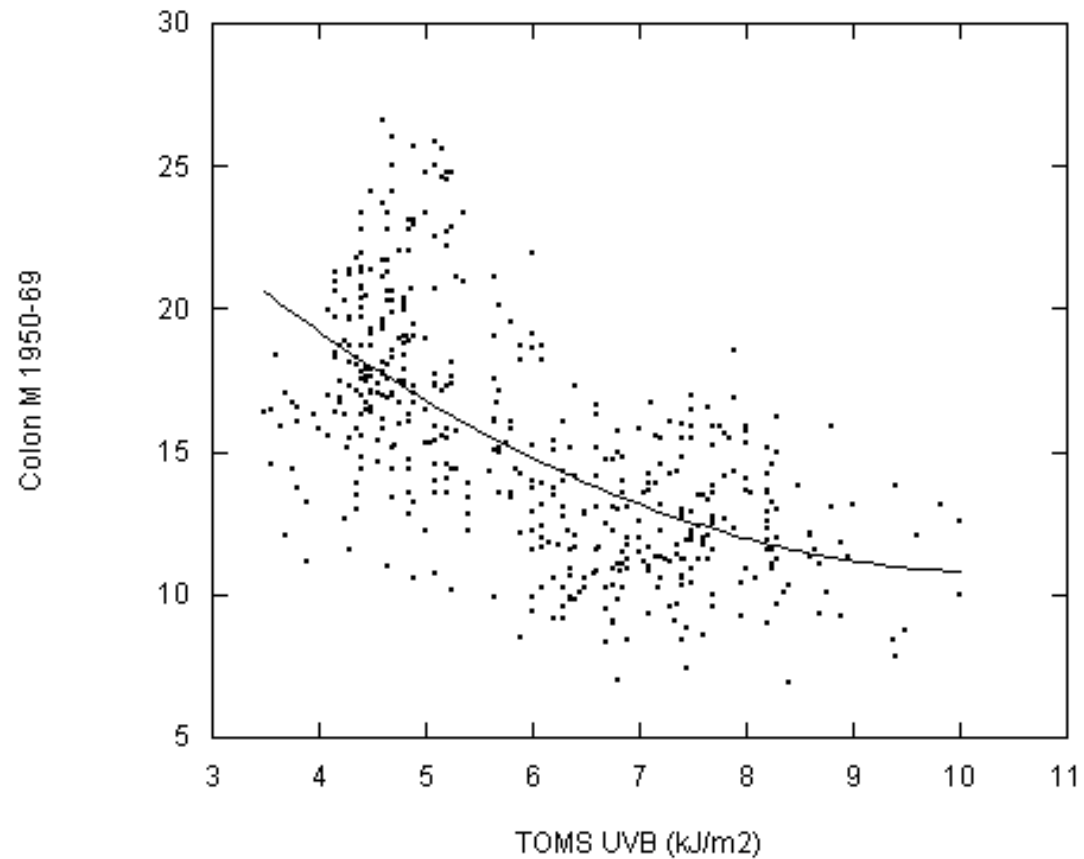
Higher UVB in the west is due to higher surface elevation and thinner stratospheric ozone layer, and greater aerosols and cloud cover in the east.



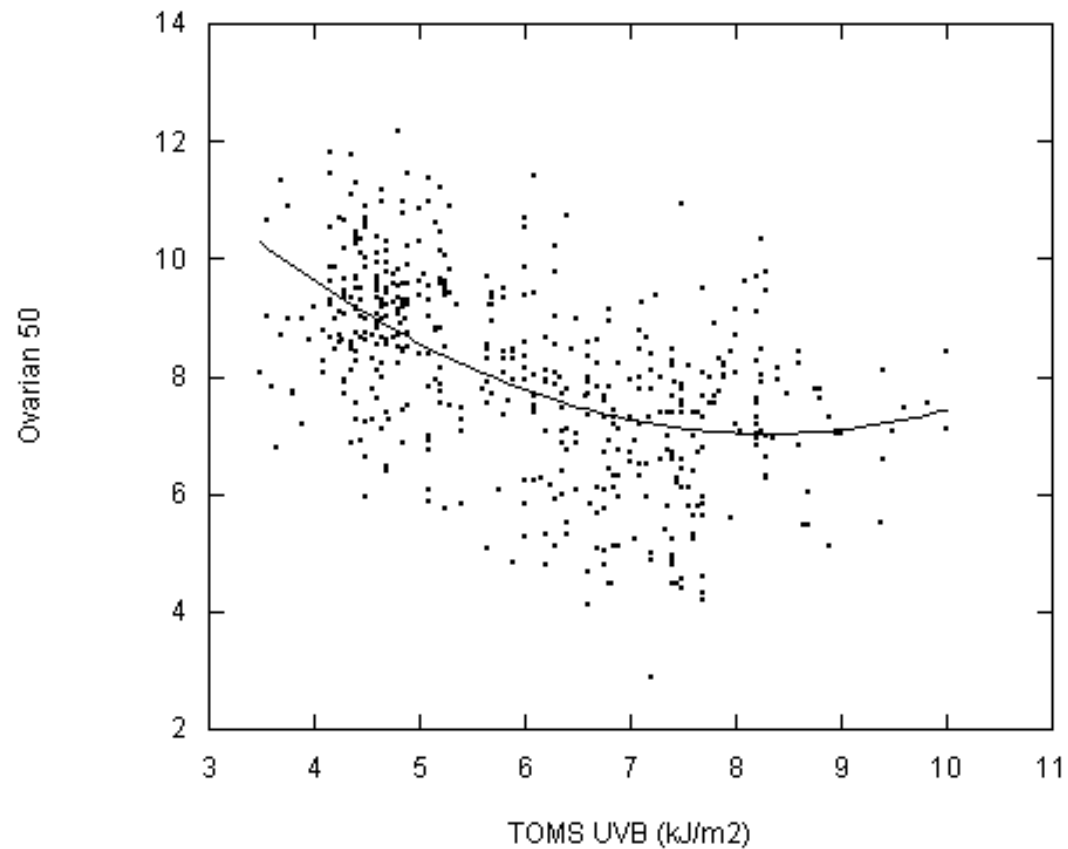
# Breast Cancer, White Females, 1950-69 vs. July UVB



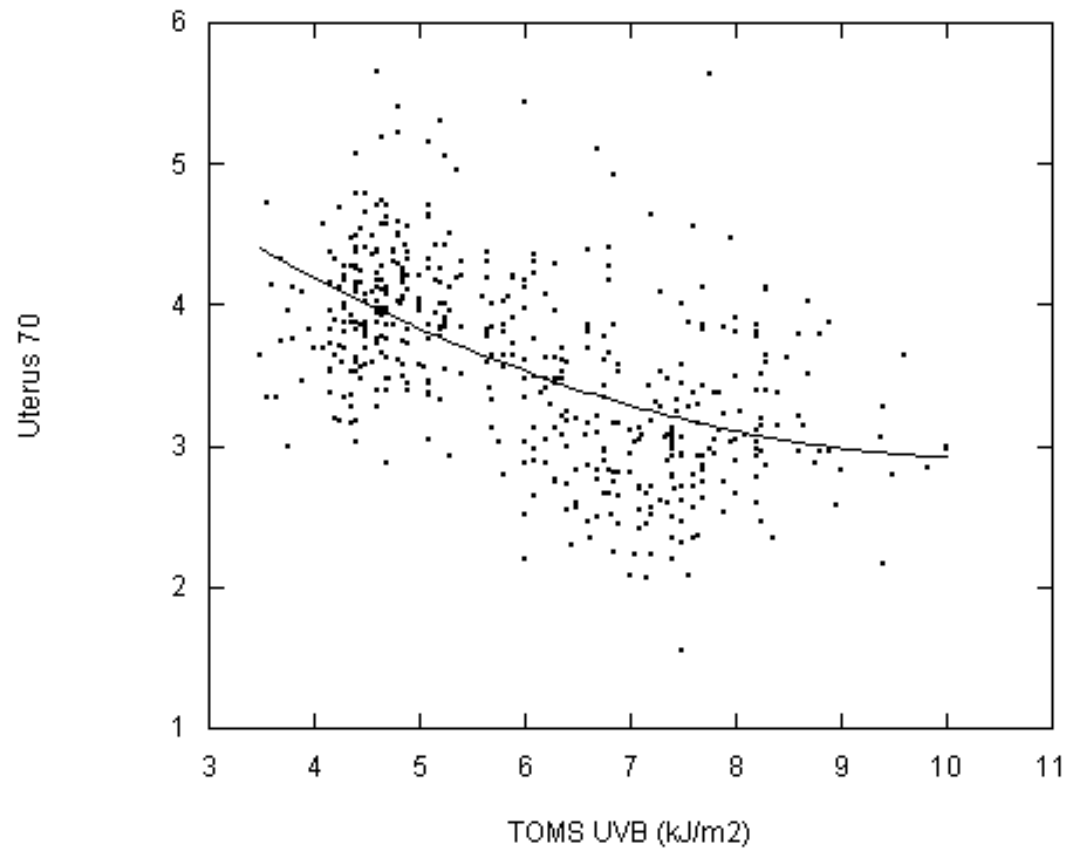
# Colon Cancer, White Males, 1950-69 vs. July UVB



# Ovarian Cancer, 1950-69 vs. July UVB

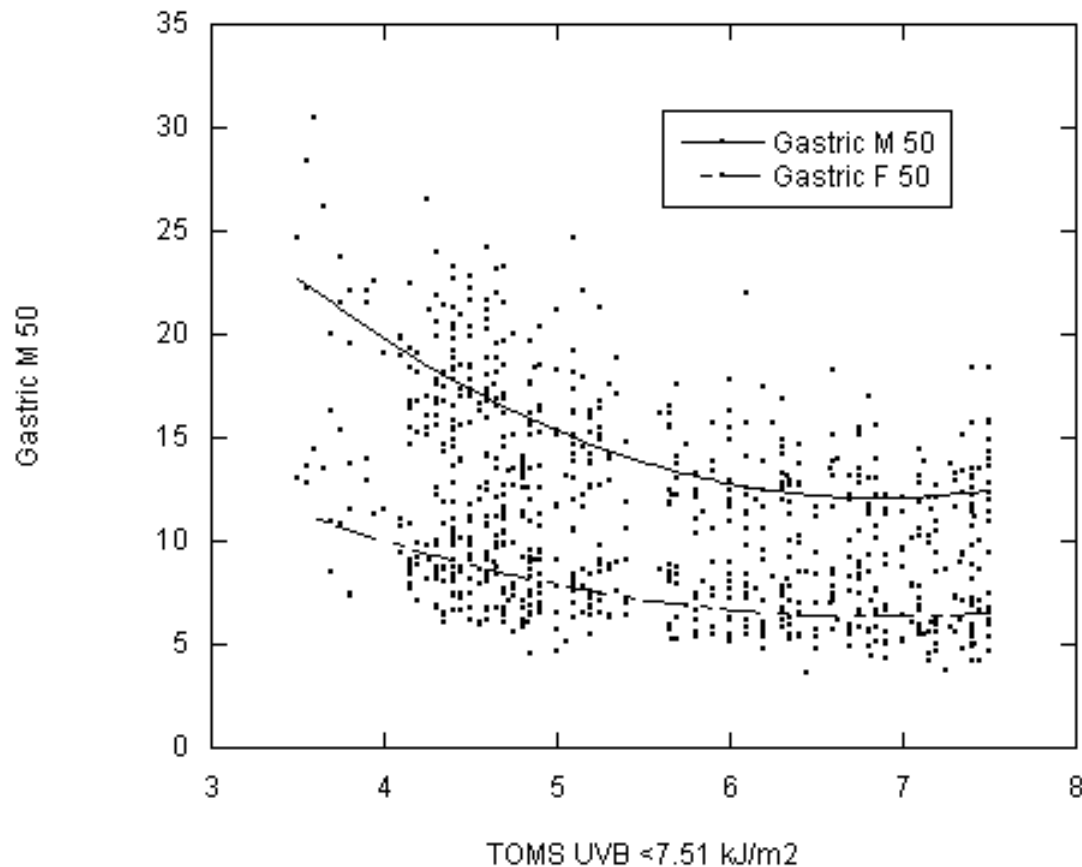


# Corpus Uteri Cancer, 1970-94 vs. July UVB





# Gastric Cancer, 1950-69 vs. July UVB



Truncated at 7.5 kJ/m<sup>2</sup> since many Hispanics live in regions with >7.5 kJ/m<sup>2</sup> and have much higher risk due to increased prevalence of *H. pylori* infection.

# Ecological Study Results for Cancer, USA, 1950-69 and 1970-94



- ★ Models were developed that explained much of the variance in cancer mortality rates, with stronger correlations for the earlier period (1950-69).
- ★ Fifteen types of cancer were inversely-associated with solar UVB doses.
- ★ In the period 1950-69, most of the associations of cancer death rates for white Americans agreed well with the literature for alcohol consumption (nine), Hispanic heritage (six), and the proxy for smoking (ten).

# Non-melanoma Skin Cancer as the Index of Solar UVB Exposure in Spain



- ★ An ecological study of cancer mortality rates in Spain was done using non-melanoma skin cancer (NMSC) rates as the index of solar UVB exposure by the population of each continental province.
- ★ Spaniards have skin well-adapted for UV in Spain, so NMSC is an index of high UVB exposure.
- ★ This index was found inversely correlated with 14 types of cancer.
- ★ In my opinion, the fear of solar UV spread by well-meaning organizations reduces overall health. Moderate sunlight exposure with as much body surface area exposed as possible when the sun elevation is above 45 degrees is nature's way of obtaining vitamin D.

# Ecological Study in U.S. by Boscoe and Schymura, 2006 (low vs. high UVB)

| Cancer        | Mortal/Inc – Males | Mortal/Inc-Female  |
|---------------|--------------------|--------------------|
| Bladder       | RR(M)/RR(I) = 1.10 | RR(M)/RR(I) = 1.05 |
| Breast        |                    | 1.08               |
| Colon         | 1.04               | 1.09               |
| Esophageal    | 1.07               | 1.12               |
| Gallbladder   | 1.40               | 1.06               |
| Kidney        | 1.03               | 1.03               |
| Non-Hodgkin's | 1.04               | 1.06               |
| Rectal        | 1.20               | 1.20               |
| Thyroid       | 0.95               | 1.18               |
| Vulvar        |                    | 1.64               |

# Interpretation



- ★ There are many cancer risk-modifying factors that affect cancer initiation. Vitamin D is but one of these factors.
- ★ There are few natural ways the body fights cancer once it starts to progress. Vitamin D is one of these: it reduces angiogenesis around tumors and inhibits metastasis.
- ★ Thus, the effects of vitamin D might be expected to affect cancer mortality rates more strongly than cancer incidence rates.

# 17 Vitamin D-Sensitive Cancers



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

# 13 Vitamin D-Sensitive Cancers with Support from Oral Intake Studies



- ★ Vitamin D-sensitive cancers with moderate-to-strong support from ecological and other studies:
  - ★ Gastrointestinal: colon, esophageal, gastric, pancreatic
  - ★ Urinary: bladder, kidney
  - ★ Female: breast, cervical, endometrial, ovarian
  - ★ Blood: non-Hodgkin's lymphoma,
  - ★ Miscellaneous: melanoma, oral/pharyngeal

# Why Ecological Studies Are Powerful



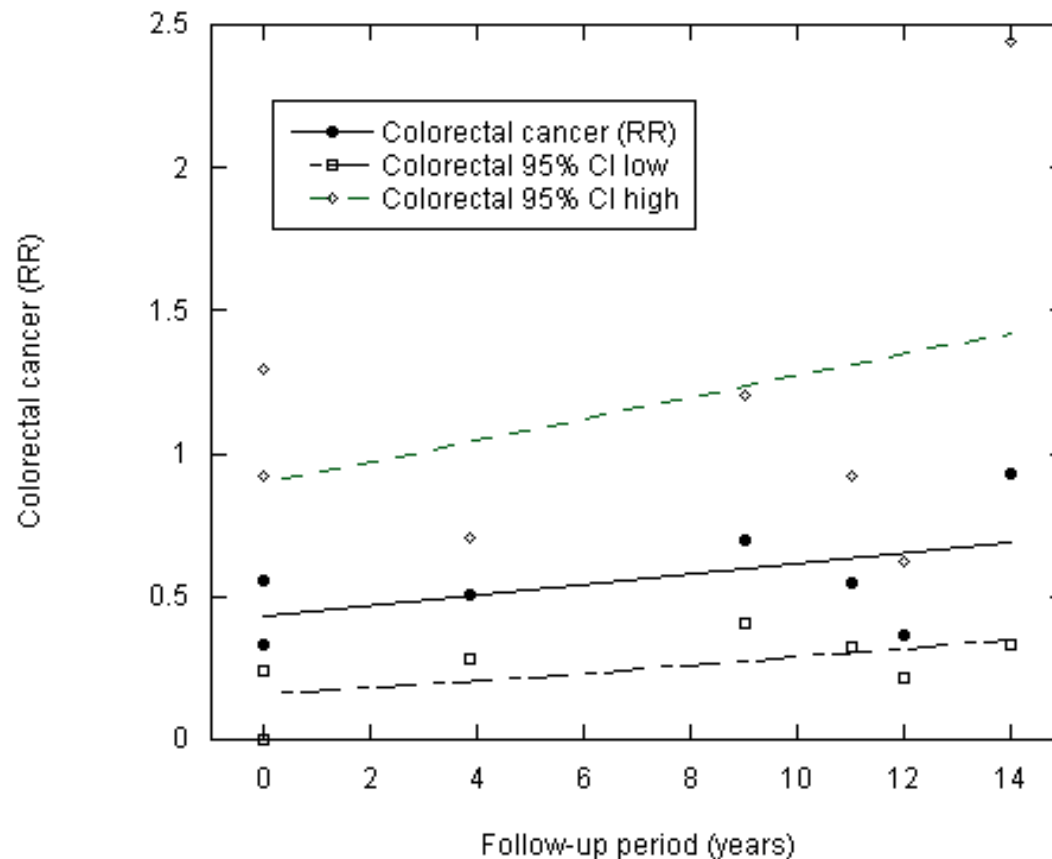
- ★ Cancers generally take 15-40 years to progress from initiation to detection or death.
- ★ Ecological studies integrate the effects of solar UVB and other factors over many years.
- ★ Large numbers of cancer cases are included.
- ★ Other cancer risk-modifying factors can be readily included in the study.
- ★ The data are already available, saving millions of dollars, pounds, or Euros, as well as many years of research.



## **(Nested) Case-Control Studies of Breast and Colorectal Cancer vs. Serum 25(OH)D**

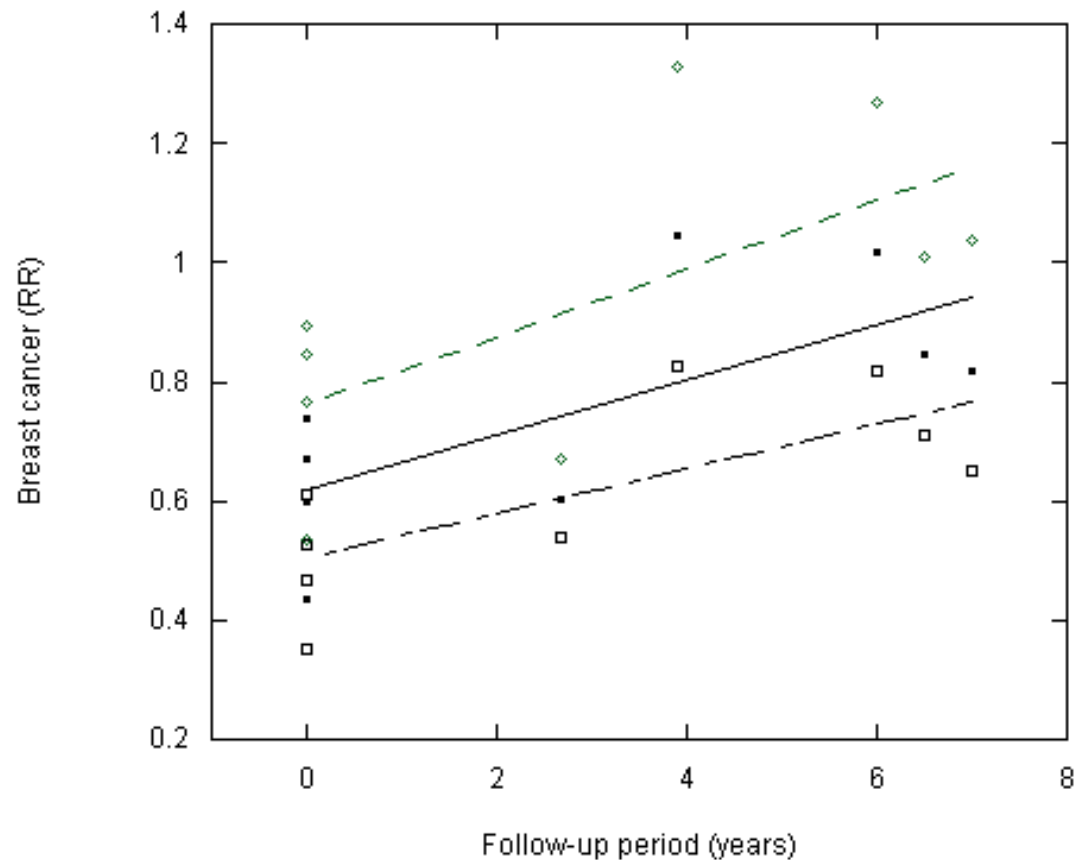
- ★ Observational studies provide useful data for determining the serum 25(OH)D level-cancer incidence rate relation for breast and colorectal cancer.
- ★ 25(OH)D is determined from blood drawn at time of enrollment; people are followed for years to obtain enough cases for good statistics.
- ★ For breast 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 Risk for High to Low 25(OH)D vs. Follow-up Period

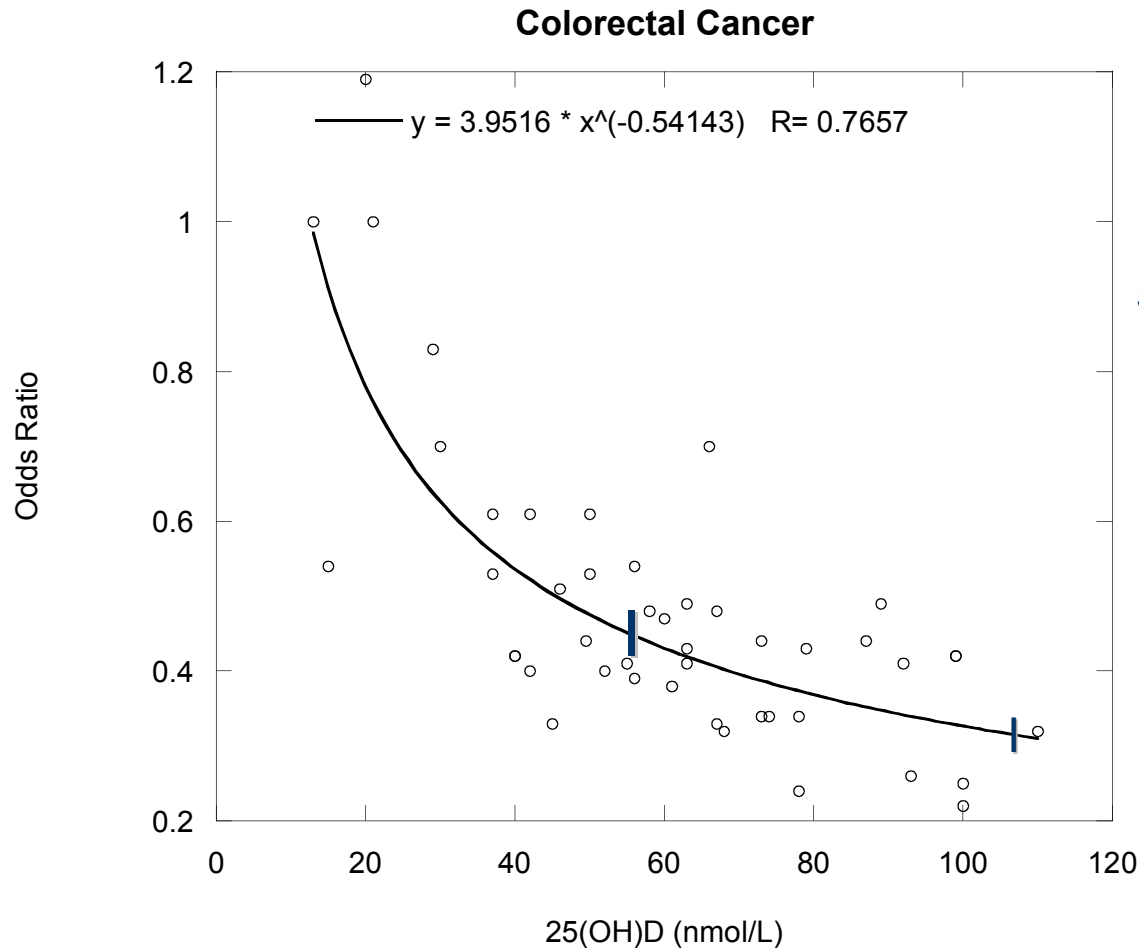


The dashed lines indicate the 95% confidence intervals. If values in a study cross 1.0, the study is regarded as statistically insignificant, i.e., the result could be the result of chance.

# Breast Cancer Risk for High to Low 25(OH)D vs. Follow-up Period



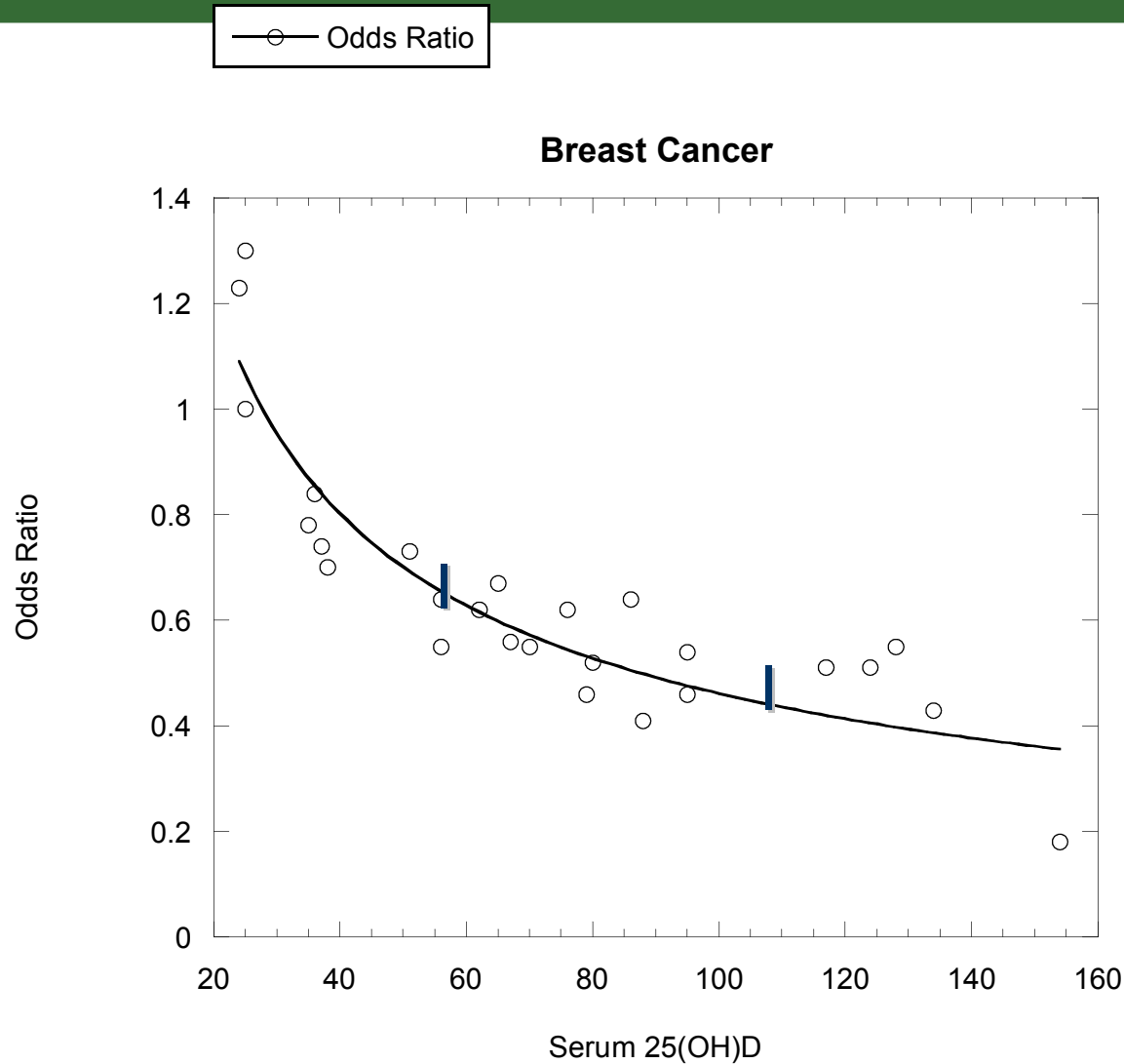
# Colorectal Cancer Incidence Rate vs. Serum 25(OH)D Level – Meta-Analysis



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

Grant, JPPB, 2010

# 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

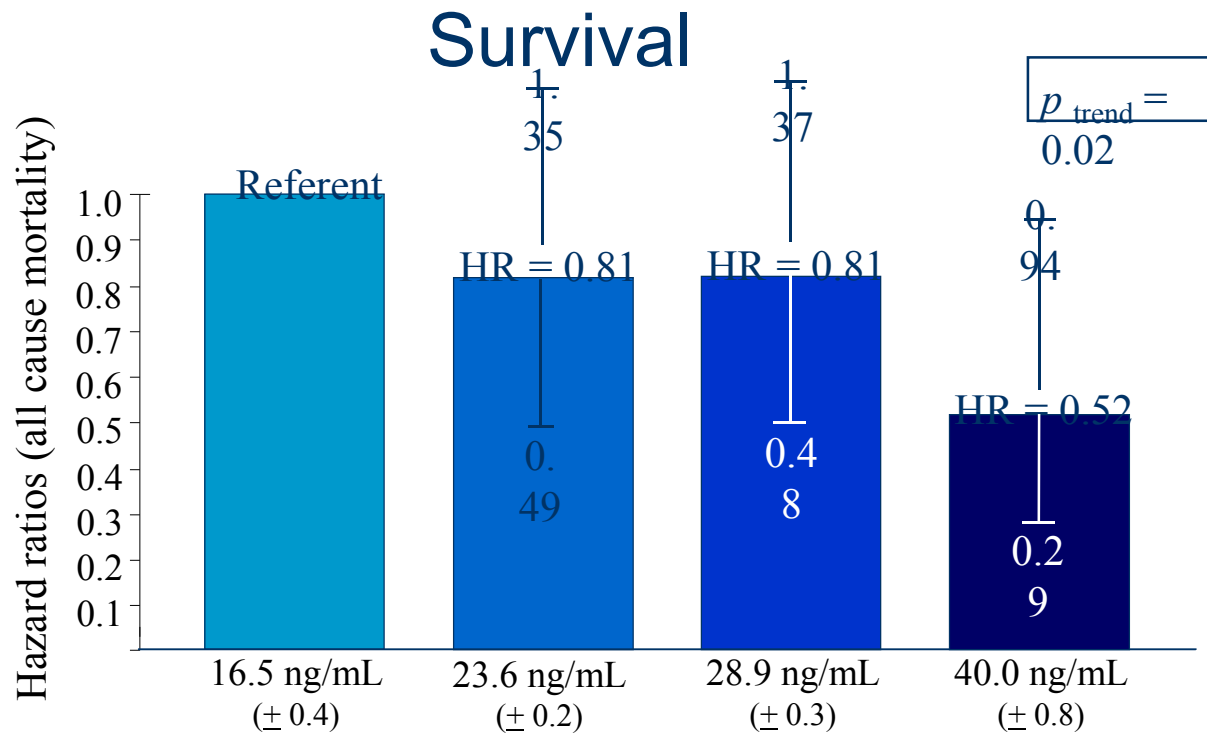
Grant, JPPB, 2010

# Vitamin D and Cancer Survival Rates



- ★ Since ecological studies indicate that UVB and vitamin D have a greater impact on survival after diagnosis of cancer than in preventing cancer, it would be expected that survival rates after diagnosis would be higher for those with higher serum 25(OH)D levels at time of diagnosis.
- ★ In fact, some cancer treatment centers and doctors are now advising their cancer patients to take 5000 IU/d or more vitamin D3.

# Colorectal Cancer Survival



Mean plasma 25-hydroxyvitamin D quartiles ng/mL ( $\pm$  se)  
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, J Clin Oncol 2008; 26: 2984-91.

# Observational Studies of Cancer Survival Rates with Respect to 25(OH)D



| Cancer                | Finding                         | Reference           |
|-----------------------|---------------------------------|---------------------|
| Breast                | 50% mortal diff                 | Goodwin, 2009       |
| Chron. lymph leuk     | Time to treatment               | Shanafelt, 2011     |
| Colorectal            | 50% mortal diff                 | Ng, 2009            |
| Lung (non-small cell) | 25% reduction                   | Zhou, 2007          |
| Melanoma              | 20% increased relapse-free surv | Newton-Bishop, 2009 |
| Multiple myeloma      | Vit D defic with stage          | Ng, 2007            |
| Non-Hodgkin's B-cell  | 50% survival diff               | Drake, 2010         |
| Prostate              | Better prognosis                | Tretli, 2009        |



# Prostate Cancer

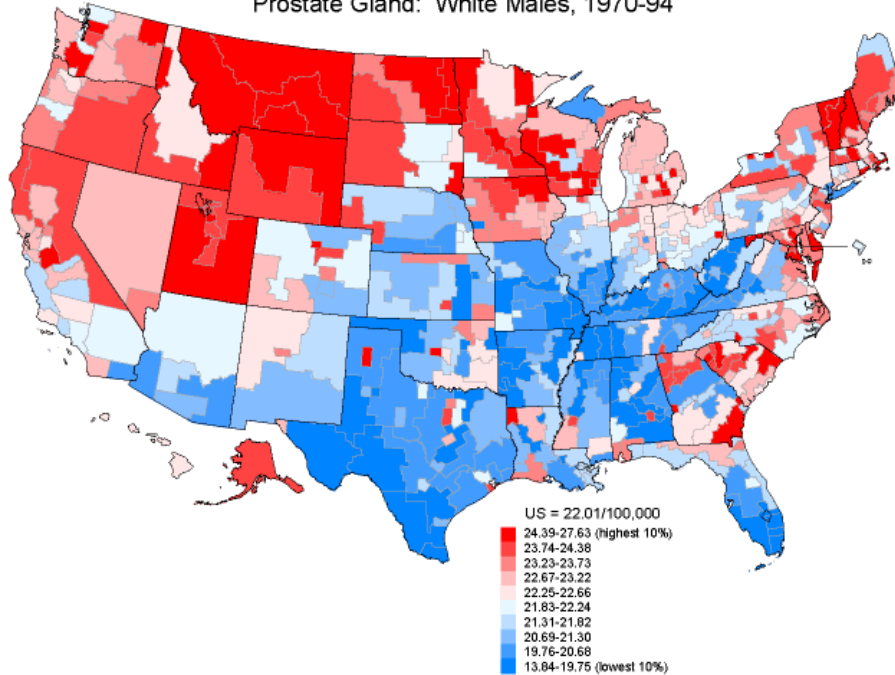


- ★ UVB exposure early in life, and sufficient UVB exposure to cause non-melanoma skin cancer has been found inversely correlated with prostate cancer incidence.
- ★ Serum 25(OH)D for follow-up periods up to 28 years has not been found correlated with prostate cancer incidence.
- ★ Vitamin D may affect risk of prostate cancer early in life and may protect against metastasis.

# Prostate Cancer vs. Colon Cancer, White Males, 1970-94

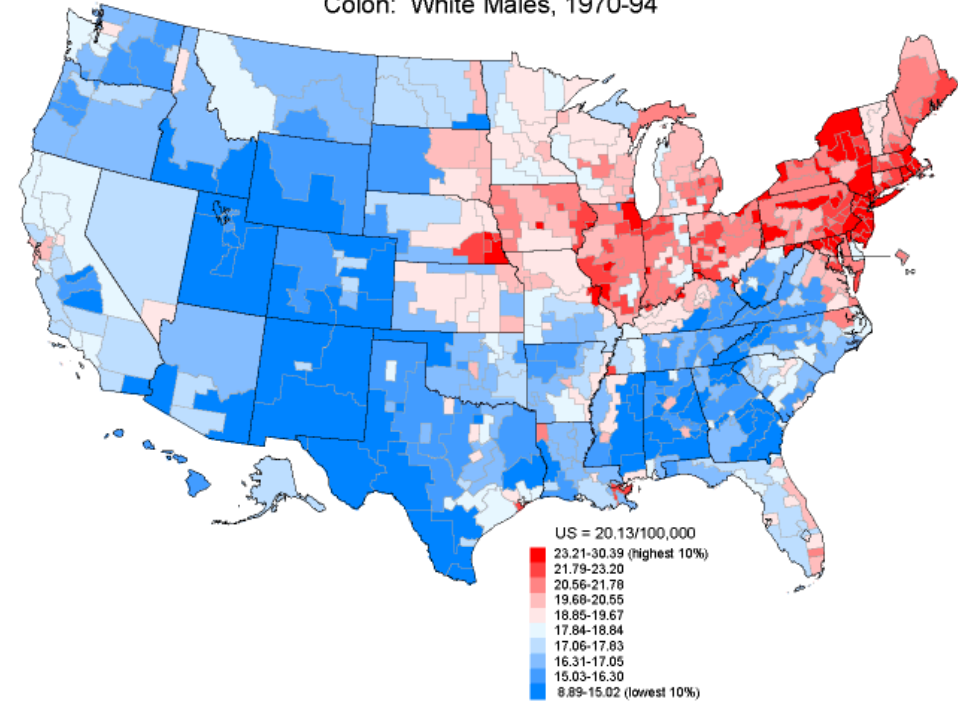


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Prostate Gland: White Males, 1970-94



Prostate

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

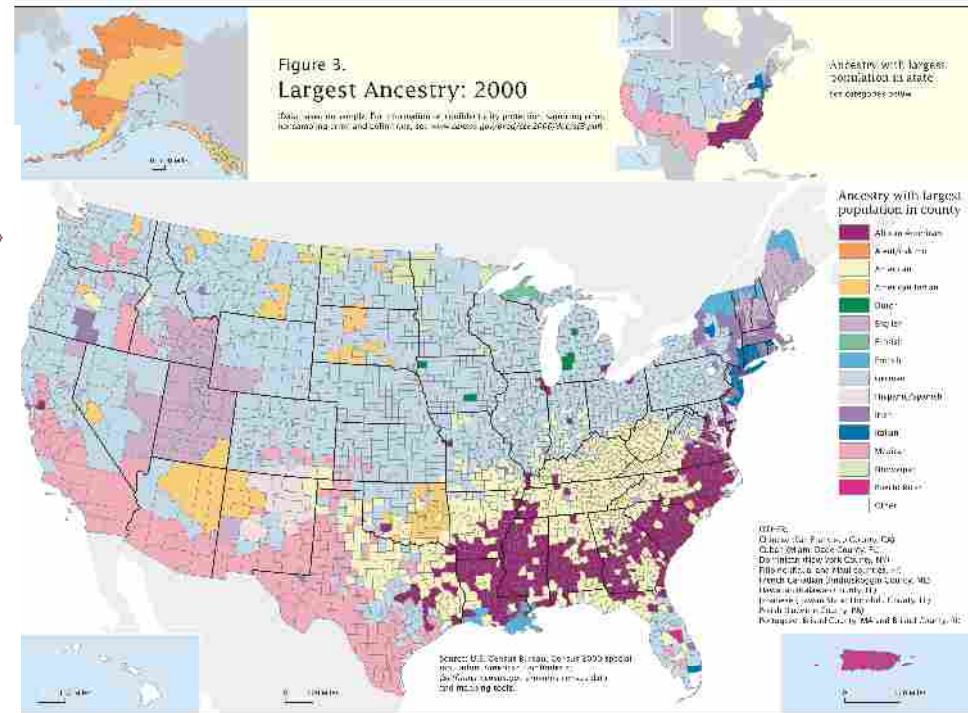
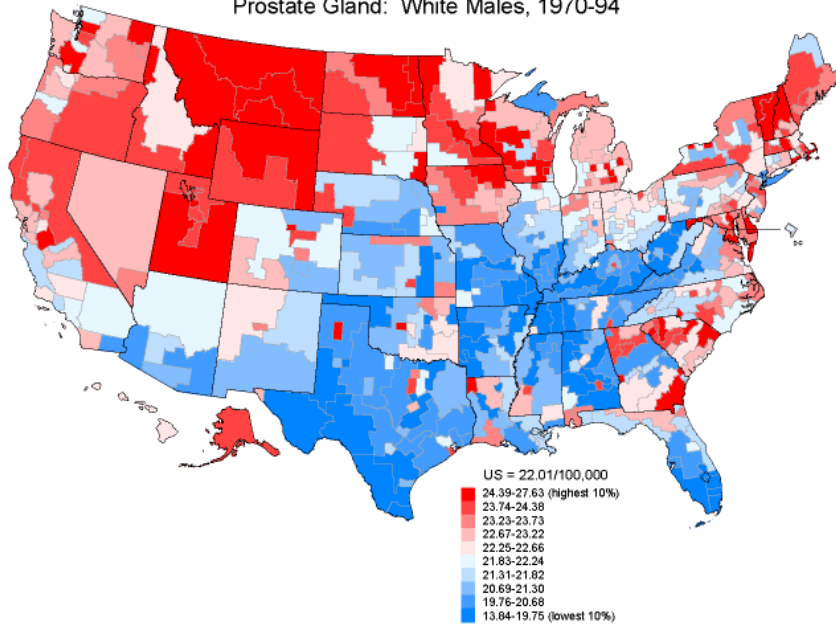


Colon

# Prostate Cancer and Ancestry



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



# Prostate Cancer – Multi-Country Ecological Study



- ★ Anticancer Res. 2010 Jan;30(1):189-99.
- ★ **A multicountry ecological study of risk-modifying factors for prostate cancer: apolipoprotein E epsilon4 as a risk factor and cereals as a risk reduction factor.**
- ★ [Grant WB.](#)
- ★ This work proposes and examines the hypothesis that the apolipoprotein E epsilon4 (ApoE4) allele and diet are important risk factors for prostate cancer. The hypothesis was evaluated in an ecological study involving 122 countries for which prostate cancer rates for 2002, ApoE4 allele prevalence, dietary supply values, and per capita gross domestic product (GDP) data were available. In addition, a subset of 102 countries with ApoE4 prevalence of less than 30% was also used.

# Results



- ★ In the full data set, per capita GDP, lack of cereal consumption, milk protein and ApoE4 were significantly correlated with incidence, explaining 60% of the variance.
- ★ In the 102-country subset of 102, per capita GDP, ApoE4 prevalence, and milk protein explained 62% of the variance of prostate cancer incidence, while lack of cereal consumption, ApoE4 prevalence and per capita GDP explained 55% of the variance of prostate cancer mortality rates.

# Interpretation




- ★ Cholesterol has been identified as an important risk factor for prostate cancer. The ApoE4 allele increases cholesterol production and cereal consumption lowers serum cholesterol levels.
- ★ The ApoE4 allele is an important risk factor for Alzheimer's disease, and cholesterol is a risk factor and cereals a risk reduction factor.
- ★ The ApoE4-diet-GDP hypothesis may explain the higher risk of prostate cancer for African Americans and should form the basis for further studies.

## Prediagnostic Plasma Vitamin D Mortality among Patients with Prostate Cancer

- ★ In models adjusted for age at diagnosis, BMI, physical activity, and smoking, we observed a HR of 1.22 (95% CI: 0.97, 1.54) for total mortality, comparing men in the lowest to the highest quartile of 25(OH)D. Men with the lowest 25(OH)D quartile were more likely to die of their cancer (HR: 1.59; 95% CI: 1.06, 2.39) compared to those in the highest quartile (P(trend)=0.006).
- ★ This association was largely explained by the association between low 25(OH)D levels and advanced cancer stage and higher Gleason score, suggesting that these variables may mediate the influence of 25(OH)D on prognosis.
- ★ Fang et al., PLoS One. 2011 Apr 6;6(4):e18625.



# Do UVB and Vitamin D Satisfy the Criteria for Causality for Cancer?



- ★ The criteria for causality in a biological system developed by the highly regarded British statistician and epidemiologist A. Bradford Hill, [1965] include:
  - ★ 1. Strength of association
  - ★ 2. Consistency (repeated observation)
  - ★ 3. Biological gradient (dose–response relation)
  - ★ 4. Plausibility (e.g., mechanisms)
  - ★ 5. Coherency (no serious conflict with the generally known facts)
  - ★ 6. Experimental verification (e.g., randomized, controlled trial)
  - ★ 7. Analogy



## Criteria for Causality - 2



- ★ My answer: yes, for over a dozen types of cancer.
- ★ W. B. Grant, How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? An examination using Hill's criteria for causality. *Dermato-Endocrinology* 2009;1(1):17-24

## Vitamin D and Cancer, Conclusion



- ★ The UVB-Vitamin D-cancer hypothesis generally satisfies the criteria for causality for a number of cancers.
- ★ Serum 25(OH)D levels above 75-100 nmol/L may provide reasonable protection against many types of cancer.
- ★ 2413 papers with vitamin D and cancer in the title or abstract are listed at [www.pubmed.gov](http://www.pubmed.gov) (May 10, 2011)

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

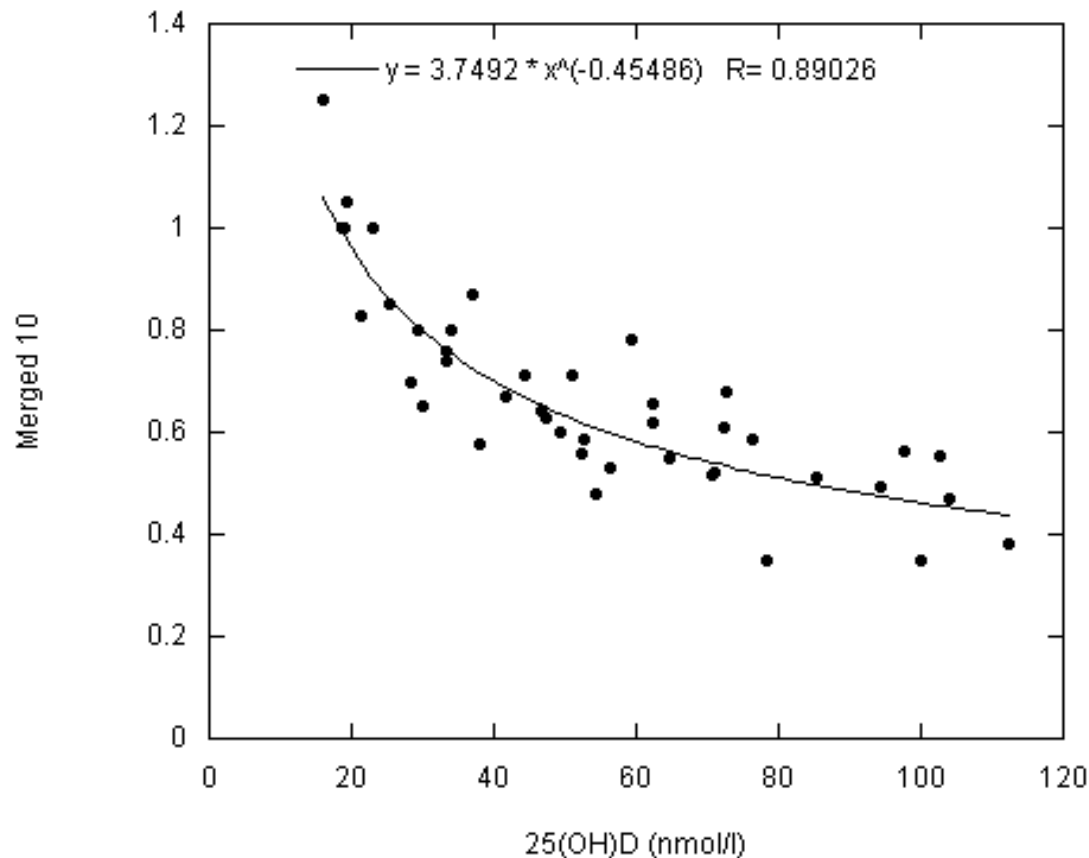
| <b>Disease</b>                 | <b>Deaths/yr<br/>(x1000)</b> | <b>Vitamin D (%)</b> | <b>Reduced<br/>(x1000)</b> |
|--------------------------------|------------------------------|----------------------|----------------------------|
| <b>Cardiovascular diseases</b> | 4,767                        | 25                   | 1,192                      |
| <b>Malignant neoplasms</b>     | 1,862                        | 25                   | 491                        |
| <b>Respiratory diseases</b>    | 374                          | 10                   | 37                         |
| <b>Respiratory infections</b>  | 244                          | 30                   | 73                         |
| <b>Diabetes mellitus</b>       | 399                          | 25                   | 100                        |
| <b>Alzheimer's disease</b>     | 137                          | 15                   | 21                         |
| <b>Tuberculosis</b>            | 78                           | 40                   | 31                         |

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

| <b>Disease</b>       | <b>Deaths/yr<br/>(x1000)</b> | <b>Vitamin D (%)</b> | <b>Reduced<br/>(x1000)</b> |
|----------------------|------------------------------|----------------------|----------------------------|
| Falls,<br>fractures  | 79                           | 25                   | 20                         |
| Parkinson's          | 29                           | 15                   | 4                          |
| Meningitis           | 11                           | 30                   | 3                          |
| Multiple scler       | 8                            | 60                   | 5                          |
| Total,<br>Vitamin D  | 7,744                        | 26                   | 1,977                      |
| Total, All<br>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 and indirect costs for health care may drop by 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 Health Conditions



- ★ I have a project for Dr. John Cannell, Vitamin D Council, to produce documents on the health benefits of sunlight and vitamin D for approximately 100 types of health conditions.
- ★ Most of the conditions 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.
- ★ 75 documents are due to go online TODAY, May 18, at [www.vitamindcouncil.org](http://www.vitamindcouncil.org).

## Additional Resources



- ★ <http://www.grassrootshealth.net/>
- ★ <http://www.healthresearchforum.org.uk/>
- ★ <http://www.pubmed.gov>
- ★ <http://www.sunarc.org/>
- ★ <http://www.vitamindcouncil.org/>
  
- ★ For a copy of this presentation,  
[wbgrant@infionline.net](mailto:wbgrant@infionline.net)