Vitamin D and Cancer

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Serum 25(OH)D Safety Limits for Healthy Adults

Serum 25(OH)D level, ng/ml
(1 ng/ml = 2.5 nmol/L)
Optimal Vitamin D Status for Colorectal Cancer Prevention
A Quantitative Meta Analysis
Edward D. Gorham, MPH, PhD, Cedric F. Garland, DrPH, Frank C. Garland, PhD, William B. Grant, PhD, Sharif B. Mohy, MPH, Martin Lipkin, MD, Harold L. Newmark, ScD, Edward Giovannucci, MD, ScD, Melissa Wei, BS, Michael F. Holick, MD, PhD

Background: Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.

Methods: Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Petos' Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose-response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.

Results: Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 1.02, 0.96, 0.90, and 0.86 (p<0.0001) for colorectal cancer. According to the DeMets-O'Brien-Lang test for homogeneity of pooled data, the studies were heterogeneous (chi2=1.90, df=4, p=0.50). The pooled odds ratio for the highest quintile versus the lowest was 0.89 (p<0.0001, 95% confidence interval, 0.75-1.08). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level ≥35 ng/mL, compared to <12 ng/mL.

Conclusions: The evidence to date suggests that daily intake of 1000-2000 IU/day of vitamin D3 could reduce the incidence of colorectal cancer with minimal risk.


Introduction
The Women's Health Initiative demonstrated that a low dose of vitamin D did not protect against colorectal cancer within 7 years of follow-up; however, a meta-analysis indicates that a higher dose may reduce its incidence.

There were approximately 145,200 new cases and 39,000 deaths from colorectal cancer in the United States during 2005.2 An observation of higher age-adjusted mortality rates of colorectal cancer in the northern and northeastern United States compared to the southwest, Hawaii, and Florida led to a theory that vitamin D of mainly solar origin may reduce risk of colorectal cancer through a mechanism involving calcium metabolism, intercellular adherence, and contact inhibition. Since then, five observational studies have explored the association of serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D) with risk of colorectal cancer.3-7 However, an overall dose-response gradient for the effect of serum levels of 25(OH)D on colorectal cancer risk has not been determined. This meta-analysis provides an estimated dose-response gradient that may be of help in planning for a useful role of vitamin D in control of colorectal cancer.

Methods

Study Inclusion
The PubMed database was searched for the period from January 1966 to December 2006 by using the terms "Vitamin D"

55% reduction in colon cancer risk associated with 38 ng/ml serum 25(OH)D

$P_{trend} < 0.0001$

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

Female Breast Cancer Incidence

Age-Adjusted to 1970 USSMP

Year of Diagnosis

Incidence Rate Per 100,000 Females

Connecticut

SEER 9
Relative risk of breast cancer mortality, by baseline serum 25-hydroxyvitamin D concentration, divided at the median, NHANES III cohort, 1988-2000

Relative risk of **all cause mortality**, by serum vitamin D level among 512 women with early stage breast cancer, followed 11.6 years, three Toronto University Hospitals, 2008

Source: P J Goodwin, Ennis M, Pritchard KI, Koo JN, Hood N. Vitamin D deficiency is common at breast cancer diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 BC. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, May 30-June 3, 2008. Abstract number: 08-AB-31397-ASCOAM.
Serum 25(OH)D Safety Limits for Healthy Adults

Breast cancer
Colorectal cancer
Ovarian cancer
Type I diabetes
Multiple sclerosis
Fractures
Myocardial infarction
Cerebrovascular accident (CVA)
Metabolic syndrome
Rickets

Serum 25(OH)D level, ng/ml
(1 ng/ml = 2.5 nmol/L)

No downside in green.
Renal stones in red arc?
Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial.

Joan M Lappe, Dianne Travers-Gustafson, K Michael Davies, Robert R Recker, and Robert P Heaney

ABSTRACT
Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking.
Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incidence of colorectal cancers.
Design: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1,179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4°N. Subjects were randomly assigned to receive 1,400–1,500 mg supplemental calcium alone (Ca-only), supplemental calcium plus 1,100 IU vitamin D₃ alone (Ca + D), or placebo.
Results: When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < 0.03). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.23 (P = 0.01) and 0.007 (P = 0.06), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for cancer in the Ca + D group fell to 0.232 (CI: 0.09, 0.60; P < 0.005) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk.
Conclusions: Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women. This trial was registered at clinicaltrials.gov as NCT00332170. Am J Clin Nutr 2007;85:1586–91.

KEY WORDS Serum 25-hydroxyvitamin D, cancer, women, calcium and vitamin D₃ supplementation

INTRODUCTION
The relation of solar radiation to reduced cancer mortality in North America was identified >60 y ago (1). Garland and Garland (2) were the first to propose that vitamin D was responsible, specifically for the association with colon cancer. The inverse association between ambient solar radiation and cancer mortality rates has subsequently been described for cancers of the breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, and uterus, as well as for non-Hodgkin lymphoma and multiple myeloma (3–10).

This seeming protective effect was presumed to be mediated by the effect of solar radiation on vitamin D status. Exploration of the connection between vitamin D nutriture and chronic disease in humans received a critical stimulus with the availability of a physiologically stable indicator of vitamin D status [serum 25-hydroxyvitamin D, or 25(OH)D] and the designation of 25(OH)D as the functional indicator of vitamin D status by the Institute of Medicine (11). These developments have facilitated a more precise definition of the relation between cancer risk and vitamin D status. The inverse association has now been established for incident colorectal cancer (12) and for prostate cancer (13), among others. Gorham et al (14), quantifying the inverse relation between serum 25(OH)D and risk of colorectal cancer, calculated a 50% reduction in cancer risk at serum 25(OH)D concentrations ≥80 nmol/L.

Giovannucci (15, 16) and Holick (17, 18) have each recently reviewed the new large body of evidence linking low vitamin D status to increased risk of cancer. Similar associations were earlier noted for high calcium intake and reduced cancer risk (19–21), most prominently for colorectal cancer, whereby a luminal effect of high calcium intake provided a plausible mechanism.

The human evidence to date linking cancer and vitamin D has been observational in character, although several of the many positive studies linking vitamin D and cancer have been prospective. We had the opportunity to examine the relation of these nutrients to cancer incidence in a 4-y, double-blind, placebo-controlled trial of calcium and vitamin D supplementation for which cancer was the principal secondary endpoint. The null hypothesis was that there would be no difference in all-cancer incidence between the 3 calcium and vitamin D treatment groups.

SUBJECTS AND METHODS
Participants
The participants have been described in detail in an article describing their vitamin D status (22). Briefly, participants were recruited as a population-based sample from a 9-county, largely rural area in eastern Nebraska (latitude 41.4°N), with the use of random telephone dialing of all listed telephones in the counties of...
Randomized Controlled Trial of Vitamin D and Calcium

- Four years, N = 1,179 healthy women in Omaha NE
- Mean age 66.7 ± 7.3 years
- N = 1,032 finished trial (87.5%)
- Baseline serum 25(OH)D: 29 ± 8 ng/ml (72 ± 20 nmol/L)
- Three treatment groups:
  - Vitamin D₃ (1,100 IU/day) and calcium (1450 mg/day)
  - Calcium (1,450 mg/day)
  - Placebo
- Outcome: All cancers (mainly breast, lung and colon)

Randomized Controlled Trial

HAPPY BIRTHDAY DARWIN!
Figure 9A. Disjunction–Initiation–Natural Selection–Overgrowth–Metastasis-Involution-Transition (DINOMIT) Cancer Model

<table>
<thead>
<tr>
<th>Phase</th>
<th>Diagram</th>
<th>Process</th>
<th>Preventive or therapeutic action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D replete (normal)</strong></td>
<td><img src="image" alt="Diagram" /></td>
<td>Tight junctions intact. Intercellular communication intact. Contact inhibition functional. Most mature cells not mitotic. Normally scheduled apoptosis.</td>
<td>Serum 25(OH)D level of 40-60 ng/ml maintains functions at left via 1,25(OH)D local biosynthesis.</td>
</tr>
<tr>
<td>1. Disjunction due to low vitamin D and calcium</td>
<td><img src="image" alt="Diagram" /></td>
<td>Cells separate slightly. Tight junctions and E-cadherins are downregulated, intercellular communication is reduced or lost, contact inhibition is lost.</td>
<td>Upregulates E-cadherins, catenins, and intercellular junctions.</td>
</tr>
<tr>
<td>2. Initiation</td>
<td><img src="image" alt="Diagram" /></td>
<td>DNA errors or epigenetic events occur that support faster mitosis of some mature or developing epithelial cells.</td>
<td>Upregulates E-cadherin, contact inhibition, and return of mature cells to postmitotic status.</td>
</tr>
<tr>
<td>3. Natural selection</td>
<td><img src="image" alt="Diagram" /></td>
<td>Rapidly dividing, most aggressive progeny of these predominate; a cell with a 2% growth advantage will fill a tissue compartment in 9000 generations.</td>
<td>Inhibits mitosis of mature cells, reducing chances of natural selection of rapidly mitotic clone.</td>
</tr>
<tr>
<td>4. Overgrowth penetration of basement membrane</td>
<td><img src="image" alt="Diagram" /></td>
<td>Rapidly mitotic cells compete for nutrients and blood supply, dissolve and penetrate basement membrane</td>
<td>Re-establishes intercellular junctions and contact inhibition</td>
</tr>
</tbody>
</table>
4. **Overgrowth**

**stromal invasion**

Prevent lymphatic entry and transport

Re-establish tight junctions

Inhibit growth

4. (cont.)

**Overgrowth**

**lymphatic entry and transport**

Lymph vessel invasion, growth, and transport to lung, liver, brain

Re-establish tight junctions

Prevent lymphatic entry

Inhibit growth

5. **Metastasis**

Malignant cells colonize remote host site

If VDR still present, re-establish tight junctions, downregulate VEGF, reduce growth rate, restore contact inhibition

6. **Involution**

(growth arrest)

Onset of summer levels of 25(OH)D slows or arrests growth of malignant cells

Re-establishment of tight junctions, Reduction in growth rate, restoration of contact inhibition

7. **Transition**

Temporary transition to quiescent status

Maintenance of adequate serum 25(OH)D would support temporary transition to quiescent status. Low 25(OH)D would allow metastases to grow and spread
- Benefit/risk ratio for 2000 IU/day vitamin D is infinite

- There is no known risk of intake of 2000 IU/day of vitamin D, in healthy people

- There is no known risk to maintaining serum 25(OH)D of 50 ng/ml
Serum 25(OH)D Safety Limits for Healthy Adults

Breast cancer
Colorectal cancer
Ovarian cancer
Type I diabetes
Multiple sclerosis
Fractures
Myocardial infarction
Cerebrovascular accident (CVA)
Metabolic syndrome
Rickets

Serum 25(OH)D level, ng/ml
(1 ng/ml = 2.5 nmol/L)

No down side in green.
Renal stones in red arc?
Why can’t we all get along?
-- Rodney King, 1991

2000 IU/day vitamin D3
50 ng/ml serum target 25(OH)D
Relative risks* and 95% confidence limits for incident kidney stones by dietary calcium intake among men less than 60 years of age, N=1,496 incident cases in 266,772 participants, Health Professionals Follow-Up Study, 1986-2000

* Adjusted for age, body mass index, thiazide diuretics use, alcohol use, and intake of animal protein, potassium, sodium, vitamin C, and magnesium


Source: Curhan et al., 1997

\[ Y = -3 \times 10^{-6}x + 0.0018 \]

\[ R^2 = 0.82 \]

\[ P_{\text{trend}} = 0.0001 \]

\[ N = 864 \text{ Cases/903,848 person-years} \]
Incidence rate of kidney stones according to group, Women's Health Initiative clinical trial, 7-Year Follow-up