UVB, Vitamin D and Cancer

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Outline

• What causes cancer
• How vitamin D fights cancer
• Important cancers for Mediterranean countries
• Types of evidence
• Evidence for several types of cancer
• Vitamin D randomized controlled trials
• Recommendations
What Causes Cancer

• Cancer results from uncontrolled growth of cells due to DNA mutations as well as loss of mitochondrial function in cells.

• Major risk factors for cancer include smoking, alcoholic beverages, pollutants including pesticides, meat-rich diets, and obesity.
How Does Vitamin D Fight Cancer?

• The active form of vitamin D is 1,25-dihydroxyvitamin D (calcitriol).
• Most organs convert 25-hydroxyvitamin D to calcitriol as needed.
• It works by entering vitamin D receptors, which are bound to chromosomes, to affect gene expression, upregulating some genes, downregulating others.
Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms

Lamprecht, Lipkin, Nature Reviews Cancer 2003
1α,25(OH)2D3 differentially regulates miRNA expression in human bladder cancer cells

Ma et al., JSBMB, 2015
Actions of Vitamin D Against Cancer

• Vitamin D reduces risk of cancer by controlling cellular differentiation, proliferation, and destruction.

• Vitamin D helps maintain healthy mitochondria, the energy source of cells.

• Vitamin D helps main tight epithelial junctions.

• Vitamin D reduces angiogenesis around tumors, and reduces metastasis.
### Ranking of Cancers by Numbers of Cases, Deaths

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cases, MENA Countries</th>
<th>Deaths, MENA Countries</th>
<th>Cases, S. European Countries</th>
<th>Deaths, S. European Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>Lung</td>
<td>Colorectal</td>
<td>Lung</td>
</tr>
<tr>
<td>2</td>
<td>Lung</td>
<td>Colorectal</td>
<td>Prostate</td>
<td>Colorectal</td>
</tr>
<tr>
<td>3</td>
<td>Colorectal</td>
<td>Breast</td>
<td>Breast</td>
<td>Breast</td>
</tr>
<tr>
<td>4</td>
<td>Prostate</td>
<td>Stomach</td>
<td>NMSC</td>
<td>Prostate</td>
</tr>
<tr>
<td>5</td>
<td>Stomach</td>
<td>Pancreatic</td>
<td>Lung</td>
<td>Pancreatic</td>
</tr>
</tbody>
</table>

NMSC, non-melanoma skin cancer
## Ranking of Cancers by Numbers of Cases, Deaths, continued

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cases, MENA Countries</th>
<th>Deaths, MENA Countries</th>
<th>Cases, S. European Countries</th>
<th>Deaths, S. European Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Pancreatic</td>
<td>Leukemia</td>
<td>Bladder</td>
<td>Stomach</td>
</tr>
<tr>
<td>7</td>
<td>Leukemia</td>
<td>Prostate</td>
<td>NHL</td>
<td>Liver</td>
</tr>
<tr>
<td>8</td>
<td>NMSC</td>
<td>Brain</td>
<td>Liver</td>
<td>Leukemia</td>
</tr>
<tr>
<td>9</td>
<td>NHL</td>
<td>Bladder</td>
<td>Uterine</td>
<td>Kidney</td>
</tr>
<tr>
<td>10</td>
<td>Kidney</td>
<td>Ovarian</td>
<td>Pancreatic</td>
<td>Brain</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkin’s lymphoma
Types of Evidence

• The role of vitamin D in reducing risk of cancer can be determined from:
  – Geographical ecological studies
  – Observational studies
    • Case-control at time of diagnosis
    • Prospective, generally using cohorts
  – Randomized controlled trials
  – Open-label trials
  – Mechanisms
Ecological Studies

• Easy to conduct, large numbers
• Require data on cancer risk-modifying factors averaged by population
• Work best in mid-latitude countries
• Can fail if UVB effects are masked by other effects.
• There may be non-vitamin D UVB effects (unlikely for cancer).
Case-Control Studies

• In case-control studies, measurements are taken near time of disease diagnosis.
• Such studies generally find the strongest correlations with risk-modifying factors.
• There is the concern that having a disease affects serum 25(OH)D concentration.
• Advanced cancer stage is associated with reduced serum 25(OH)D concentration, but this should not affect case-control studies.
Prospective Studies

• In prospective studies, parameters are measured at time of enrollment.

• An important problem is that serum 25(OH)D changes with time, so effects 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.
Randomized Controlled Trials (RCTs)

• Most vitamin D RCTs have not found beneficial effects for cancer or most other health outcomes.

• The main problem is that RCTs implicitly make assumptions appropriate for pharmaceutical drugs:
  – The trial is the only source of the agent;
  – There is a linear dose-response relationship.
Open-label Trials

- GrassrootsHealth.net is promoting open-label trials.
- Enrollees may be given free vitamin D$_3$ and be counseled on dosage to achieve 100 to 150 nmol/L as in a pregnancy study [McDonnell et al., 2017].
- They may purchase vitamin D$_3$ and choose their own dose as in a breast-cancer study [McDonnell et al., 2018].
Open-label Trials

- They also have serum 25(OH)D concentration measured at least every six months using a mail-in finger-prick blood-spot assay kit.
- They fill out health and lifestyle questionnaires at time of each assay.
- Data so obtained can be used to determine correlations between serum 25(OH)D concentration and health outcomes.
Garland et al., Am J Public Health. 2006

The brothers Cedric and Frank Garland published their seminal paper in 1980.
Surface UVB Doses for 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)
### Colorectal Cancer Risk, High vs. Low 25(OH)D Concentration Quantile

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun et al., 1995</td>
<td>0.400</td>
<td>0.107 - 1.496</td>
</tr>
<tr>
<td>Chandler et al., 2015</td>
<td>0.460</td>
<td>0.239 - 0.886</td>
</tr>
<tr>
<td>Feskanich et al., 2004</td>
<td>0.530</td>
<td>0.270 - 1.040</td>
</tr>
<tr>
<td>Jung et al., 2014</td>
<td>0.550</td>
<td>0.428 - 0.707</td>
</tr>
<tr>
<td>Weinstein et al., 2015</td>
<td>0.590</td>
<td>0.363 - 0.958</td>
</tr>
<tr>
<td>Tangrea et al., 1997</td>
<td>0.600</td>
<td>0.313 - 1.150</td>
</tr>
<tr>
<td>Woolcott et al., 2010</td>
<td>0.600</td>
<td>0.333 - 1.081</td>
</tr>
<tr>
<td>Wu et al., 2007</td>
<td>0.660</td>
<td>0.417 - 1.044</td>
</tr>
<tr>
<td>Garland et al., 1989</td>
<td>0.730</td>
<td>0.200 - 2.663</td>
</tr>
<tr>
<td>Wactawski-Wende et al., 2006</td>
<td>0.750</td>
<td>0.385 - 1.461</td>
</tr>
<tr>
<td>Jenab et al., 2010</td>
<td>0.770</td>
<td>0.560 - 1.059</td>
</tr>
<tr>
<td>Wong et al., 2014</td>
<td>0.880</td>
<td>0.552 - 1.403</td>
</tr>
<tr>
<td>Otani et al., 2007</td>
<td>0.920</td>
<td>0.411 - 2.058</td>
</tr>
<tr>
<td>Weinstein et al., 2011</td>
<td>1.000</td>
<td>0.491 - 2.035</td>
</tr>
<tr>
<td>Lee et al., 2011</td>
<td>1.080</td>
<td>0.622 - 1.876</td>
</tr>
<tr>
<td></td>
<td>0.667</td>
<td>0.586 - 0.760</td>
</tr>
</tbody>
</table>

Garland and Gorham, 2017
Breast Cancer Mortality Rates, White Females, 2000-04

Reduced geographical variation with respect to solar UVB doses due to less time in the sun, use of sunscreen, increased risk from other factors such as obesity, and improved survival rates.
Breast Cancer, Risk vs. 25(OH)D from 11 Case-Control Studies

Grant and Boucher, PLoS One, 2017
Breast Cancer Risk Markedly Lower with Serum 25(OH)D Concentrations $\geq 60$ ng/ml

Breast Cancer Survival with Respect to 25(OH)D at Diagnosis

Ismail et al., Asian Pac Cancer Prev, 2018
Overall Survival with Respect to 25(OH)D at DX for Breast Cancer

Ismail et al., Asian Pac Cancer Prev, 2018
Breast Cancer Survival for De Novo Vitamin D Supplement Use after DX

Madden et al., Breast Cancer Research & Treatment, 2018
Lung Cancer Mortality Rates, Black Males, 1970-94

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

\[\text{US} = 94.08/100,000\]
\[118.92-183.33 \text{ (highest 10%)}\]
\[110.42-118.91\]
\[105.41-110.41\]
\[100.74-105.41\]
\[94.65-100.73\]
\[88.98-94.50\]
\[84.60-88.97\]
\[78.90-84.59\]
\[72.61-78.89\]
\[38.70-72.60 \text{ (lowest 10%)}\]
Sparse data (114 SEAs; 6.19% of deaths)
Lung Cancer Risk vs. High vs. Low 25(OH)D Concentration

Summary relative risk = 0.84 (0.78, 0.90)

Zhang et al., Cell Physiol Biochem, 2015
Lung Cancer Survival vs. Serum 25(OH)D at Time of Diagnosis

Tretli et al, Cancer Causes Control, 2012
Prostate Cancer Mortality Rates, White Males, 1970-94
Prostate Cancer Incidence vs. 25(OH)D Concentration

Figure 3 Nonlinear dose–response relationship between 25(OH)D concentration and risk of prostate cancer.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RR, relative risk.
Prostate Cancer and Calcium

• Higher calcium and milk intake, and higher serum calcium concentrations are risk factors for prostate cancer.
• One of the important roles of vitamin D is to increase calcium absorption from the intestines.
• Thus, higher 25(OH)D concentrations may increase risk of prostate cancer through increased calcium uptake.
Prostate Cancer Survival vs. 25(OH)D Concentration, Finland

Mondul et al., Cancer, Epidemiol, Biomarkers, Prevent, 2016

23 yrs Follow up
Bladder Cancer Mortality Rates, White Males, 1950-69

Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Bladder: White Males, 1950-69
Bladder Cancer Risk, High vs. Low 25(OH)D Concentration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afzal(2013)</td>
<td>0.2469</td>
<td>0.0962</td>
<td>49.8%</td>
<td>1.28 [1.06, 1.55]</td>
</tr>
<tr>
<td>Amaral(2012)</td>
<td>0.6043</td>
<td>0.2196</td>
<td>9.6%</td>
<td>1.83 [1.19, 2.81]</td>
</tr>
<tr>
<td>Brinkman(2010)</td>
<td>0.5446</td>
<td>0.3196</td>
<td>4.5%</td>
<td>1.72 [0.92, 3.23]</td>
</tr>
<tr>
<td>Brinkman(2011)</td>
<td>0.2746</td>
<td>0.2452</td>
<td>7.7%</td>
<td>1.32 [0.81, 2.13]</td>
</tr>
<tr>
<td>Giovannucci (2006)</td>
<td>0.1044</td>
<td>0.182</td>
<td>13.9%</td>
<td>1.11 [0.78, 1.59]</td>
</tr>
<tr>
<td>Mondul(2010)</td>
<td>0.5481</td>
<td>0.2646</td>
<td>6.6%</td>
<td>1.73 [1.03, 2.91]</td>
</tr>
<tr>
<td>Mondul(2012)</td>
<td>0.1655</td>
<td>0.241</td>
<td>7.9%</td>
<td>1.18 [0.74, 1.89]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.34 [1.17, 1.53]

Heterogeneity: Chisq = 5.15, df = 6 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.27 (P < 0.0001)

Risk ratio, high vs. low 25(OH)D = 1.34 (1.17, 1.53)
Zhang et al., Cell Physiol Biochem, 2015
Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia

Overall survival for patients with 25OHD >63 nmol/l vs <63 nmol/l

Shanafelt, Blood, 2011
Kidney Cancer Incidence vs. 25(OH)D

A. Adjusted for age, season, etc.  B. Add for smoking, Alcohol. Muller et al., Am J Epidemiol, 2014
Ovarian Cancer Mortality Rate, White Females, 1970-94
Ovarian Cancer & Lifetime Ambient UVB Dose in Australia

Tran et al., Cancer Prev Res, 2012
Other Vitamin D-sensitive Cancers Identified in Ecological Studies

- Endometrial (uterine)
- Esophageal
- Gallbladder
- Laryngeal
- Stomach
- Vulvar
- Leukemia
- Non-Hodgkin’s lymphoma
Vitamin D (Plus Calcium) RCTs

• There have been three RCTs that found reduced cancer incidence rates with respect to vitamin D (plus calcium) supplementation.
  • 1100 IU/d vitamin D₃ plus 1.5 g/d calcium [Lappe, 2007]
  • 400 IU/d vitamin D₃ plus 1.0 g/d calcium [Bolland, 2011]
  • 2000 IU/d vitamin D₃ plus 1.5 g/d calcium [Lappe, 2017]
1100 IU/d vitamin D₃ plus 1.5 g/d calcium, 4-yr trial [Lappe, 2007]

• This study found a non-significant reduced risk of all cancer in the calcium arm.
• It found a significant effect in the calcium plus vitamin D arm.
• The effect was stronger for years 2-4 than year 1.
• The authors concluded that vitamin D significantly reduced all-cancer incidence.
Reanalysis of the Women’s Health Initiative Study [Bolland, 2011]

• In 15,646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, 1 g Ca/d, 400 IU/d vitamin D significantly decreased the risk of total, breast, and invasive breast cancers by 14-20% and nonsignificantly reduced the risk of colorectal cancer by 17%. In women taking personal calcium or vitamin D supplements, CaD did not alter cancer risk (HR: 1.06-1.26).
A 4-year, double-blind, placebo-controlled, population-based randomized clinical trial in Nebraska, a rural state (June 24, 2009, to August 26, 2015—the final date of follow-up).

A total of 2303 healthy postmenopausal women 55 years or older were randomized. Mean BMI was 30 kg/m². Mean baseline serum 25(OH)D level was 82 nmol/L [SD, 26].
Vitamin D + Calcium RCT for Cancer

• The treatment group received 2000 IU/d of vitamin D$_3$ and 1500 mg/d of calcium; the placebo group received identical placebos.
• The primary outcome was the incidence of all-type cancer (excluding nonmelanoma skin cancers).
• At year 1, serum 25(OH)D levels were 110 nmol/L in the vitamin D$_3$ + calcium group and 79 nmol/L in the placebo group.
Vitamin D + Calcium RCT for Cancer

• Kaplan-Meier incidence over 4 years was 0.042 (95% CI, 0.032 to 0.056) in the vitamin D3 + calcium group and 0.060 (95% CI, 0.048 to 0.076) in the placebo group; P = 0.06.

• Thus, according to intention to treat, the RCT failed the p = 0.05 significance test by one cancer case in the treatment arm.
Vitamin D + Calcium RCT for Cancer

Age Adjusted Hazard Ratio of Cancer by 25(OH)D
90 and 95 Percent Confidence Bands Shown

Serum 25(OH)D Level in ng/mL
How to Conduct Vitamin D RCTs

• Start with the of serum 25(OH)D concentration-health outcome relationship.
• Measure baseline 25(OH)D values.
• Recruit non-replete subjects.
• Measure serum 25(OH)D during the trial for adjustment of supplemental doses.
• Analyze health outcomes in relation to achieved 25(OH)D concentrations.
• Heaney, 2014; Grant et al., 2018
Concern about High 25(OH)D Concentrations

• The concern arose since a number of prospective observational studies found U-shaped 25(OH)D concentration-health outcomes.
• The researchers did not ask participants when they started supplementing with vitamin D.
• As a result, many with high 25(OH)D concentration were put in the wrong 25(OH)D category based on long-term values.
• [Grant et al., 2016]
Frailty vs. 25(OH)D, Men

Ensrud et al., 2011

Adjusted for age, race, clinic site, season, and BMI
Frailty vs. 25(OH)D, Women

Ensrud et al., 2010

*Adjusted for age, site, season, and BMI
Recommendations

• To reduce cancer risk, raise serum 25(OH)D concentration to 100 to 150 nmol/L.

• This could take 2000 to 5000 IU/d vitamin D₃ daily or weekly doses.

• Taking magnesium helps convert vitamin D to 25(OH)D.

• Note that one can produce 10,000 to 20,000 IU/d vitamin D₃ with whole-body sun exposure, so 5000 IU/d is a physiological dose.
Sensible Sun Exposure

• Sensible sun exposure during the sunny time of the year and day helps, too.

• Sunburning is not a risk factor for melanoma; however, people who sunburn frequently have increased risk of melanoma due to pale skin.

Treatment

• Vitamin D₃ (cholecalciferol) can also be used in cancer treatment.
• Organs will make 1,25(OH)₂D₃ from 25(OH)D₃
• Do not use vitamin D₂ (ergocalciferol).
• If chemotherapy is used, monitor both 25(OH)D and chemo concentrations.
Additional Resources

Vitamin D Advocacy Organizations

• European Vitamin D Association (EVIDAS)
• GrassrootsHealth.net
• VitaminDCouncil.org
• VitaminDSociety.org
• VitaminDWiki.com