Evidence That UVB and Vitamin D Reduce the Risk of Cancer Incidence and Death

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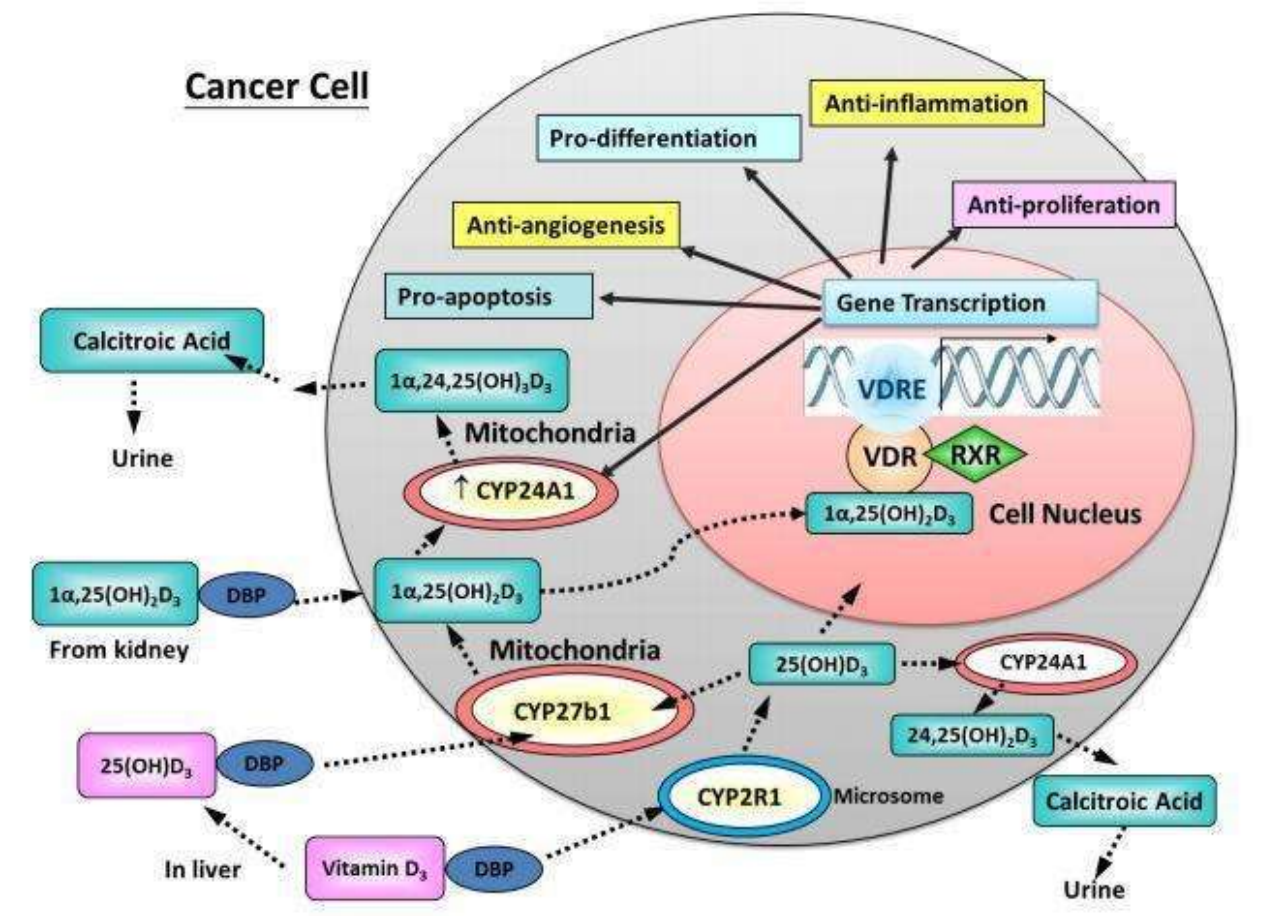
Disclosure

- I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR), a supplier of research-grade vitamin D at low cost.

Outline

- Mechanisms include cellular effects, anti-angiogenesis and anti-metastasis mechanisms
- Solar UVB and vitamin D reduce risk of 15-20 types of cancer.
- Evidence comes from:
  - Ecological studies (historically very important)
  - Observational studies
  - Vitamin D supplementation studies
  - Studies of mechanisms of vitamin D
- Treatment with vitamin D
- Recommendations

Vitamin D and Cancer



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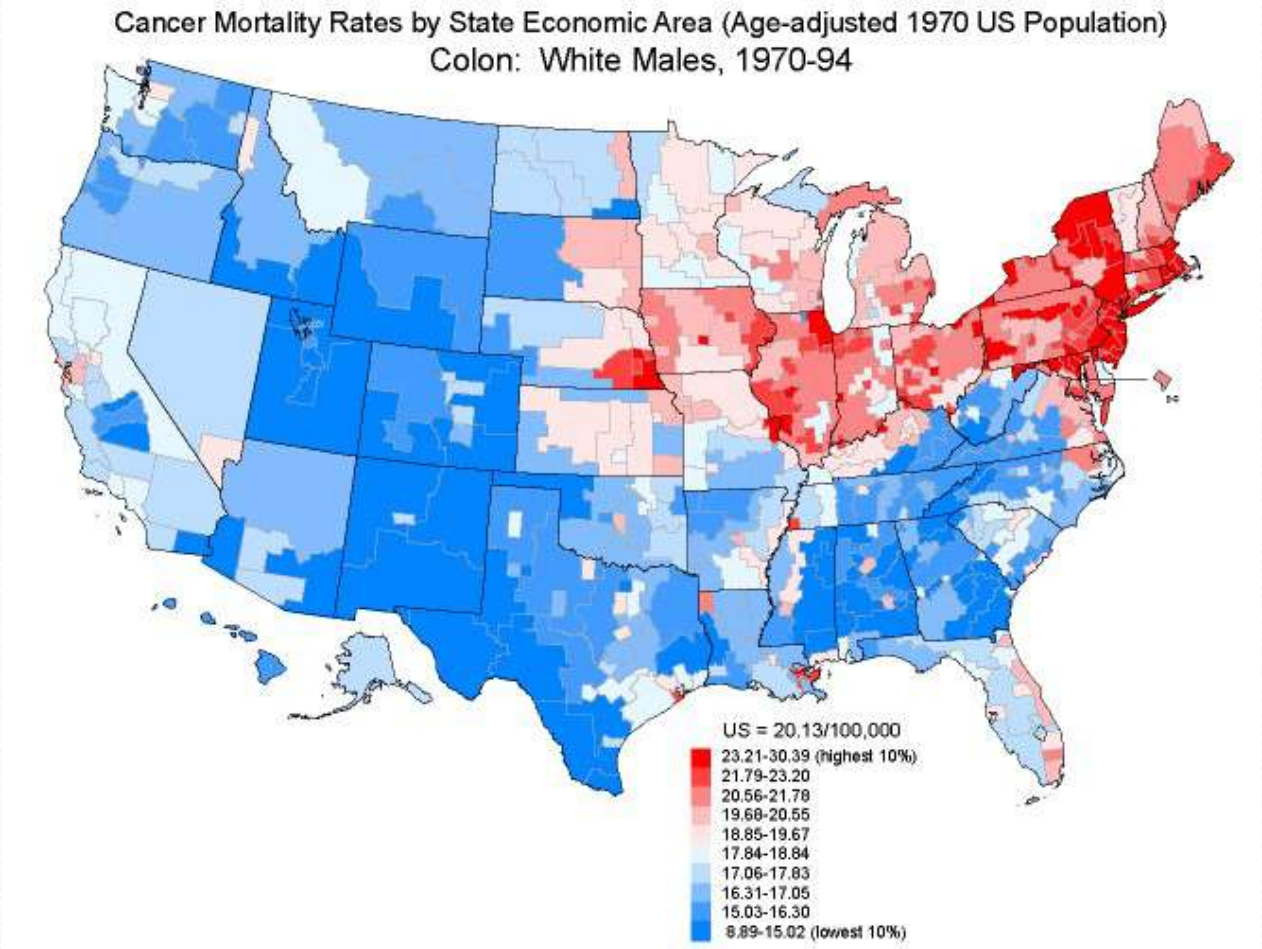
Geographical Ecological Studies

- Such studies group populations by geographical region and use population-averaged values for health outcomes and risk-modifying factors such as indices for solar UVB doses, urban/rural residence, smoking, alcohol consumption, ethnic background, and income.
- This approach revealed some relationships between UVB doses and cancer mortality rates and was used to develop the hypothesis that UVB exposure and vitamin D reduce the risk of cancer.
- Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol. 1980 Sep;9(3):227-31.

Colorectal Cancer Mortality Rates, White Males, 1970-94

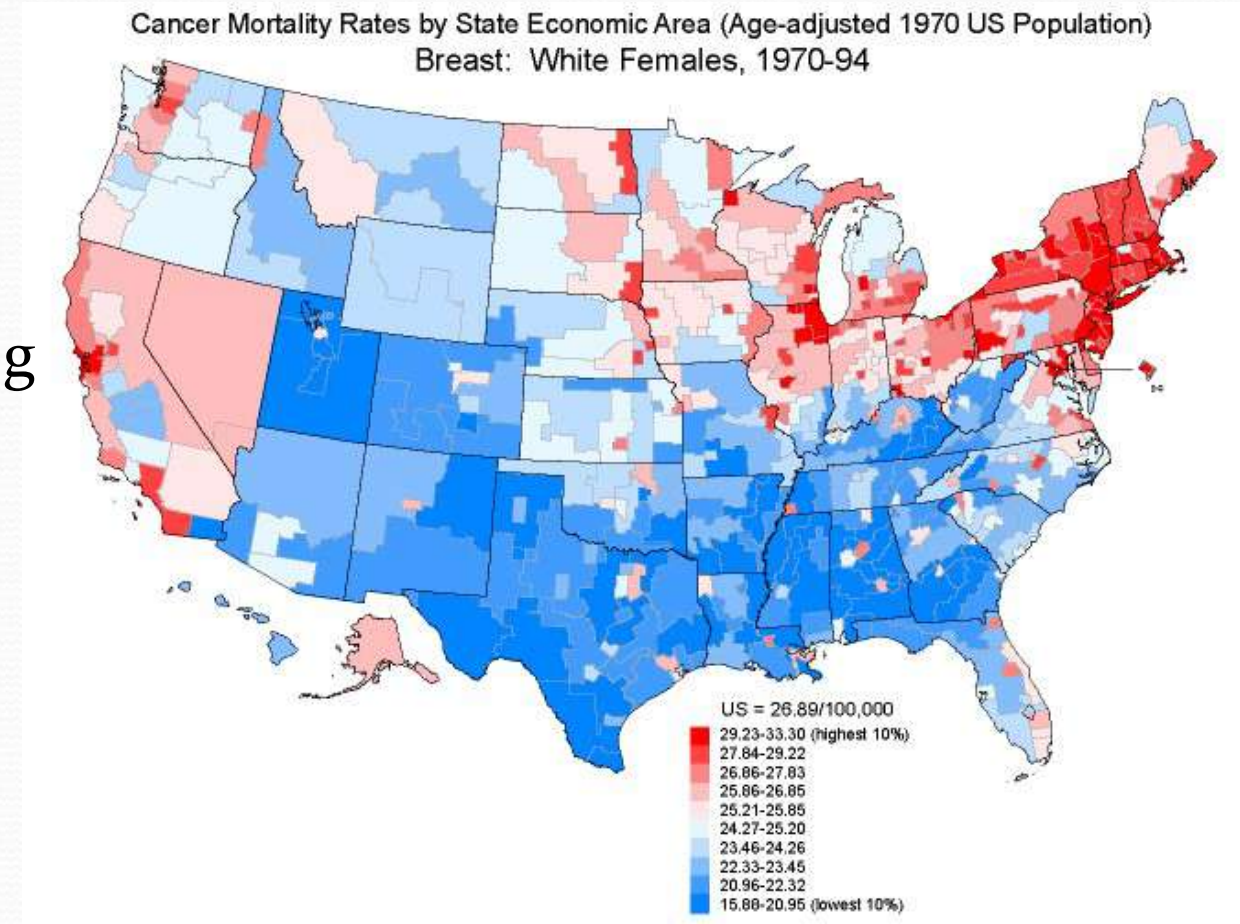


Garland et al., Am J Public Health. 2006

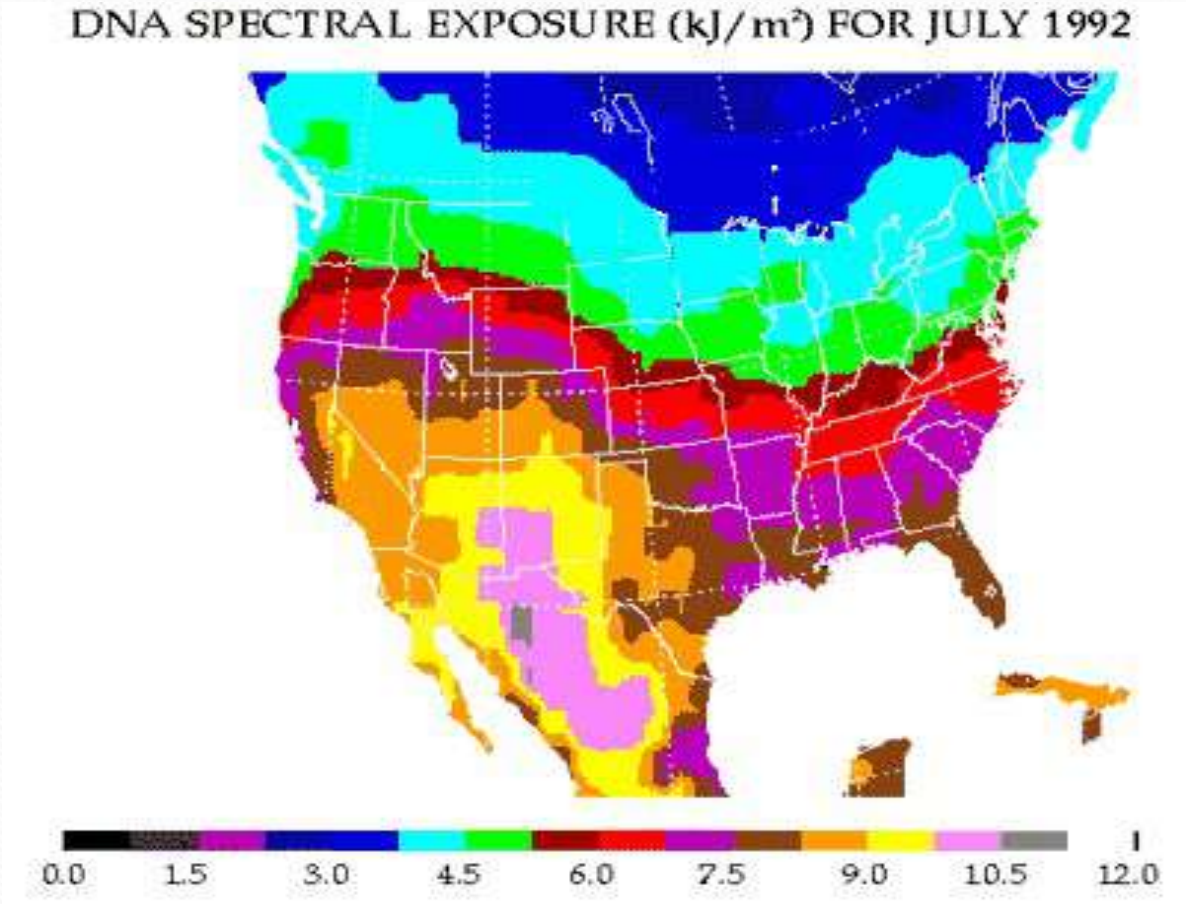
The brothers Cedric and Frank Garland published their seminal paper in 1980

Breast Cancer Mortality Rates, White Females, 1970-94

Effect of fog & clouds along the coast



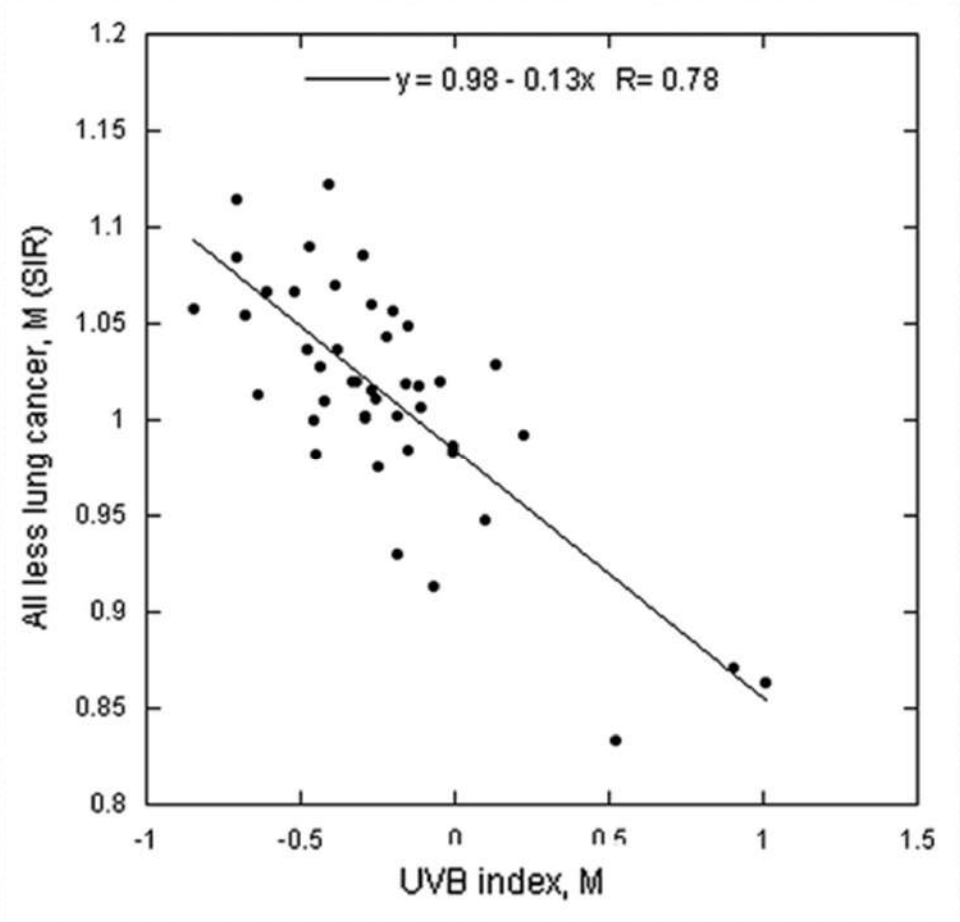
Solar UVB Doses, July 1992



High doses in SW due to thinner stratospheric ozone
layer and higher surface elevation.

Data from the NASA Total Ozone Mapping Spectrometer (TOMS)

Role of solar UVB irradiance in cancer incidence rates by occupation in Nordic countries



Grant. Darmato-Endocrinology 2012 https://is.gd/mSabWu

Farmers, forestry workers, and gardeners.

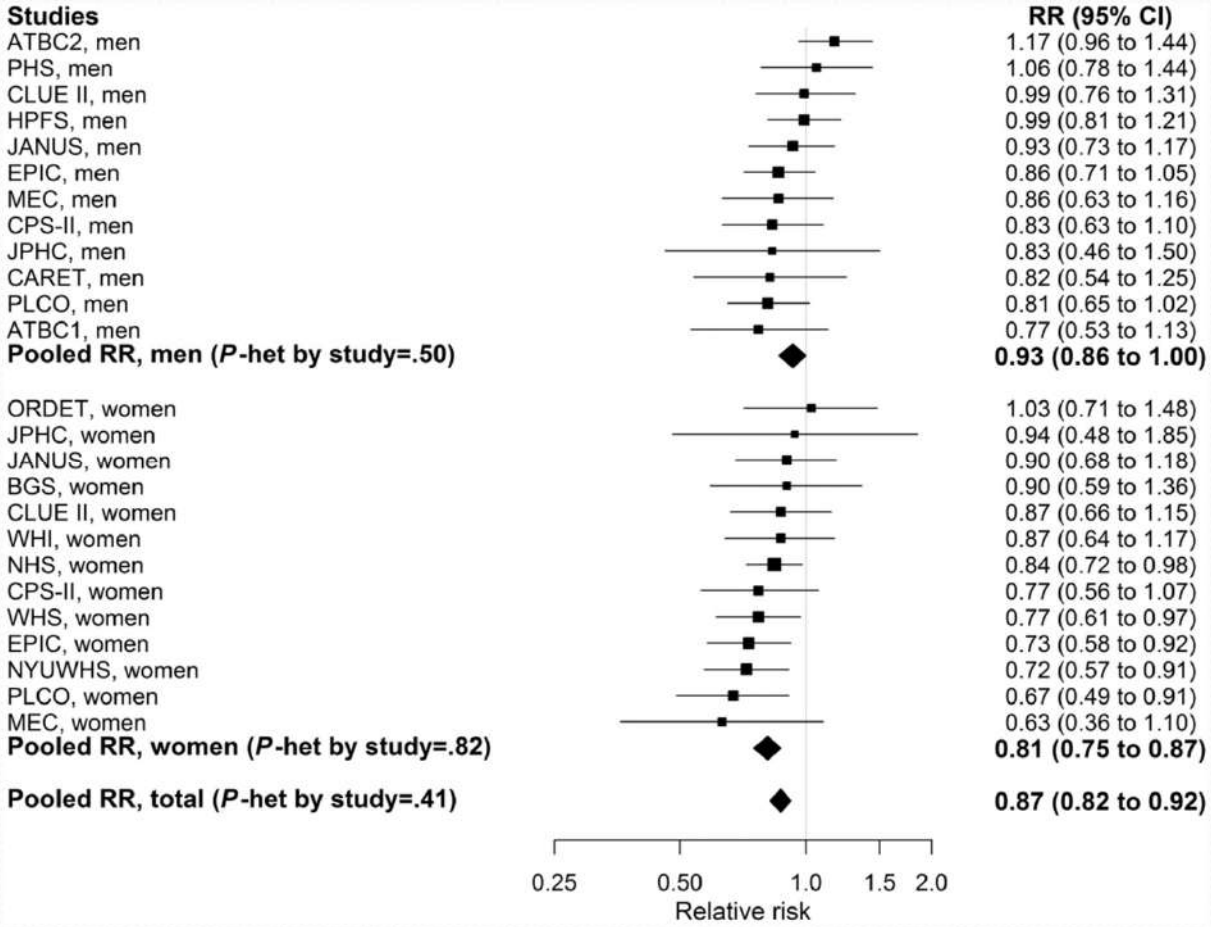
Cancers with Incidence and/or Mortality Rates Inversely Correlated with Solar UVB Indices

- The best ecological studies are from single mid-latitude countries: Australia, China, France, Japan, Spain, and the U.S.
- Cancer types: Bladder, breast, colon, endometrial, esophagus, gallbladder, leukemia, lung, non-Hodgkin's lymphoma, oral, ovary, pancreas, prostate, rectum, stomach, vulva

Prospective Observational Studies

- In prospective studies, variables including 25(OH)D are measured at time of enrollment.
- An important problem is that serum 25(OH)D may change due to supplementation, time spent in the sun, and age, observed correlations with health outcomes decrease with increasing follow-up time.
- Also, serum 25(OH)D changes seasonally, so unless seasonal adjustments are made, the 25(OH)D values may not be appropriate.

Meta-analysis of High vs. Low 25(OH)D for Colorectal Cancer



McCullough et al. JNCI: Volume 2019;111:158-169. https://is.gd/gYo7hb

Meta-analysis of Colorectal Cancer Incidence vs. 25(OH)D

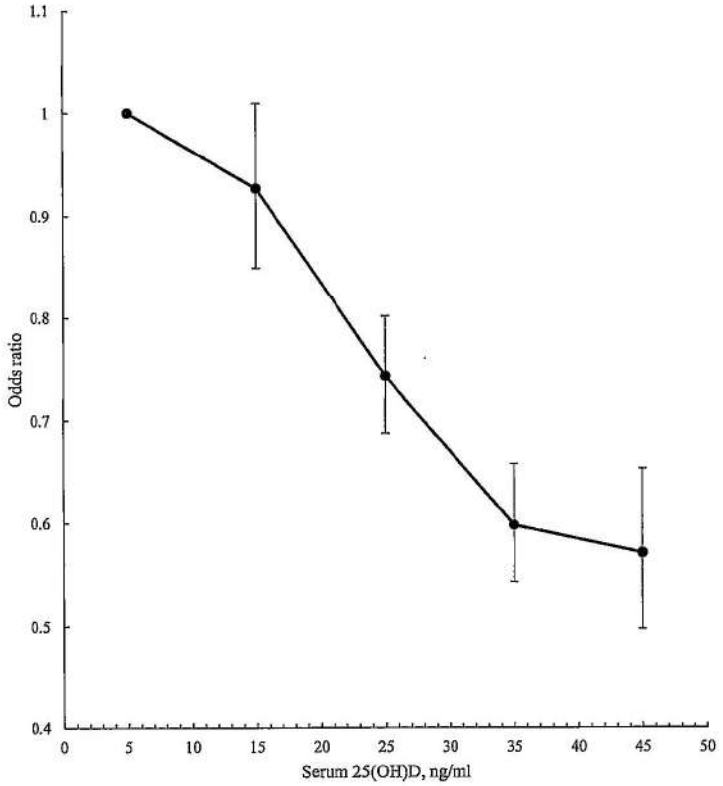
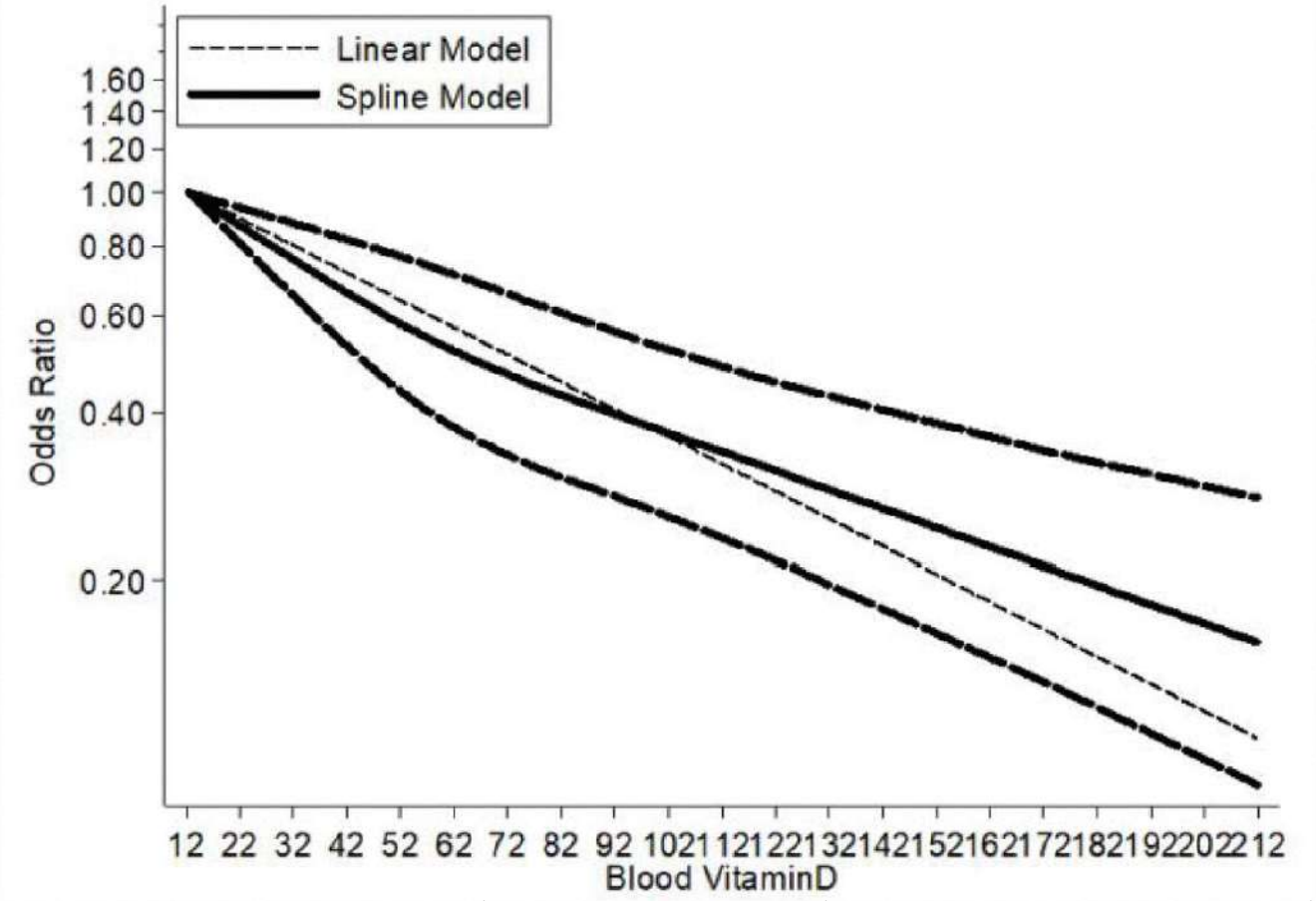


Fig. 1. The pooled dose-response curve for the 15 studies showed lower risk of colorectal cancer in association with higher 25-hydroxyvitamin D concentration

Garland CF, Gorham ED. Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: A meta-analysis. J Steroid Biochem Mol Biol. 2017;168:1-8. https://is.gd/oRme45

Breast Cancer Incidence with 25(OH)D from 36 Case-Control and 4 Cohort Studies [Song, *Aging*, 2019] https://is.gd/CxYhbG

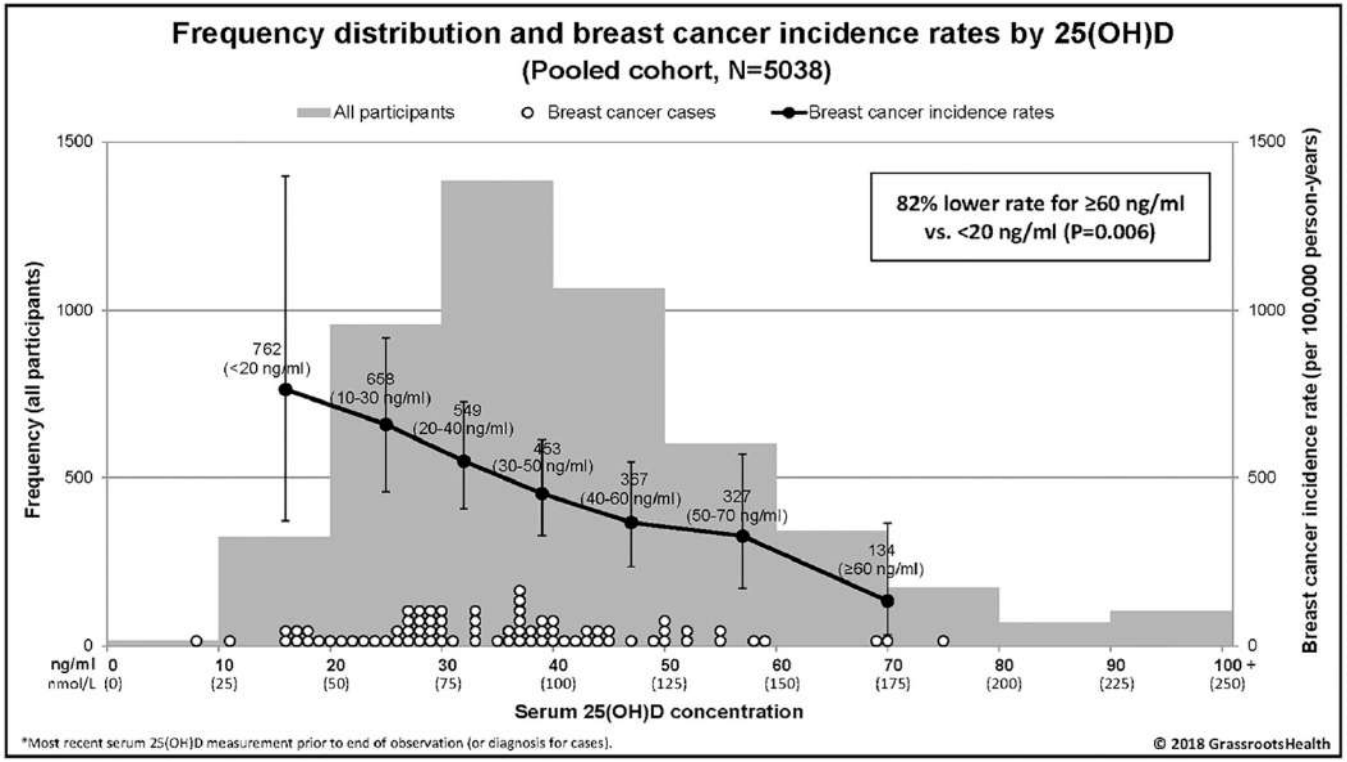


nmol/L 40 ng/ml 85 ng/ml

Pooled Results Based on Vitamin D Supplementation and 25(OH)D

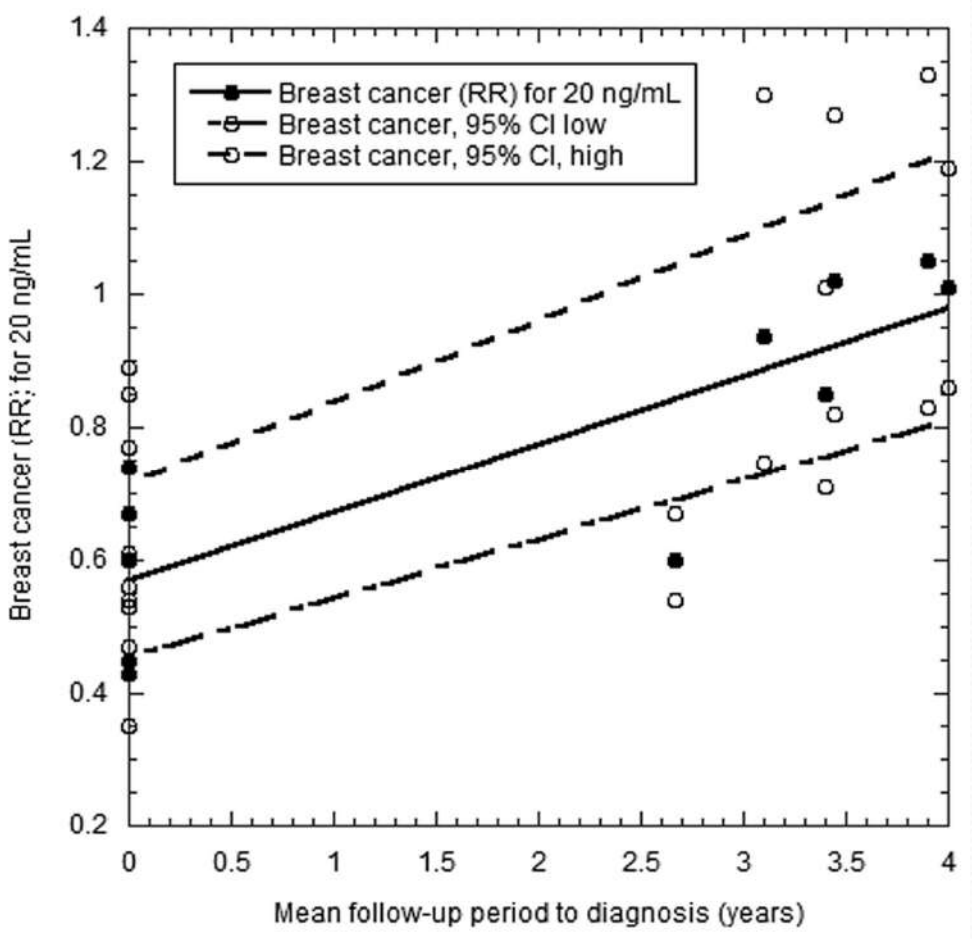
- GrassrootsHealth.net has published several papers pooling individual participant data for 25(OH)D measured frequently in comparison with outcomes for cancer and pregnancy.
- This approach is better than relating outcomes to vitamin D dose since both health outcomes are related to 25(OH)D concentration, not vitamin D dose.

Breast Cancer Risk Markedly Lower with Serum 25(OH)D ≥60 ng/ml



Combined results from two RCTs (Lappe [2007], [2017]) and community-based volunteers. McDonnell et al. PLoS One, 2018. https://is.gd/r7AN9H

Effect of Follow-up Time on Odds Ratio for Breast Cancer



Grant, Anticancer Res 2015
https://is.gd/aKDawo

Meta-analyses of Cancer vs. 25(OH)D

Cancer site	N studies, cases	Type of study	RR (95% CI) (high vs. low)	Reference
Bladder	5	cc	0.70 (0.56 to 0.88)	(Zhao, Chen et al. 2016)
Bladder	2	cohort	0.80 (0.67 to 0.94)	(Zhao, Chen et al. 2016)
Breast	44	cc	0.57 (0.48 to 0.66)	(Song, Deng et al. 2019)
Breast	6	cohort	1.17 (0.92 to 1.48)	(Song, Deng et al. 2019)
Colorectal	11	cc	0.60 (0.53 to 0.68)*	(Hernandez-Alonso, Boughanem et al. 2021)
Colorectal	6	cohort	0.80 (0.66 to 0.97)*	(Hernandez-Alonso, Boughanem et al. 2021)
Head & neck	5		0.68 (0.59 to 0.78)	(Pu, Zhu et al. 2021)
Liver	6		0.53 (0.41-0.68)	{Zhang Y, 2021}
Lung	8	cohort	0.72 (0.61 to 0.85)	(Liu, Dong et al. 2017)
NHL	30, 56,458		0.97 (0.82 to 1.15)	{Park, 2019}
Pancreatic	5	cohort, incidence	1.02 (0.66 to 1.57)	(Zhang, Huang et al. 2017)
Pancreatic	5	cohort, mortality	0.81 (0.68 to 0.96)	(Zhang, Huang et al. 2017)
Renal	5	4 cohort + 1 cc	0.76 (0.64 to 0.89)	(Wu, Yang et al. 2021)
Renal	1	cc	0.30 (0.13 to 0.72)	(Wu, Yang et al. 2021)
Thyroid	14		Deficiency 1.30 (1.00 to 1.69) P = 0.05	{Zhao, 2019

(*) fixed effects model; cc = case-control study

Cancers with Incidence Rates Inversely Correlated with 25(OH)D

- Meta-analyses: all, bladder, breast, colorectum, larynx, lung, thyroid.
- Aggressive prostate cancer but not non-aggressive prostate cancer.
  - Possibly due to increased calcium absorption; calcium is a risk factor for prostate cancer.
- Note: results for minor cancers are generally missing due to small numbers

Cancer Incidence vs. Survival: Role of Vitamin D

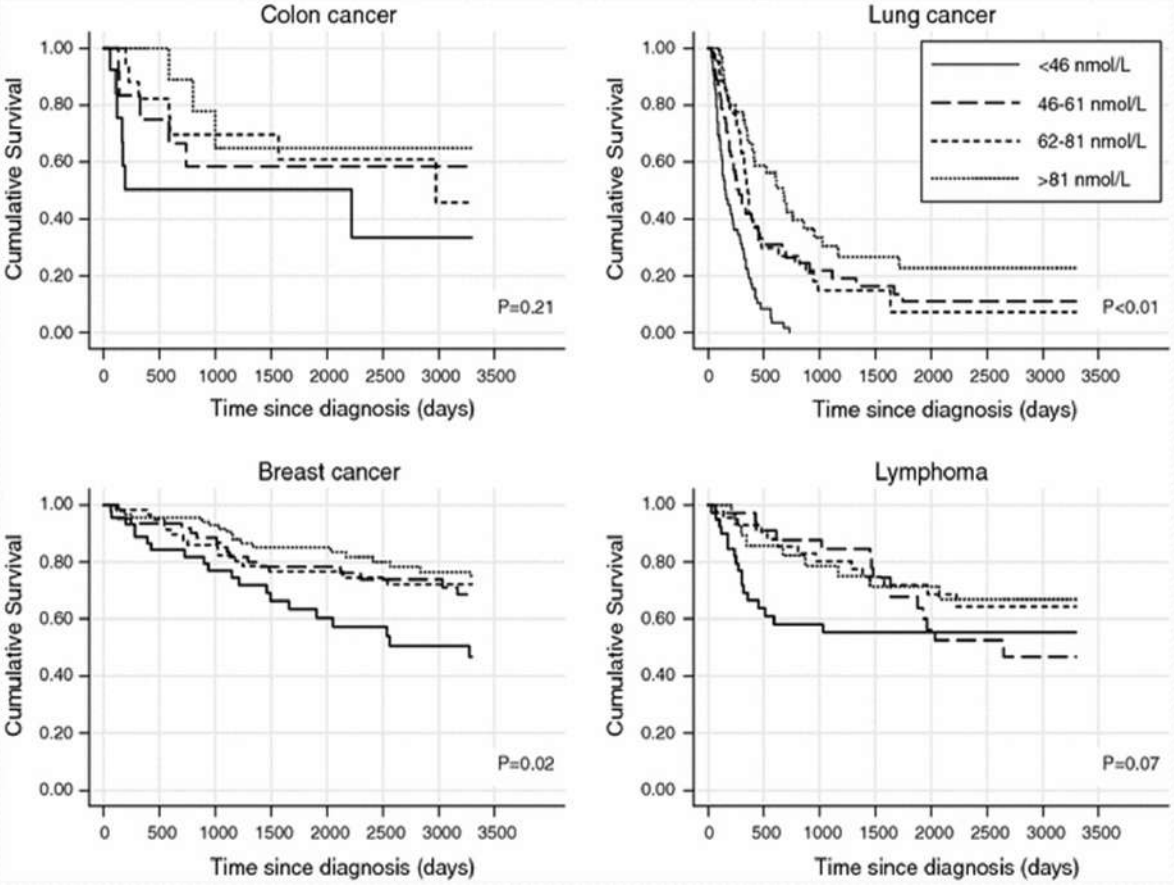
- In general, vitamin D has a greater impact on cancer survival and mortality rates than on cancer incidence.
- My thoughts are that there are many risk-modifying factors for cancer incidence but few for cancer progression and metastasis.
- Vitamin D reduces angiogenesis around tumors and reduces metastasis :
  - Moukayed M, Grant WB. The roles of UVB and vitamin D in reducing risk of cancer incidence and mortality: A review of the epidemiology, clinical trials, and mechanisms. Rev Endocr Metab Disord. **2017**;18(2):167-182. https://is.gd/3TbH2I

Survival after diagnosis of cancer with respect to 25(OH)D at DX

Cancer type	Number of studies	HR (95% confidence interval)
Breast	8	0.75 (0.56 – 0.95)
Colorectal	7	0.75 (0.60 – 0.90)
Hematological	11	0. 59 (0.42 – 0.77)
Prostate	4	0.84 (0.63 – 1.06)
Pancreatic	2	0.83 (0.36 – 1.29)
Skin	2	0.64 (0.20 – 1.07)
Liver	1	0.50 (0.26 – 0.88)
Stomach	1	0.59 (0.37 – 0.91)
Ovarian	1	0.69 (0.66 – 0.82)
Overall from all studies	44	0.74 (0.66 – 0.82)

Vaughan-Shaw, et al., Br J Cancer. 2017. https://is.gd/8Rqqyj

25(OH)D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma

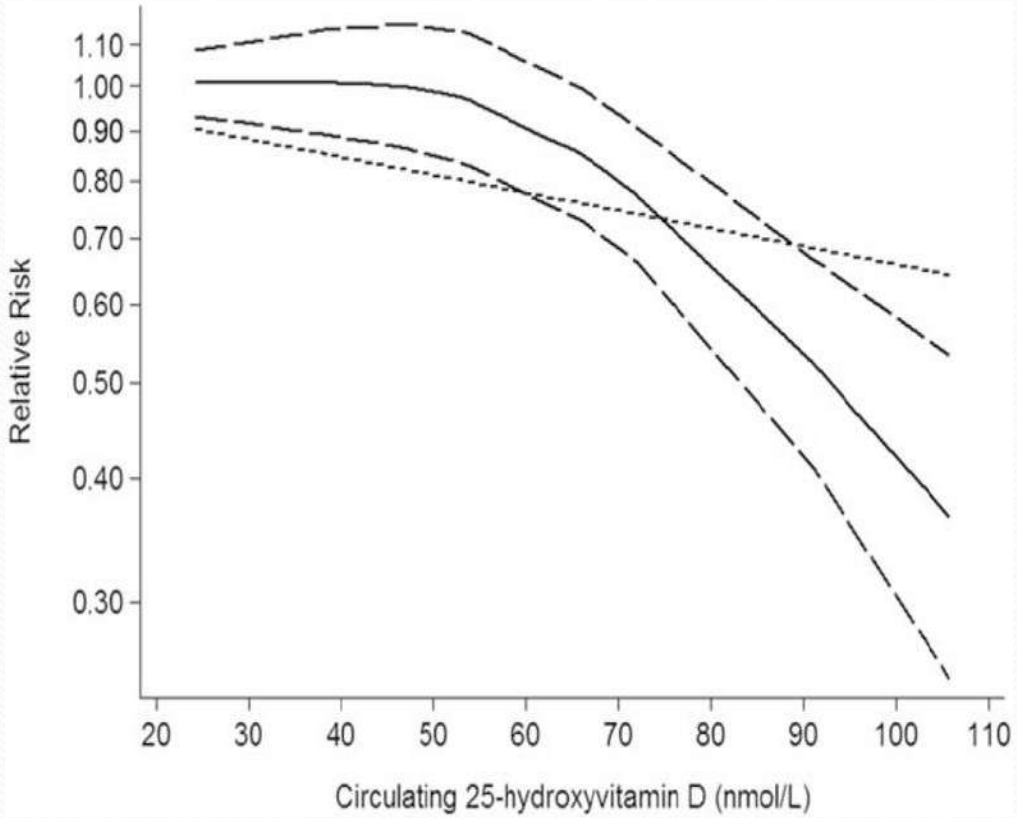


Results of a nine-year study:
25(OH)D >32 ng/ml was associated with one-third the mortality rate vs. <18 ng/ml.
Tretli et al.,
Cancer Causes Control.
2012;23:363-70
https://is.gd/pwa076

De novo vitamin D supplement use post-diagnosis is associated with breast cancer survival

- **METHODS:** Women aged 50-80 years with a record of invasive breast cancer were identified on the National Cancer Registry Ireland database (n = 5417). Initiation of de novo vitamin D post-diagnosis was identified from linked national prescription data (n = 2581, 49%).
- **RESULTS:** There was a 20% reduction in breast cancer-specific mortality in de novo vitamin D users (modelled as a time-varying variable) compared to non-users and the reduction was greater at 49% if vitamin D was initiated soon after the breast cancer diagnosis (within 6 months).
- Madden et al. Breast Cancer Res Treat. 2018;172:179-190. https://is.gd/f2Rebv

25(OH)D and lung cancer mortality



To convert nmol/l to ng/ml, divide by 2.5.

Feng Q et al. Circulating 25-hydroxyvitamin D and lung cancer risk and survival: A dose-response meta-analysis of prospective cohort studies. Medicine (Baltimore). 2017;96:e8613. https://is.gd/attlbL

Randomized Clinical Trials

- Randomized clinical trials (RCTs) are considered the strongest type of evidence.
- However, most vitamin D RCTs have been based on vitamin D dose and generally with participants with above average 25(OH)D given modest doses of vitamin D.
- The change in 25(OH)D with respect to vitamin D dose is nonlinear; so is health outcome with respect to 25(OH)D.

The VITAL Study from Harvard University, Manson et al., 2019

- There were ~25,000 participants including ~5,000 black participants followed for a median of 5.3 years. Baseline 25(OH)D = 31 ng/ml for those supplying values.
- A small vitamin D dose (2000 IU/d) reduced risk of all-cancer incidence by 25% for participants with low baseline 25(OH)D concentrations (Blacks) or low BMI <25 kg/m^2) but not the entire set of participants.
- It also reduced risk of cancer death by 25% regardless of baseline 25(OH)D.
- https://is.gd/fwuEvU

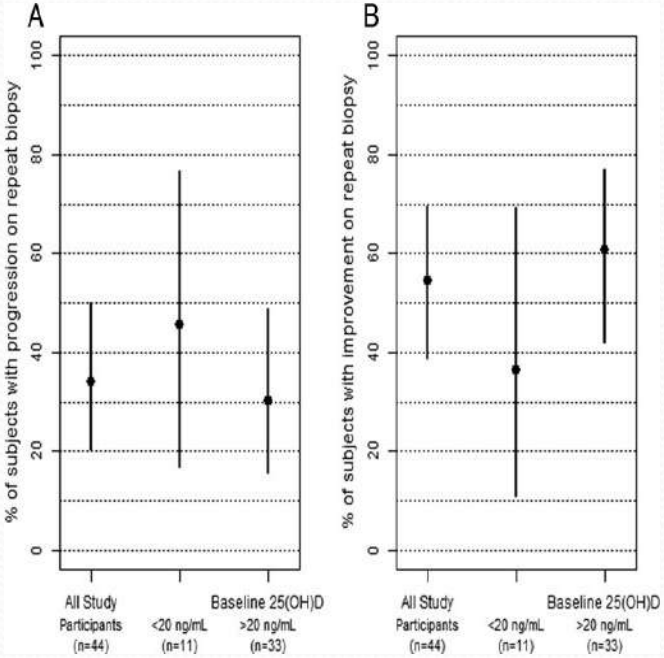
Effect of Vitamin D on All-Cancer Risk

- It is reasonable to assume that the relationship found for breast cancer incidence and vitamin D level is similar to that for all-cancer incidence. Evidence:
- In the VITAL study, the changes in all-cancer incidence with respect to changes in vitamin D level were very similar to those found in observational studies.
- In a Nordic occupational study, the correlations for the solar UVB index were similar for all cancer less lung cancer as for the strongest individual cancers including bladder, breast, colon, kidney.
- Grant WB. Dermatoendocrinol. 2012;4(2):203-11. https://is.gd/My8w97

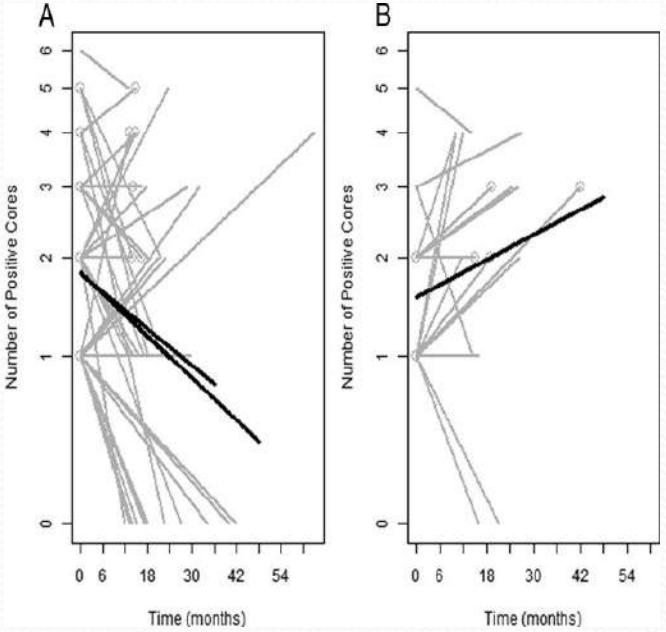
Improved Clinical Outcomes Associated With Vitamin D Supplementation During Adjuvant Chemotherapy in Patients With HER2^{+} Nonmetastatic Breast Cancer

- We identified 2 groups of patients for comparison—those who received VD supplementation during neoadjuvant chemotherapy (n = 134) and those who did not (n = 112).
- More than half of the patients received VD during neoadjuvant chemotherapy (55%), with 60% receiving a dose < 10,000 units/wk and 33% having a VD deficiency at the start of therapy. In our final multivariate model, VD use was associated with improved disease free survival, (DFS) (hazard ratio [HR], 0.36; 95% CI, 0.15-0.88; *P* = 0.03], whereas larger tumor size was associated with worse DFS (HR, 3.52; 95% CI, 1.06-11.66; *P* = 0.04).
- Zeichner et al. Clinical Breast Cancer 2015 https://is.gd/DavXlX

Prostate Cancer Treatment: Vitamin D3 supplementation at 4000 international units per day for one year



Change in 25(OH)D



Change in number of positive cores
untreated treated

Marshall et al., J Clin Endocrinol Metab. 2012 https://is.gd/4QjpB3

patients with oral neoplasms and effect of vitamin D supplementation on quality of life in advanced cancer treatment

- Vitamin D receptor expression and vitamin D scores were analyzed in normal oral mucosa (n = 95), leukoplakia (n = 23) and oral cancer (n = 87). 45 patients with advanced oral cancer subjected to chemoradiation were evaluated for the effect of vitamin D supplementation on most observable QOL parameters such as oral mucositis, swallowing performance and overall QOL.
- Vitamin D receptor expression was increased in oral neoplastic lesions. Vitamin D scores were significantly lower in cases compared to healthy controls (p = 0.002). Vitamin D supplementation significantly reduced the therapy-related toxicities in advanced cancer, thus reducing morbidity and improving QOL.
- Anand et al. Contemp Oncol (Pozn) 2017 https://is.gd/x8L7Xq

Ionizing Radiation as a Source of Oxidative Stress—The Protective Role of Melatonin and Vitamin D

- Both substances meet the conditions for use as agents that protect humans against IR-induced tissue damage.
- Deficiencies in melatonin and vitamin D are common in modern societies and may contribute to the severity of adverse side effects of medical IR exposure. Hence, supporting supplementation with both substances seems to be of first importance. Interestingly, both melatonin and vitamin D have been found to selectively radiosensitise cancer cells, which makes them promising adjuvants in radiotherapy.
- Nuszkiewicz. Int J Mol Sci. 2020. https://is.gd/AZtEOC

Vitamin D supplementation (1000 IU/d) to the older adult population in Germany has the cost-saving potential of preventing almost 30 000 cancer deaths per year

- We estimated costs and savings for preventing cancer deaths by vitamin D supplementation of the population aged 50+ years in Germany in 2016. The number of preventable cancer deaths was estimated to be (13%). End-of-life cancer care costs (€40 000). Annual costs of vitamin D supplementation were estimated at 25€ per person above age 50. In the main analysis, vitamin D supplementation was estimated to prevent almost 30 000 cancer deaths per year at approximate costs of €900 million and savings of €1.154 billion, suggesting net savings of €254 million.
- Niedermaier et al. Molecular Oncology, 2021 https://is.gd/34EgpO

Cancer Mortality Rates in Poland, 2016

Compared to Germany, approximately 11,000 cancer deaths/year prevented by 1000 IU/d vitamin D_3; Increases to 35,000 deaths/yr for 25(OH)D >60 ng/ml (approximately 5000 IU/d vitamin D_3)

Cancer	Mortality rate,* males	Mortality rate,* females	Cancer	Mortality rate,* males	Mortality rate,* females
Population	18.5 million	19.8 million	Corpus uteri		4.3
All	207	116	Ovary		7.9
Mouth, etc.	8.2	1.9	Prostate	19	
Esophagus	4.7	0.9	Kidney	7.0	2.8
Stomach	14	5.2	Bladder	11	1.9
Colorectum	27	14	Brain	7.1	4.7
Liver	4.3	2.2	Gallbladder	2.4	3.4
Pancreas	9.4	6.2	Larynx	5.5	0.5
Lung	61	20	Thyroid	0.4	0.5
Melanoma	3.1	1.9	Mesothelioma	0.8	0.3
Breast	0.2	18	Lymphoma	7.2	4.5
Cervix		5.5	Leukemia	6.6	3.6
Corpus uteri		4.3	Corpus uteri		4.3
Ovary		7.9	Ovary		7.9

*deaths/100,000/year

Recommendations

- For cancer risk reduction, 25(OH)D concentrations should be at least 40-60 ng/ml, perhaps higher.
- Those diagnosed with cancer should have 25(OH)D measured and then supplemented with a bolus dose to rapidly raise 25(OH)D, then supplement with 5000-10,000 IU/d or more (one can make ~20,000 IU/d in the sun).

Recommended Websites

- Additional cancer mortality maps
  - www.sunarc.org
- Outstanding vitamin D advocacy and research organization, GrassrootsHealth Nutrient Research Organization
  - https://www.grassrootshealth.net/
- Sources for many vitamin D papers:
  - https://vitamindwiki.com/VitaminDWiki
  - https://scholar.google.com/
  - https://www.ncbi.nlm.nih.gov/pubmed/