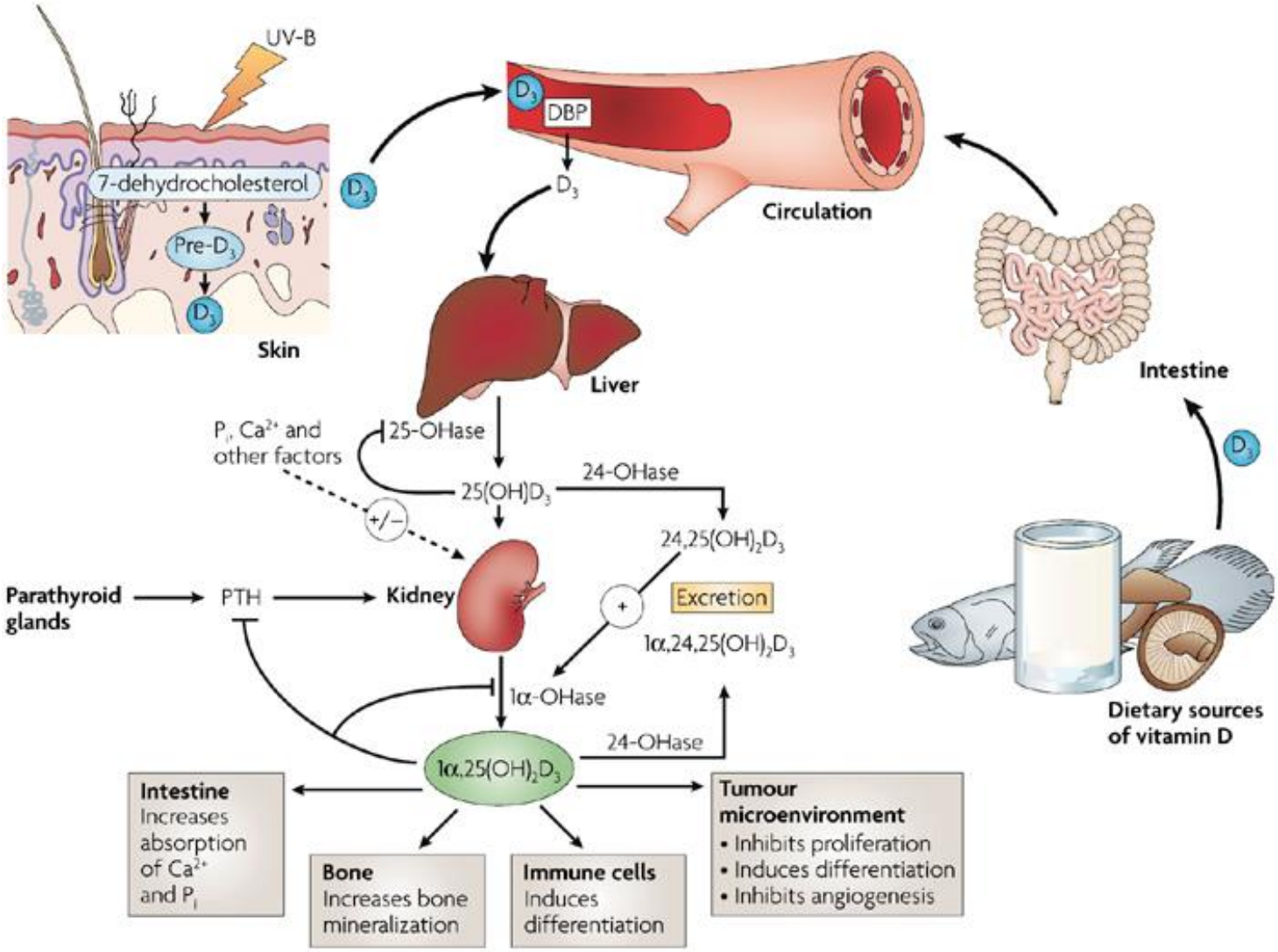
Metabolism of vitamin D



National Nutrition Survey dietary intake data were analysed for vitamin D in 1992. The main sources of dietary vitamin D intake in 1992 were margarine, fish, eggs and milk (LINZ 1992).

Nature Reviews | Cancer

Genetic Determinants of Vitamin D Status

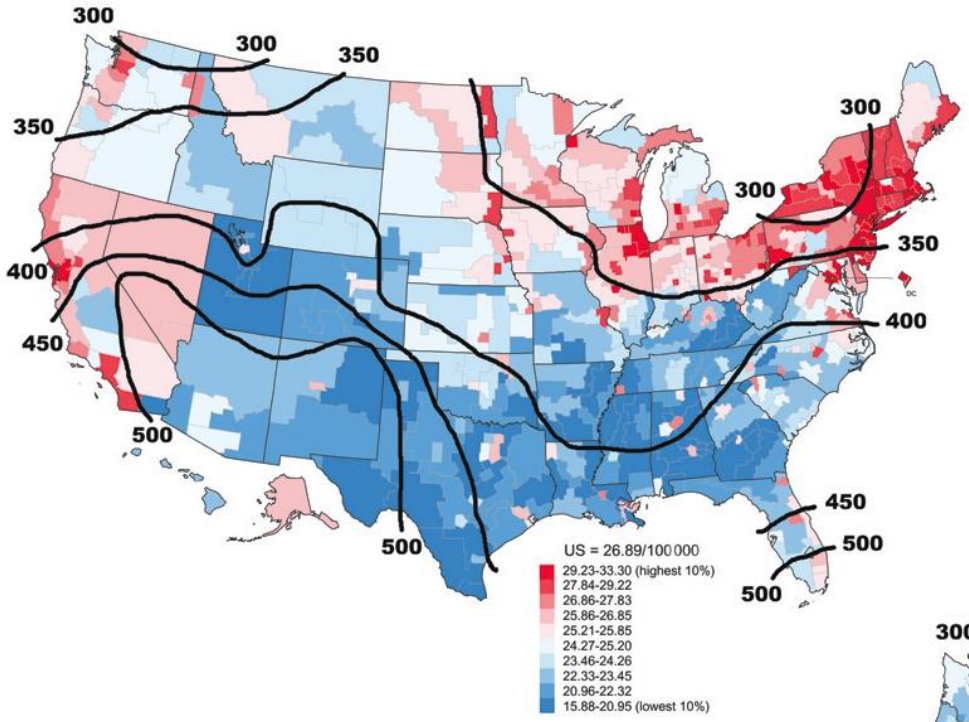
Wang et al [2010, PMID: 20541252]:

- 30,000 Caucasian subjects from 15 major cohorts (Europe, N. America)
- Show that 25OHD concentration is modulated by 4 genes encoding for:
  - **7-dehydro cholesterol (7-DHC) reductase**
    - responsible for skin 7-DHC availability, removes substrate from the vitamin D synthetic pathway
  - **liver 25-hydroxylase (CYP2R1)**
    - microsomal enzyme for conversion of vitamin D to 25OHD
  - **vitamin D binding protein (GC gene)**
    - hepatic transport protein for vitamin D and metabolites
  - **24-hydroxylase (CYP24A1)**
    - key enzyme in degradation of 25OHD and $1,25(OH)_2D$
- Combination of harmful alleles double risk of vitamin D insufficiency
  - what degree of variation in 25OHD level is due to genetic variation?
  - alter observed associations with disease risk?

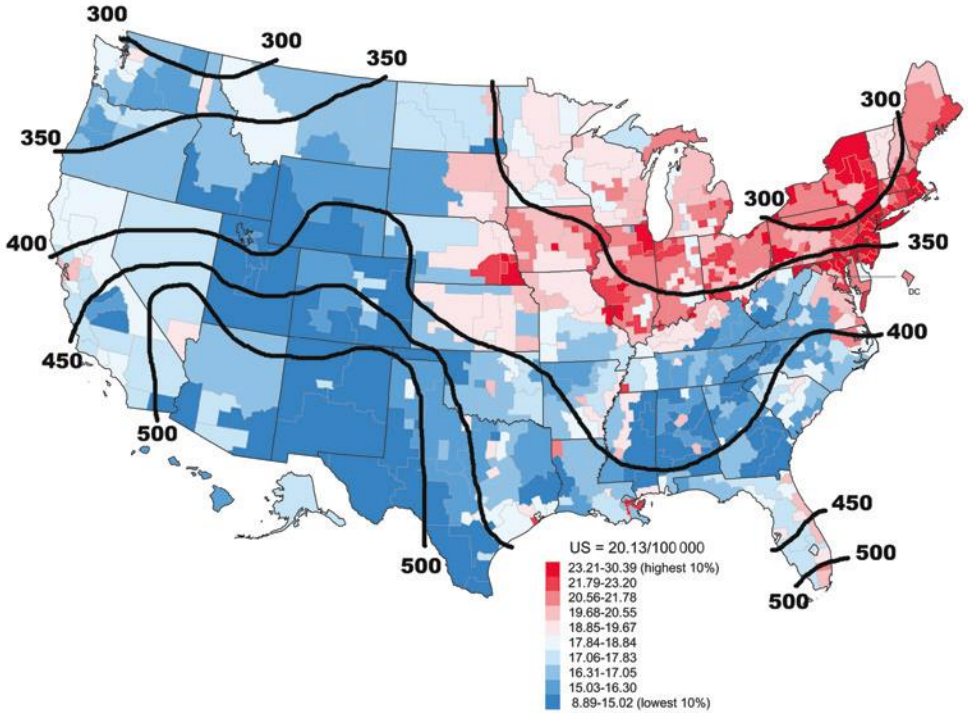
Other Factors that Affect Vitamin D Status

Sex	**Women lower vs. men**
Body weight / obesity	**Inverse association**
Skin pigmentation / ethnicity	**Lower with darker skin**
Age	**Lower with age**
Degree of sun exposure	**Lower with less exposure**
Physical / outdoor activity	**Lower with less activity**
Sunscreen use	**Inverse association**
Type, extent of clothing / veiling	**Inverse association**
Smoking	**Inverse association**
Medical conditions requiring reduced sun exposure (e.g. xeroderma pigmentosum)	**Lower**
Some medications	**Lower**
Intestinal absorption disorders	**Lower**

Reference: IARC. Vitamin D and Cancer. IARC Working Group Reports Vol.5, International Agency for research on Cancer, Lyon, 25 November 2008

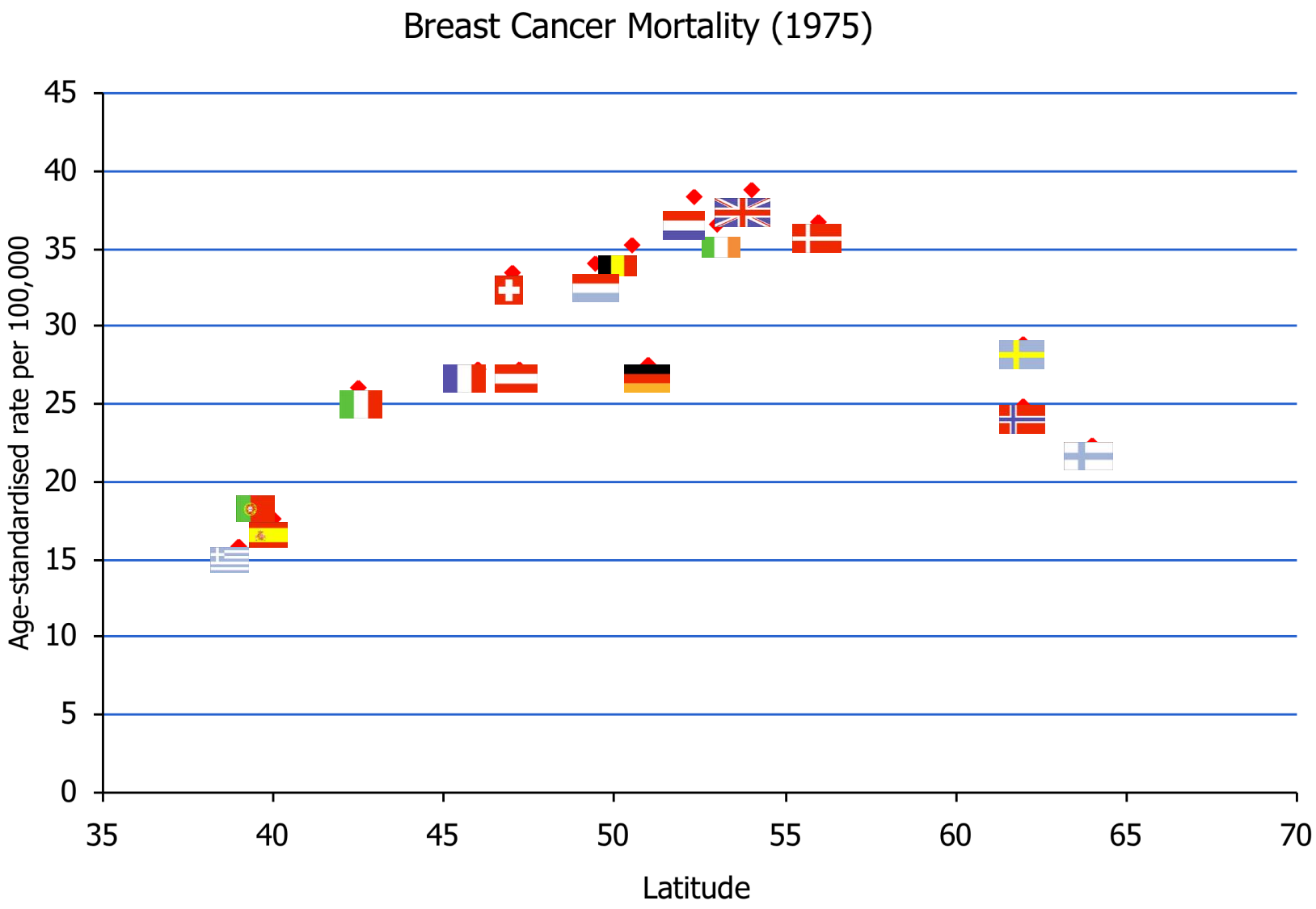


Age-adjusted colon cancer mortality rates by county area and contours of annual mean daily solar irradiance (Calories/cm2), USA, 1970-1994



Breast cancer…

Garland & Garland *Am J Public Health*, 2006;96:252-261


Breast Cancer Mortality (1975)
Age-standardised rate per 100,000
45
40
35
30
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45
50
55
60
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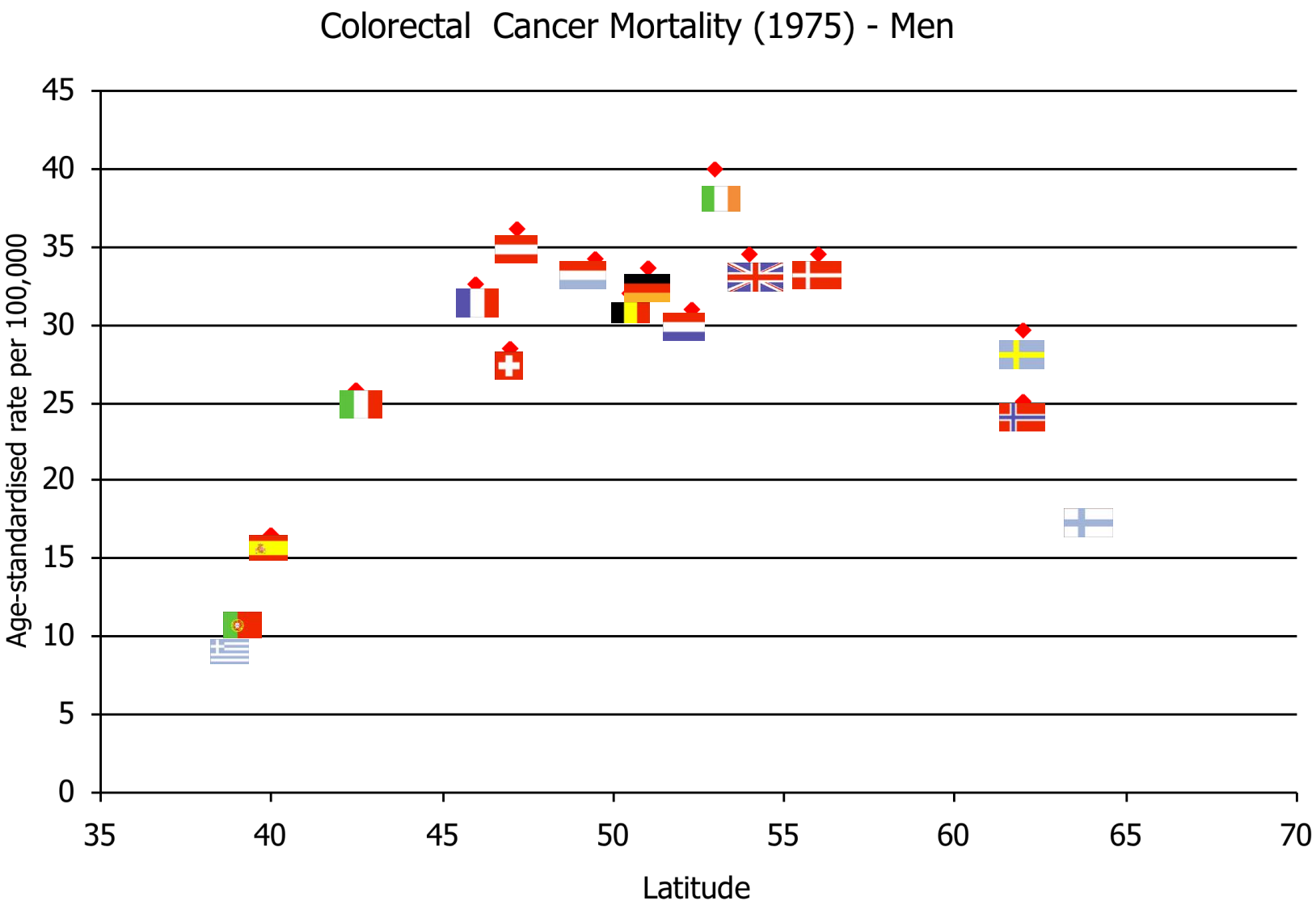
Latitude


Colorectal Cancer Mortality (1975) - Men
Age-standardised rate per 100,000
0
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30
35
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45
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40
45
50
55
60
65
70
Latitude

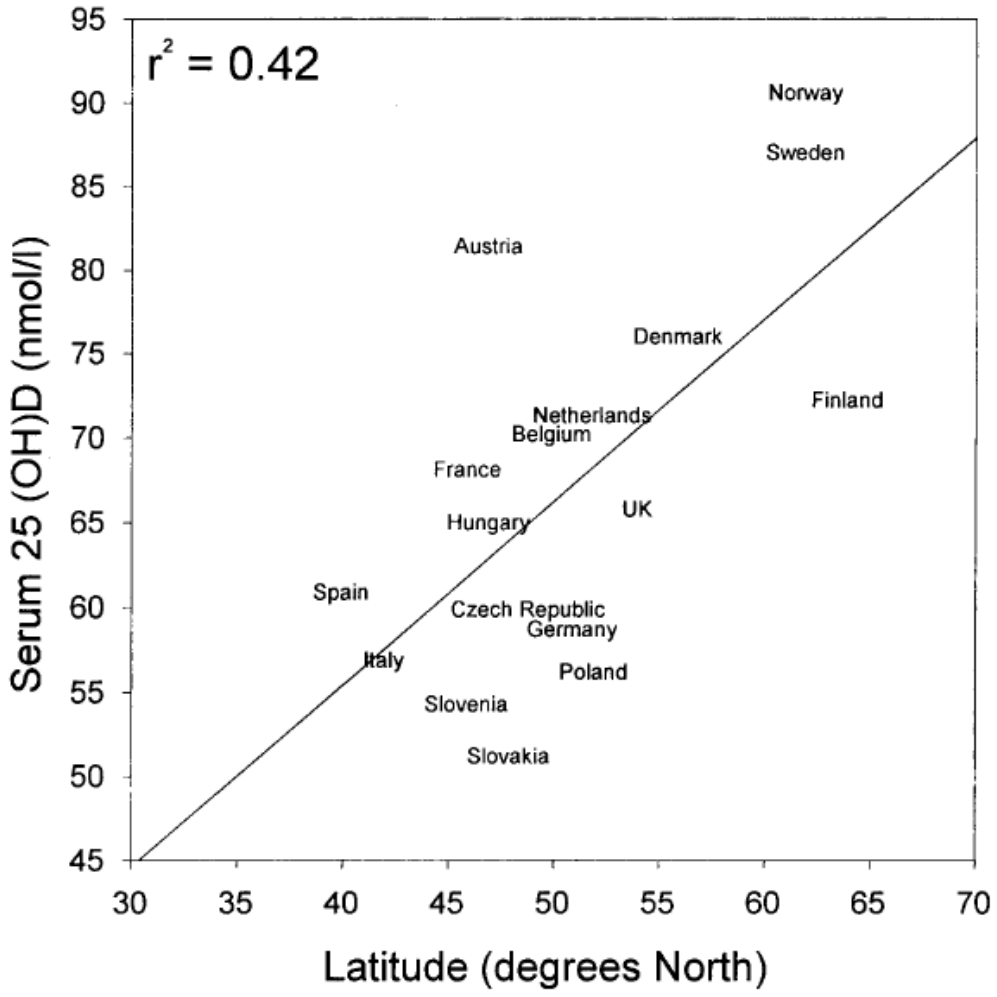

FIG. 2. Relationship between the serum 25OHD concentration and northern latitude in Europe. The relationship was very significant ($P < 0.001$).

Ogbah et al. BMC Medical Genetics 2013, 14:26
http://www.biomedcentral.com/1471-2350/14/26

BMC Medical Genetics

RESEARCH ARTICLE Open Access

Serum 25-hydroxyvitamin D3 levels and vitamin D receptor variants in melanoma patients from the Mediterranean area of Barcelona

Zighereda Ogbah[1*], Laura Visa[1], Celia Badenas[2,3], José Ríos[4], Joan Anton Puig-Butille[2,3], Nuria Bonifaci[5], Elisabet Guino[5], Josep Maria Augé[2], Isabel Kolm[1], Cristina Carrera[1], Miquel Ángel Pujana[5], Josep Malvehy[1,2,3] and Susana Puig[1,2,3*]

68% of patients had insufficient levels of 25-hydroxyvitamin D3 (<25 ng/ml)

The authors concluded that,

Even in Barcelona, a sunny Mediterranean area, 25-hydroxyvitamin D3 levels were sub-optimal in the majority of melanoma patients at diagnosis.

The Vitamin D Receptor (VDR)

To what degree is the human genome regulated by vitamin D and the VDR?

- lymphoblastoid cells stimulated with 1,25(OH)$_2$D:
  - 229 genes with change in expression
  - 2,776 VDR binding sites, particularly around genes identified by GWAS for a role in various conditions and diseases, including cancer:

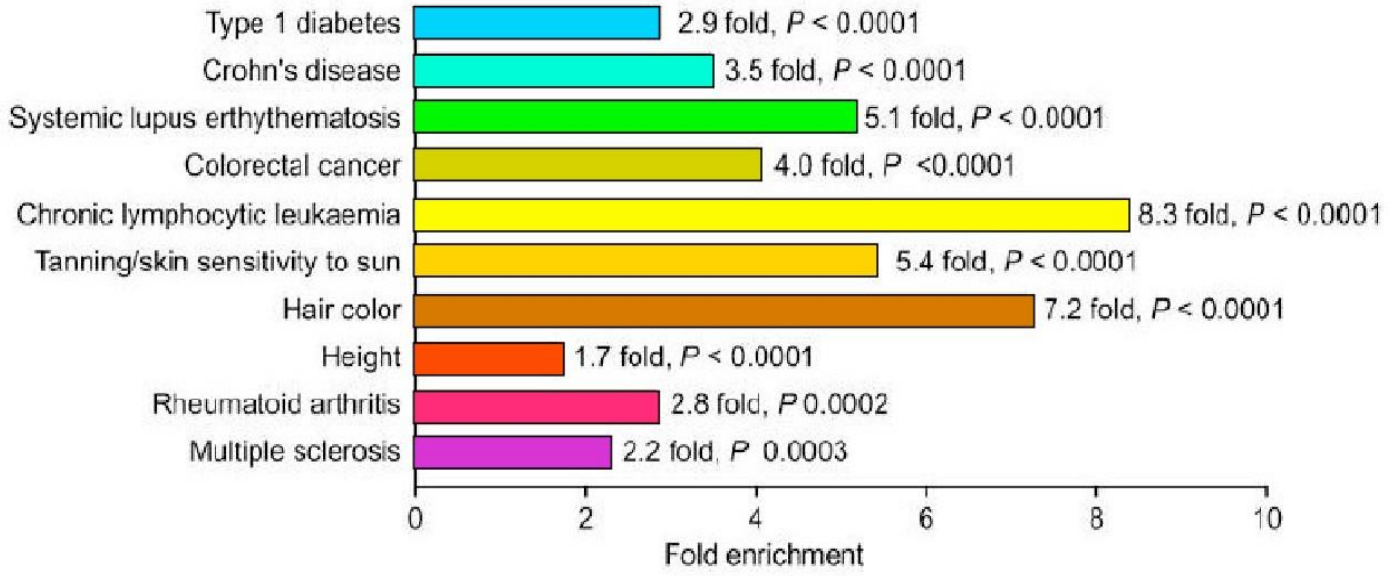

Figure 3. Common traits showing enrichment of VDR binding within intervals identified by GWAS. A total of 47 common diseases and traits were analyzed (see Methods and Supplemental Table 5) and those showing significant enrichment of VDR binding defined by ChIP-seq in two LCLs after calcitriol stimulation with a 1% FDR are shown.

Ramagopalan et al. Genome Res 2010; 20: 1352-60

Is the higher mortality in those with lowest level of Vitamin D because those that die in the follow-up period already have some chronic disease (detected or otherwise) with an associated increased localised VDR enrichment.

« Vitamin D inadequacy », a new story of disease mongering?

- Deficiency may exist in populations
- Evidence that deficiency of Vitamin D is a cause of disease in apparently healthy people is not at all proven.
- Many apparently healthy subjects living in sunny areas have low vitamin D status: why = ??

Vitamin D supplementation and total mortality – a meta-analysis of randomized controlled trials
Autier and Gandini (2007) Arch Intern Med 167:1730

RR for total mortality 0.93 (95%CI 0.87-0.99)

IARC Working Group

Working Group Membership

Michaël John Barry	Massachusetts General Hospital, Harvard Medical School	USA (chair)
Esther De Vries	Erasmus MC	The Netherlands
Dallas English	University of Melbourne	Australia
Edward Giovannucci	Harvard School of Public Health	USA
Bodo Lehmann	Medical School "Carl Gustav Carus, Dresden Univ. of Tech.	Germany
Henrik Møller	King's College London, School of Medicine	UK (co-chair)
Paola Muti	Italian National Cancer Institute "Regina Elena,"	Italy
Eva Negri	Istituto di Ricerche Farmacologiche "Mario Negri,"	Italy
Julian Peto	London School of Hygiene and Tropical Medicine	UK
Arthur Schatzkin	National Cancer Institute, Bethesda	USA
Lars Vatten	Norwegian University of Science and Tech., Trondheim	Norway
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Mathieu Boniol	IARC, Lyon	France
Graham Byrnes	IARC, Lyon	France
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Geneviève Deharveng	IARC, Lyon	France
Jean François Doré	INSERM + IARC, Lyon	France
Sara Gandini	European Institute of Oncology, Milano	Italy
Mary Heanue	IARC, Lyon	France
Mazda Jenab	IARC, Lyon	France
Patrick Mullie	Jules Bordet Institute, Brussels	Belgium
Mary Jane Sneyd	Otago Medical School, University of Otago	New Zealand

Observer

Tahera E. van Deventer	World Health Organization, Geneva	Switzerland

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global cancer control

IJC
International Journal of Cancer

Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma

Sara Gandini[1], Mathieu Boniol[2], Jarl Haukka[3], Graham Byrnes[4], Brian Cox[5], Mary Jane Sneyd[5], Patrick Mullie[6] and Philippe Autier[2]

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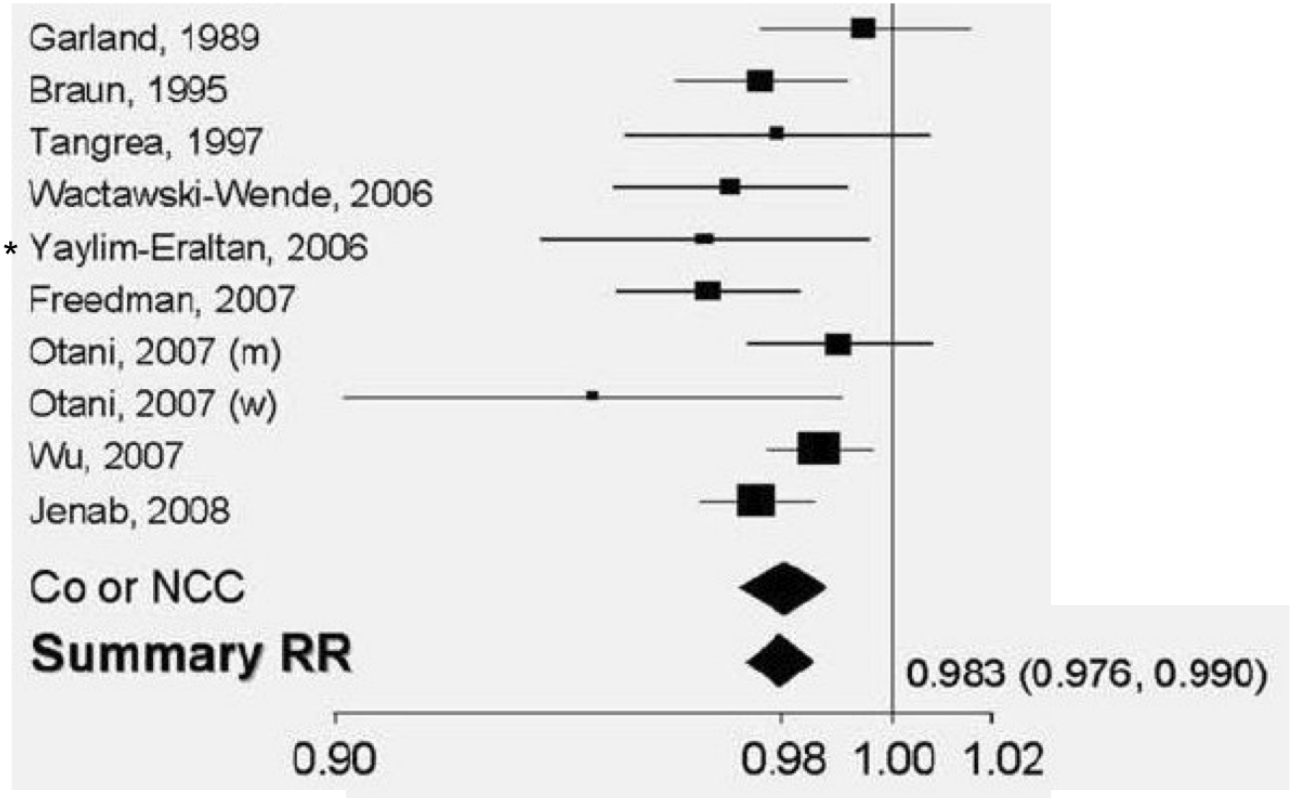
[5] Hugh Adam Cancer Epidemiology Unit, Dunedin School of Medicine, University of Otago, New Zealand
[6] Department of Nutrition, Preventive Medicine and Leuven Food Science and Nutrition Research Centre (LFoRCe), Catholic University Leuven, Leuven, Belgium

Vitamin D and Colorectal Cancer: Epidemiologic Evidence

RR for 1ng/ml (2.496 nmol/l) increase in blood 25OHD concentration:

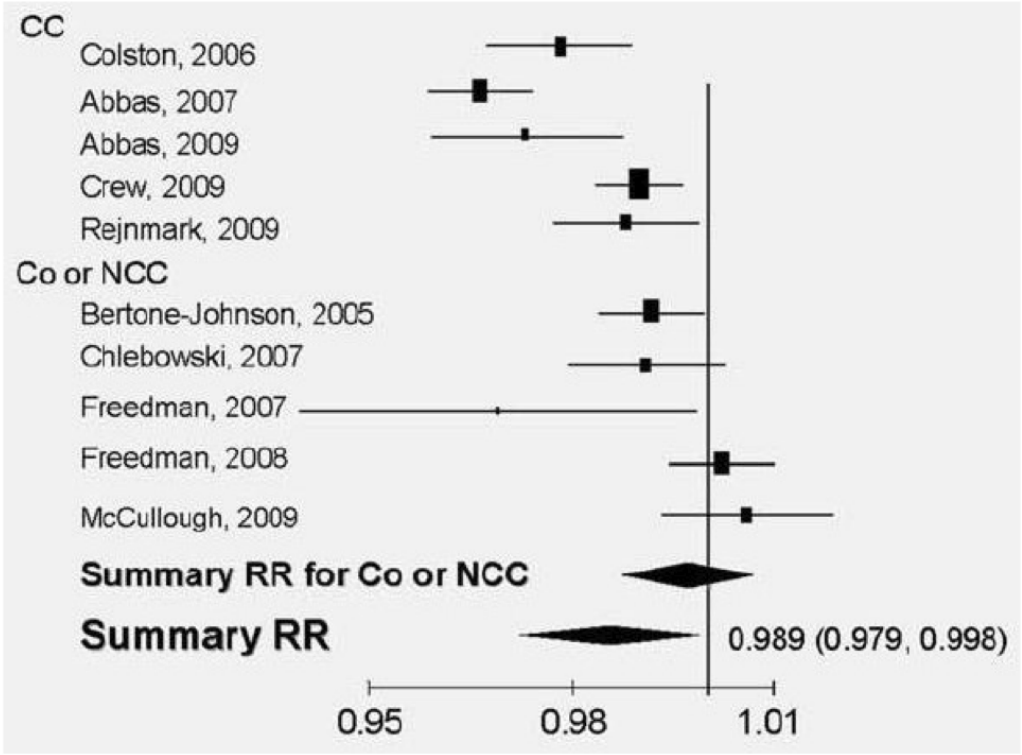


Country
USA
USA
Finland
USA
Turkey
USA
Japan
USA
Europe

Reference: Gandini, S, 2010, PMID: 20473927

Vitamin D and Breast Cancer: Epidemiologic Evidence

RR for 1ng/ml (2.496 nmol/l) increase in blood 25OHD concentration:

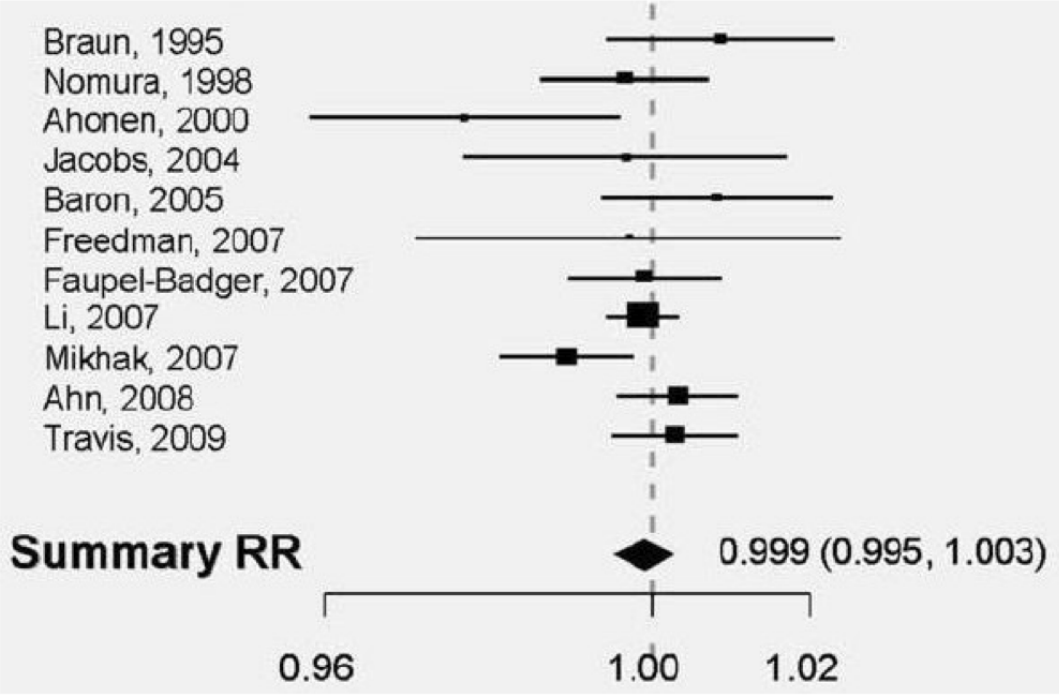


Country
UK
Germany
Germany
USA
Denmark
USA
USA
USA
USA
USA

Reference: Gandini, S, 2010, PMID: 20473927
Similar findings reported by: Yin, L et al, 2010, PMID: 20456946

Vitamin D and Prostate Cancer: Epidemiologic Evidence

RR for 1ng/ml (2.496 nmol/l) increase in blood 25OHD concentration:



Country
USA
USA
Finland
USA
Denmark
USA
Finland
USA
USA
USA
Europe

- All studies are cohort or nested case-control

Reference: Gandini, S, 2010, PMID: 20473927
Not included in above: Barnett, CM, 2010, PMID: 20383574, No prostate cancer risk association.

Meta-analysis

- Observational studies provide evidence for a decreased risk of colorectal cancer associated with higher serum 25(OH)Vitamin D.
- This evidence is supported by a decrease in colonic adenoma with higher serum 25(OH)Vitamin D.
- A non-significant decreased risk of breast cancer risk may be associated with higher serum 25(OH)Vitamin D, but study results are very heterogeneous. Further cohort studies are warranted.

Meta-analysis

- Observational studies provide no evidence for an association between higher serum 25(OH)Vitamin D and prostate cancer risk.

RCTs on vitamin D supplements and cancer

- Results from a meta-analysis including 18 randomized trials provided evidence that supplementation with vitamin D in the range of 400 to 600 IU par day could significantly decrease all-cause mortality.
- The contribution of specific causes of mortality in the reduction of all-cause mortality remains unknown.

RCTs on vitamin D supplements and cancer

- Reasons for discrepancies in the results from cohort studies and from randomized trials on vitamin D and colorectal cancer are not clear, but the hypothesis that vitamin D dosages and trial durations were too low merit further investigation.

Overall conclusions: non-cancer mortality

- Previous conclusions are consistent with the hypothesis that vitamin D supplementation may lower CRC, but also CVD and all-cause mortality. These hypotheses should be tested in appropriately designed RCTs.

Overall conclusions: adverse events

- Data are lacking on the hazards of maintaining healthy subjects with high 25(OH)D serum levels over long periods of time.
- Past experience with other compounds (eg, anti oxidants) has shown serious adverse effects of chronic use of supplements or long-term maintenance of high serum levels

Consensus Statement
on Vitamin D and Sun Exposure in New Zealand

MARCH 2012

MINISTRY OF HEALTH
MANATŪ HAUORA

Cancer Society

ARPC

25-hydroxyvitamin D blood levels

- In general, asymptomatic, at-risk people should be prescribed supplements without testing for 25-hydroxyvitamin D.
- There is consensus that 25-hydroxyvitamin D levels below 25 nmol/L are 'deficient'.

- Although no safe upper level of 25-hydroxyvitamin D has been identified, treatment to levels above 125 nmol/L is not recommended.

At-risk groups

- The following three groups are at a particularly **high** risk of vitamin D deficiency and negative health outcomes, and may require vitamin D supplementation:
    1. people with naturally very dark skin – this includes many people from Africa, the Indian subcontinent and the Middle East, especially if they are covered by veils and full-body-coverage clothing
    2. people who completely avoid sun exposure because they have had skin cancer, skin damage from the sun or are on photosensitising medications
    3. people with low mobility, who are frail or who are housebound either in residential care or living in the community, including people who are bed-ridden or chair-bound: adverse musculoskeletal outcomes include musculoskeletal pain and osteomalacia.
- People who live in the cooler, southern regions **and** spend little time outdoors in the middle of the day between May and August (with mostly only their face and hands exposed) may be at risk of vitamin D deficiency and may wish to consider vitamin D supplementation during those months.
- People who have liver or kidney disease, or are on certain medications that affect vitamin D levels may also be at risk of vitamin D deficiency.

Supplementation

- For the bulk of the population with no specific medical issues or risk factors for vitamin D deficiency (as identified above), supplementation is not necessary and not recommended. There is no conclusive evidence that supplementing with vitamin D is beneficial for the general population.
- At-risk groups (as identified above) may benefit from vitamin D supplementation.

- There are a number of contraindications and precautions for vitamin D supplements. Supplementation is generally not recommended when hypercalcaemia, hypervitaminosis D or renal osteodystrophy with hyperphosphatemia is present. Care should be taken when considering supplementation in the presence of atherosclerosis or cardiac function impairment, hypersensitivity to vitamin D, renal function impairment, or sarcoidosis.

Should concerns about vitamin D status lead to relaxing sun protection recommendations?

Should concerns about vitamin D status lead to relaxing sun protection recommendations?

No!