Vitamin D and Cancer: Overview, Priorities and Challenges

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The Vitamin D Story

Evolutionary Concepts

• Ability to produce vitamin D developed in phytoplankton
• Vitamin D thought to have played a key role in the evolution of mammals
  – calcium maintenance and skeletal formation

References: (1) IARC. Vitamin D and Cancer. IARC Working Group Reports Vol. 5, International Agency for research on Cancer, Lyon, 25 November 2008
(2) Holick, MF., 2008, PMID: 18844847; (3) DeLuca, H., 1988, PMID: 3280376
The Vitamin D Story

Evolutionary Concepts

• Ability to produce vitamin D developed in phytoplankton
• Vitamin D thought to have played a key role in the evolution of mammals
  – calcium maintenance and skeletal formation

Recent History

• Vitamin D discovered in the 1920s
  – observations that UV irradiation of skin and some foods could heal rickets, widespread in northern Europe / USA
  – spurned research into the treatment of metabolic bone diseases
  – elucidation of vitamin D structure resulted in its synthesis and fortification of foods for the elimination of rickets
• Vitamin D toxicity – hypercalcemia – observed in the UK due to over-fortification of milk
  – resulted in regulations on food fortification

Vitamin D: Production and Food Sources

**Diet**
- dairy products, fatty fish, eggs, butter

**Sun Exposure (UVB)**
- 7-dehydrocholesterol → cholecalciferol

**Vitamin D**

25-hydroxylase [CYP27A1]
Liver

**25OHD**

- Represents >95% of circulating vitamin D
- Has a ½ life of 2-3 weeks
- Biomarker of total vitamin D from dietary sources and endogenous production
Vitamin D: Production and Food Sources

Diet
- dairy products, fatty fish, eggs, butter

Sun Exposure (UVB)
7-dehydrocholesterol → cholecalciferol

Vitamin D

25-hydroxylase [CYP27A1]

Liver

25OHD

25-hydroxylase [CYP27A1]

1-α-hydroxylase [CYP27B1]

- Kidney and other tissues (e.g. colorectum)
- Local production possible in normal and neoplastic cells

1,25(OH)₂D₃
(Calcitriol; active hormone)
Vitamin D: Biological Effects

$1,25(\text{OH})_2\text{D}_3$
(Calcitriol; active hormone)
Vitamin D: Biological Effects

\[ 1,25(\text{OH})_2 \text{D}_3 \]
(Calcitriol; active hormone)

**Classical Functions**
Role in Calcium Homeostasis

**Intestine:**
Increase absorption of calcium and phosphate

**Bone:**
Increase bone mineralization

**Kidney:**
Inhibit calcium loss
Vitamin D: Biological Effects

$1,25(\text{OH})_2\text{D}_3$ (Calcitriol; active hormone)

**Classical Functions**
Role in Calcium Homeostasis

- **Intestine:** Increase absorption of calcium and phosphate
- **Bone:** Increase bone mineralization
- **Kidney:** Inhibit calcium loss

**Roles Relevant to Cancer**

- **Cell cycle kinetics:**
  - Modulates cell proliferation, differentiation, apoptosis
  - Control of cell cycle checkpoints
  - Regulation of steroid receptor inducible genes

- **Immune Function:**
  - Activity of NK cells and phagocytic activity of macrophages

- **Oxid Strs:**
  - Oxidative DNA damage

- **Inflammation:**
  - crp levels with supplementation
  - cox-2 enzyme with suppl.
  - TNF$\alpha$ levels in deficiency

- **Hormonal:**
  - Expression of aromatase, estrogen receptor

- **Others:**
  - Growth factor signaling, cell adhesion, angiogenesis, DNA repair
The Vitamin D Receptor (VDR)

Vitamin D actions are mediated by the VDR:
- a nuclear hormone receptor
- present in numerous cell types
- binding of active hormone leads to formation of a heterodimer with retinoid X receptor, binding to VDRE
- can up or down regulate gene transcription; modulate signal transduction pathways
- effects of vitamin D may differ based on variations of VDR activity

Adapted from McCullough ML et al, 2009, PMID: 19400699
The Vitamin D Receptor (VDR)

- The VDR is expressed in numerous tissues:

  - Vitamin D has a broad range of molecular and cellular effects on various tissues
  - VDR knockout models show that vitamin D is essential for regulation of:
    - innate and adaptive immune response
    - glucose and fat metabolism
    - muscle and brain function
    - cell cycle control

Adapted from: 1) Norman AW et al, 2010, PMID: 20667908
2) Bouillon R et al, 2008, PMID: 18694980

<table>
<thead>
<tr>
<th>Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
</tr>
<tr>
<td>Adrenal</td>
</tr>
<tr>
<td>Bone, osteoblasts</td>
</tr>
<tr>
<td>Brain, general</td>
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<tr>
<td>Brain, amygdala</td>
</tr>
<tr>
<td>Brain, hypothalamus</td>
</tr>
<tr>
<td>Brain, glial cells</td>
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<tr>
<td>Breast</td>
</tr>
<tr>
<td>Cartilage</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Eggshell gland</td>
</tr>
<tr>
<td>Epididymus, seminiferous tubules</td>
</tr>
<tr>
<td>Gill (fish)</td>
</tr>
<tr>
<td>Hair follicle</td>
</tr>
<tr>
<td>Intestine</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Lymphocytes (B&amp;T)</td>
</tr>
<tr>
<td>Muscle, cardiac</td>
</tr>
<tr>
<td>Muscle, embryonic</td>
</tr>
<tr>
<td>Muscle, smooth</td>
</tr>
<tr>
<td>Ovary</td>
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<td>Pancreas β-cell</td>
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<td>Parotid</td>
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<td>Testis</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Tonsils, dendritic cells</td>
</tr>
<tr>
<td>Uterus</td>
</tr>
</tbody>
</table>

Table 1: Tissues that express the VDR for the steroid hormone, 1α,25(OH)₂D₃.
The Vitamin D Receptor (VDR)

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

- comprehensive, high resolution map of genomic VDR binding, using next generation DNA-sequencing to identify protein-DNA binding
- 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](#)  

**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.  

Ref: Ramagopalan SV et al, 2010, PMID:20736230
Potential Gene-Diet-Nutrient Interactions

Diet

Use of Biomarkers to Assess Dietary Exposures

Dietary Exposures

Risk May Be Modulated By Variability in Genes Related to Nutrient Metabolism

Effect on Cancer Risk

• direct or indirect

Impact on Dietary Biomarker Measures

Differences in the metabolic effects of nutrients

Differences in digestion, absorption, transport, metabolism, bio-transformation, excretion etc of nutrients or bio-active food components

Gene-Gene Interactions

Gene-Diet/Nutrient Interactions

Other factors that may affect biomarker measurement:
- Lifestyle or physiologic factors
- Dietary factors
- Type of biological sample
- Analytical methodology

Genetic Influence on Dietary Choices and Food Intake

• Many gene functions are unknown
• Study size and statistical power issues limit exploration of gene-nutrient interactions
• It is very likely that many subtle interactions exist, but remain unexplored

Genetic Determinants of Vitamin D Status

Wang et al. [2010, PMID: 20541252]:

- GWAS-25OHD interaction study, a priori discovery / replication phases
- 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

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

Global Vitamin D Levels

- Concern for widespread vitamin D insufficiency and deficiency

<table>
<thead>
<tr>
<th>USA:</th>
<th>NHANES 1988-1994 $^1$</th>
<th>NHANES 2001-2004 $^1$</th>
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</thead>
<tbody>
<tr>
<td>Mean 25OHD level</td>
<td>75 nmol / l</td>
<td>60 nmol / l</td>
</tr>
<tr>
<td>% &lt; 25 nmol/l</td>
<td>2% (9%)</td>
<td>6% (29%)</td>
</tr>
<tr>
<td>% &gt; 75 nmol/l</td>
<td>45% (12%)</td>
<td>23% (3%)</td>
</tr>
</tbody>
</table>

Numbers in parentheses: Prevalence in African Americans

References:
(1) Ginde, A, 2009, PMID: 19307527
Global Vitamin D Levels

• Concern for widespread vitamin D insufficiency and deficiency

<table>
<thead>
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<td>45% (12%)</td>
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</tr>
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</table>

• > 1 billion people worldwide affected ²

• Hagenau et al³:
  • performed an ecologic meta-regression analysis of 394 studies worldwide with measures of blood 25OHD concentration.
  • results: global mean of 54 nmol/l, widespread insufficiency / deficiency
  • highest values: Northern Europe
  • lowest values: Latin America, Southern Europe

• Mithal et al⁴:
  • review of studies worldwide with measures of blood 25OHD concentration
  • concluded that vitamin D insufficiency is apparent worldwide
  • deficiency is most prevalent in the Middle East

References:
Vitamin D and Cancer: Epidemiologic Evidence

Conclusions of the IARC Report on Vitamin D and Cancer (2008)

• Consistent, persuasive evidence for an inverse association between vitamin D and colorectal cancer
  – evidence for a causal link is limited
  – RCTs inconclusive
• Weak evidence for an inverse association with breast cancer
• No evidence for an association with prostate cancer
• Insufficient studies of other cancers
• Vitamin D supplementation may reduce all cause mortality

Reference:
Vitamin D and Colorectal Cancer (CRC): Mechanisms of CRC Development

- Cell proliferation
- Inflammation
  - systemic
  - local
- Oxidative stress
- Cell differentiation
- Apoptosis
- Immune modulation
  - immunosurveillance
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RR for 1ng/ml (2.496 nmol/l) increase in blood 25OHD concentration:

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<tr>
<th>Study</th>
<th>N case / con.</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garland, 1989</td>
<td>34 / 67</td>
<td>USA</td>
</tr>
<tr>
<td>Braun, 1995</td>
<td>57 / 114</td>
<td>USA</td>
</tr>
<tr>
<td>Tangrea, 1997</td>
<td>146 / 290</td>
<td>Finland</td>
</tr>
<tr>
<td>Wactawski-Wende, 2006</td>
<td>306 / 306</td>
<td>USA</td>
</tr>
<tr>
<td>Yaylim-Eraltan, 2006</td>
<td>26 / 52</td>
<td>Turkey</td>
</tr>
<tr>
<td>Freedman, 2007</td>
<td>66 / 16818</td>
<td>USA</td>
</tr>
<tr>
<td>Otani, 2007 (m)</td>
<td>375 / 750</td>
<td>Japan</td>
</tr>
<tr>
<td>Otani, 2007 (w)</td>
<td>372 / 739</td>
<td>USA</td>
</tr>
<tr>
<td>Wu, 2007</td>
<td>1248 / 1248</td>
<td>Europe</td>
</tr>
<tr>
<td>Jenab, 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co or NCC</td>
<td>2630 / 20384</td>
<td>USA</td>
</tr>
</tbody>
</table>

Summary RR: 0.85 (0.79-0.92)

* case-control design

RR for 10 ng/ml increase:

Co or NCC: 0.85 (0.79-0.91)
Summary RR: 0.85 (0.79-0.92)

Reference: Gandini, S, 2010, PMID: 20473927
The European Prospective Investigation into Cancer and Nutrition (EPIC)

- Over 520,000 participants recruited from 23 centers in 10 Western European countries

**Strengths of the study:**
- large size and inclusion of multiple populations
- incorporation of areas with varying cancer rates
- heterogeneity of dietary intakes, dietary patterns and lifestyle habits
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Geographical North-South gradient:
- above latitude 60° to below latitude 40°
- north-central-south dietary differences often observed
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Methodology of dietary assessment:
- dietary questionnaires (DQ)*: detailed, validated, country-specific
- 24-hour recall (EPIC-Soft): prospectively built-in, standardized recalls taken from a subset (8%; 37,000 subjects) for correction of systematic between centre estimation errors in DQ assessments

EPIC Nutrient Database (ENDB):
- standardized, common food composition database for selected nutrients

* validated within source population; detailed: 150 to 300 food items, capturing local foods and dietary habits; self administered or face-to-face; quantitative (France, Greece, Germany, Italy, Netherlands, Spain); semi-quantitative (Denmark, Norway, Umeå); combined methods (UK, Malmo)
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**EPIC Nutrient Database (ENDB):**
- standardized, common food composition database for selected nutrients

**Nested Case-Control Study:**
- 1248 incident CRC cases matched* to 1248 controls
- 25OHD: measured in serum by OCTEIA enzyme immunoassay
- Incidence rate ratio (IRR) estimated by conditional logistic regression with multivariate adjustment

* Matching criteria: age, gender, study centre, date of blood collection, fasting status, menopausal status
- In men, a greater percentage of vitamin D is consumed from fish/shellfish, added fats and meats.

- In women, a greater percentage of vitamin D is consumed from dairy products, eggs and cakes.
Dietary Vitamin D Intake in EPIC

Values are means adjusted by age, weighted for day and season of 24h recall

p<0.0001 for a difference by gender in each country

Dietary Vitamin D* (µg / day)

(1 µg = 40 IU)

Men
Women

EPIC Region:

North
Central (France: north & east only)
South (+ South of France)

Men and Women Combined

* Values are means adjusted by age, weighted for day and season of 24h recall
p<0.0001 for a difference by gender in each country

* Different letters indicate a significant difference by European region, p<0.05
Vitamin D and Colorectal Cancer: EPIC

Quintiles of Dietary VitD
µg / day

< 2.1
≥ 2.1 to < 3.1
≥ 3.1 to < 4.2
≥ 4.2 to < 5.8
≥ 5.8

IRR of CRC Risk

n case / control
251 / 243
255 / 245
249 / 244
235 / 246
230 / 244

1 µg = 40 IU

* Model conditioned on the matching factors plus adjustments for BMI, physical activity, smoking status / duration / intensity, level of schooling, intake of total energy, total fruits, total vegetables, meats

WCRF Grant Number: 2005/12
25OHD Status by Month of Blood Draw

Cases are depicted as filled in circle and controls as open squares.

Values are geom. means adjusted by age, sex, study centre

WCRF Grant Number: 2005/12
Serum 25OHD concentration:
Cases = 52.8 nmol/l
Controls = 56.5 nmol/l  p<0.01

p trend=0.0002

IRR of CRC Risk

* Model conditioned on the matching factors plus adjustments for BMI, physical activity, smoking status / duration / intensity, level of schooling, intake of total energy, total fruits, total vegetables, meats

WCRF Grant Number: 2005/12
Vitamin D and Colorectal Cancer: EPIC

Serum 25OHD nmol/L

< 25.0

≥ 25.0 to < 50.0

≥ 50.0 to < 75.0

≥ 75.0 to < 100.0

≥ 100.0

Colon

Rectum

p trend = 0.0001
OR 10% increase = 0.95 (0.93-0.98)

p trend = 0.3
OR 10% increase = 1.00 (0.97-1.03)

p heterogeneity colon/rectum = 0.05

Vitamin D and Breast Cancer: Epidemiologic Evidence

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

<table>
<thead>
<tr>
<th>Study</th>
<th>N case / con.</th>
<th>Country</th>
</tr>
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<tbody>
<tr>
<td>CC</td>
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<tr>
<td>Colston, 2006</td>
<td>179 / 179</td>
<td>UK</td>
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<td>Abbas, 2007</td>
<td>1394 / 1365</td>
<td>Germany</td>
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<td>Abbas, 2009</td>
<td>289 / 595</td>
<td>Germany</td>
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<td>Crew, 2009</td>
<td>1026 / 1075</td>
<td>USA</td>
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<td>Rejnmark, 2009</td>
<td>142 / 420</td>
<td>Denmark</td>
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<td>Co or NCC</td>
<td></td>
<td></td>
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<td>Bertone-Johnson, 2005</td>
<td>701 / 724</td>
<td>USA</td>
</tr>
<tr>
<td>Chlebowski, 2007</td>
<td>895 / 898</td>
<td>USA</td>
</tr>
<tr>
<td>Freedman, 2007</td>
<td>28 / 16818</td>
<td>USA</td>
</tr>
<tr>
<td>Freedman, 2008</td>
<td>1005 / 1005</td>
<td>USA</td>
</tr>
<tr>
<td>McCullough, 2009</td>
<td>516 / 516</td>
<td>USA</td>
</tr>
</tbody>
</table>

Summary RR for Co or NCC: 0.989 (0.979, 0.998)

Summary RR: 0.89 (0.81-0.98)

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:**

- Braun, 1995
- Nomura, 1998
- Ahonen, 2000
- Jacobs, 2004
- Baron, 2005
- Freedman, 2007
- Faupel-Badger, 2007
- Li, 2007
- Mikhak, 2007
- Ahn, 2008
- Travis, 2009

<table>
<thead>
<tr>
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<th>N case / con.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>61 / 122</td>
</tr>
<tr>
<td>USA</td>
<td>136 / 136</td>
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<tr>
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<td>149 / 566</td>
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<tr>
<td>USA</td>
<td>83 / 166</td>
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<td>Denmark</td>
<td>33 / 672</td>
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<td>USA</td>
<td>47 / 16818</td>
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<td>Finland</td>
<td>296 / 296</td>
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<td>USA</td>
<td>1066 / 1618</td>
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<td>USA</td>
<td>684 / 692</td>
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<tr>
<td>USA</td>
<td>749 / 781</td>
</tr>
<tr>
<td>Europe</td>
<td>3956 / 21947</td>
</tr>
</tbody>
</table>

**Summary RR:** 0.999 (0.995, 1.003)

- All studies are cohort or nested case-control

**RR for 10 ng/ml increase:**

Summary RR: 0.99 (0.95-1.03)

Reference: Gandini, S, 2010, PMID: 20473927

Table 3. Odds Ratios (and 95% Confidence Intervals) for Prostate Cancer by Predefined Categories of 25-Hydroxyvitamin D Concentration in the European Prospective Investigation into Cancer and Nutrition, 1994–2000

<table>
<thead>
<tr>
<th>Category of 25-Hydroxyvitamin D Concentrationa</th>
<th>1</th>
<th>2c</th>
<th>3</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range, nmol/L</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.82, 1.32</td>
<td>1.17</td>
<td>0.82, 1.58</td>
<td>0.265, 0.188</td>
</tr>
<tr>
<td>50–74.9</td>
<td>1.11</td>
<td>1.17</td>
<td>1.14</td>
<td>0.265</td>
</tr>
<tr>
<td>75</td>
<td>1.04</td>
<td>1.17</td>
<td>1.11</td>
<td>0.265</td>
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<tr>
<td>No. of cases</td>
<td>286</td>
<td>283</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>No. of controls</td>
<td>353</td>
<td>113</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Odds ratiod</td>
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<td>1.17</td>
<td>0.82, 1.58</td>
<td>0.265, 0.188</td>
</tr>
<tr>
<td>Adjusted odds ratioe</td>
<td>0.78, 1.28</td>
<td>1.14</td>
<td>0.82, 1.58</td>
<td>0.265, 0.188</td>
</tr>
<tr>
<td>Prostate cancer stagec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>1.06</td>
<td>1.02</td>
<td>0.64, 1.62</td>
<td>0.508</td>
</tr>
<tr>
<td>Advanced</td>
<td>1.22</td>
<td>1.17</td>
<td>0.44, 3.13</td>
<td>0.364</td>
</tr>
<tr>
<td>Histologic gradege</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.95</td>
<td>1.19</td>
<td>0.76, 1.88</td>
<td>0.097</td>
</tr>
<tr>
<td>High</td>
<td>1.25</td>
<td>1.29</td>
<td>0.62, 2.70</td>
<td>0.846</td>
</tr>
<tr>
<td>Age at blood collectionf</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1.08</td>
<td>1.00</td>
<td>0.62, 1.62</td>
<td>0.046</td>
</tr>
<tr>
<td>≥60 years</td>
<td>0.83</td>
<td>1.33</td>
<td>0.81, 2.18</td>
<td>0.594</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a Serum concentrations of vitamin D were standardized for month of blood collection.

b Values were obtained with the logarithm of plasma 25-hydroxyvitamin D replacing the categorical plasma 25-hydroxyvitamin D variable in the model.

c All values of 1 are odds ratios.

d Conditioned on matching variables by using conditional logistic regression.

e Conditioned on matching variables and adjusted for body mass index, smoking, alcohol intake, education, marital status, and physical activity by using conditional logistic regression.

Reference: Travis, R, 2009, PMID: 19359375
Vitamin D and Other Cancers: Epidemiologic Evidence

Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

• More than 12,000 subjects from 10 prospective cohorts:
  – USA: CPS-II, CLUE, HPFS, MEC, NYU-WHS, NHS, PLCO
  – Finland: ATBC
  – China: SMHS, SWHS

• Studied 7 rarer cancer sites:
  – Endometrium
  – Ovary
  – Kidney
  – Pancreas
  – Non-Hodgkins Lymphoma
  – Upper GI tract [esophagus and stomach]

• Large heterogeneity in ethnicity, latitude of residence, vitamin D intake

# Vitamin D and Other Cancers: Epidemiologic Evidence

## Kidney

<table>
<thead>
<tr>
<th>Status</th>
<th>N cases</th>
<th>N controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>50-75nmol/l</td>
<td></td>
</tr>
</tbody>
</table>

**Asian subjects:** decreased risk with lower 25OHD

## Upper GI

- (esophagus, stomach)
- N cases: 1065
- N controls: 1066

## Pancreas

- N cases: 952
- N controls: 1333

## Endometrium

- N cases: 830
- N controls: 992

## Ovary

- N cases: 516
- N controls: 770

Vitamin D and Cancer: Critiques of the Epidemiologic Evidence

- Insufficient information for many cancer sites, particularly rarer cancers
- Many studies to date are small
  - insufficient power for sub-group analyses, or consideration of gene-diet/nutrient, gene-lifestyle/environment or gene-gene interactions
  - collaborations and consortia may be necessary
- Most studies are from North American or European populations
  - lack of information from many other populations
- Relevant period of vitamin D exposure for cancer prevention is not well studied
  - most studies consider blood 25OHD concentration at one time-point
  - if long term cumulative exposure is important, then studies in adults, with a short follow-up may not be enough
Vitamin D and Cancer Survival: Epidemiologic Evidence

Is vitamin D insufficiency or deficiency related to poor prognosis / survival in some cancers?

• Season of diagnosis appears to be a predictor for survival

• ↓ 25OHD levels linked to ↓ survival for:
  – Colorectal cancer [PMID: 20594355, 19690551]
  – Breast cancer [PMID: 19451439, 20004077]
  – Non-Hodgkin’s lymphoma [PMID: 20713849]

• Variation in vitamin D pathway genes associated with recurrence, progression or survival:
  – Prostate cancer [PMID: 20687218]
  – Epithelial ovarian cancer [PMID: 19904266]
Vitamin D and Cancer: Evidence for Causality?

- Causality can be judged on: strength and consistency of the evidence, temporal relationship and biological plausibility
  - Vitamin D causal: supplementation will reduce cancer incidence
  - Vitamin D marker of health status: supplementation will not affect cancer incidence
  - In most situations, definitive establishment of causality requires randomised controlled trials
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- IARC Report, Final Conclusion\(^1\): “Hypotheses on vitamin D status and colorectal cancer, cardiovascular disease and all-cause mortality should be tested in appropriately designed randomised controlled trials.”

To date, only 3 trials have been published:

- Trivedi trial, 2003, UK
- Women’s Health Initiative trial, 2006/2008, USA
- Nebraska trial, 2007, USA

Reference:
Vitamin D and Cancer: Randomised Controlled Trials

1) Trivedi trial [2003; PMID: 12609940]
   - **design:** n men & women=1345, 65-84yrs; intervention: 41µg/d (1640 IU/d), 5 yrs.
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3) Nebraska trial [2007; PMID: 17556697]
   - design: n postmenop women=1179; intervention: 1400-1500mg/d Ca alone vs. Ca + 27.5µg/d (1100 IU/d) vitamin D (no vitamin D only group); 4 yrs.
   - results: all cancer incidence significantly lower in the Ca + D group (vs. placebo).
   - critiques: small size, low power, little info on specific cancers, no observed difference of calcium+vitamin D with the calcium alone group over 4 yrs.
Colorectal Cancer Etiology – Multi-Factorial, Multi-Mechanistic
Colorectal Cancer Etiology – Multi-Factorial, Multi-Mechanistic

**Lifestyle**
- Alcohol
- Smoking
- Physical Inactivity
- SES

**Diet**
- Food Groups: Fruits / vegetables, Red / proc. meats, Fat / fat sub-types, Cereals, Dairy, Fibre, Total Energy
- Diet / Nutrient Patterns, GI/GL
  - Nutrients, phytochemicals
    - Vitamin D

**Metabolic Disorders**
- Anthropometry, Body weight
- Biomarkers of obesity / hyper-insulinemia: c-peptide, HbA1c, adiponectin, fetuin, leptin
  - Blood lipid variables

**Oxidative Stress and Antioxidant Status**
- Anti-oxidant nutrients: vitamins A/C/E, carotenoids
- Pro-oxidant nutrient: iron
  - Selenium

**Colonic Microbiota and Luminal Factors**
- Barrier function
- Endotoxin exposure
- SCFA production
- Entero-hepatic circulation
  - Bile acids

**Hormones and Hormonal Factors**
- Estrogens, testosterone, growth hormone, PTH, etc.
- Phytoestrogens

**Growth Factors**
- IGFs, IGFBPs etc

**Genetic Predisposition / Gene-Diet-Nutrient Interactions**

**Various Interactions?**

**Risk of CRC**

**Modulators of Cell Cycle Kinetics**
- Cell proliferation, Differentiation, Apoptosis

**Other Potential Factors/Mech.**
- e.g. Stress, behaviour
- Carcinogen metabolism
- Environment
- Immunity Modulation

**Chronic / Localised Inflammation**
- CRP, IL-6, TNFα etc
Vitamin D: Key Priorities, Challenges and Future Research Opportunities

Summary: Body vitamin D status appears to be associated with risk of some cancers, particularly colorectal cancer

- Associations with various other cancers, particularly pancreatic cancer, in different populations worldwide require clarification
  - Need longer term studies, with multiple measures of blood 25OHD status
  - Need a better understanding of vitamin D-gene interactions and their impact on disease risk
- Causality with cancer remains to be determined
- More prospective information is required on cancer survivorship
- Public health policy formation in terms of population wide vitamin D supplementation requires further study
  - More information is required on possible adverse effects of long term, high circulating vitamin D concentrations

Conflict of Interest Statement: none
Acknowledgements

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• The World Cancer Research Fund (WCRF) for study funding