Randomized Trial of Vitamin D3 & Calcium Supplementation to Reduce Risk of Cancer

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Solar Radiation and Cancer Mortality

- 1941 Apperly - Cancer mortality higher in northern than in southern US states.
  
  Apperly, *Cancer Research* Vol 1, No 1 (1941); 1934–1938 health statistics

- 1989 Garland – Colon cancer mortality higher in the northeastern US than in the south.

Solar Radiation and Cancer Mortality

An inverse correlation between cancer death rates and sunlight exposure has been found for numerous cancers. Some of them include:

- breast
- colon
- rectum
- prostate
- stomach
- bladder
- thyroid
- non-Hodgkins lymphoma
- ovary
- lung
- pancreas
- uterus
- kidney
- esophagus
- multiple myeloma

Grant W. Cancer 2002;94
Holick M.. Prog Biophysics Mol Biol 2006;92:
Giovannucci E. Cancer Causes and Control 2005;16
Risk of Fatal Cancer by Quartile of 25OHD

- German men and women
- Referred for coronary angiography
- Age 62±10 yrs
- 3162 cases and 95 controls
- 1997-2000
- Median follow up of 7.5 yrs
- Death due to cancer confirmed by death certificates

Pilz et al, 2008
Serum 25(OH)D & Prostate Cancer

- 13 yr longitudinal study
- 19,000 men
- 149 cases prostate CA

Ahonen et al., 2000

\[ P \text{ for trend} = 0.01 \]
Serum 25(OH)D & Prostate Cancer

those with the lowest 25(OH)D level were 70% more likely to develop prostate CA than those in the highest quartile.

*Ahonen et al., Cancer Causes & Control 11:847-852 (2000)
Risk of Breast Cancer by Quintile of 25OHD

- German women aged 50-74
- Postmenopausal
- 1394 cases and 1365 controls
- 2002-2005
- Histologically confirmed primary invasive or in situ breast cancer

Abbas et al., 2007
COLORECTAL CANCER

- Nurses’ Health Study
- ages 46–78
- nested case-control study
- 193 incident cases

Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-40</td>
<td>1.0</td>
</tr>
<tr>
<td>2nd-55</td>
<td>0.8</td>
</tr>
<tr>
<td>3rd-66</td>
<td>0.6</td>
</tr>
<tr>
<td>4th-78</td>
<td>0.4</td>
</tr>
<tr>
<td>5th-100</td>
<td>0.2</td>
</tr>
</tbody>
</table>

25(OH)D Quintiles (with medians*) *nmol/L

P = 0.02
• The preponderance of evidence from ecological, cohort, and case control studies supports an anticancer effect of vitamin D.
• However, there were studies that did not find the effect.
• A few studies showed an increased risk of cancer with higher serum 25OHD levels.
Risk of Prostate Cancer by Quintile of 25(OH)D
Example of the U-shaped Curve

Nested Case-Control Study in Nordic Men (622 cases and 1451 controls)

Randomized Clinical Trials

Women’s Health Initiative (WHI)

36,282 women randomly assigned to 400 IU vitamin D3/d and 1000 mg calcium/d or placebo for both

Primary outcome – fracture; secondary outcome colorectal and breast cancer

No effect of vitamin D intervention on cancer incidence

- Vitamin D$_3$ dose – 400 IU
- Poor treatment adherence
- 15% of placebo subjects crossed into the active group by taking their own supplements
- 58% of subjects were assigned to hormone replacement therapy in the study

WHI did find a highly significant inverse association between baseline 25OHD and incident colon cancer. Risk for lowest quartile was 2.5 times greater than highest quartile.
Cumulative survival according to treatment with vitamin D (n=1345) or placebo (n=1341)

- 2686 British men and women
- RCT
- Vit D3 100,000 IU q 4 mos/5 yrs (~800 IU/d)
- Vit D3 had no effect on overall survival or cancer survival

Trivedi et al 2003
Randomized Trial of Vitamin D3 & Calcium Supplementation and All-type Cancer

Specific Aims

• Primary: to determine the anti-fracture efficacy of supplementation with calcium or calcium and vitamin D in a population of older women.

• Secondary: to determine the efficacy of supplementation in reducing incident cancer risk of all types.

Funded by the National Institute of Aging
Randomized Trial of Vitamin D3 & Calcium Supplementation and All-type Cancer

Random sample of the population
N = 1179 post-menopausal women
Ages 55-89
Randomized, double-blind, placebo-controlled
Four yrs duration
Three groups
1. Calcium 1400-1500 mg/d
2. Vitamin D3 1100 IU/d plus calcium
3. Placebo for both

Target Population

- Healthy women in a nine-county rural Nebraska area
- At least four years postmenopausal
- 55 years of age and older
- Any ethnic background
- Living independently
Population-Based Study

- In human clinical studies, we want to make inferences from the sample about the population from which the sample is derived.
- Convenience samples are more likely to have unknown biases that render the sample different than the population.
- Probability sampling is the best way to obtain a sample that is representative of the population.
- Simple random sampling is the easiest form of probability sampling; each individual has an equal probability of being selected for the sample.
Simple Random Sampling

Midwest Survey and Research (MSR), a market research firm:

- used a complete list of telephone numbers for target area
- randomly selected numbers from all households with listed telephone numbers and called them to do an initial telephone screen.
- continued calling until 1179 women were selected who met the inclusion and exclusion criteria and were willing to participate in this four year study.
- reported 96,301 dialings and 27,713 persons contacted.
Exclusion Criteria

- History of cancer except:
  a) superficial basal or squamous cell carcinoma of the skin
  b) other malignancies treated curatively more than 10 years ago
- History of chronic kidney disease or renal calculi
- Diagnosis of Paget’s metabolic bone disease
Measurements

Annually
- Serum 25OHD (RIA –IDS, Fountain Hills AZ) Our lab participates in the international quality assessment by DEQAS.
  - A sample of each lot of vitamin D3 was analyzed at the beginning and end of each year to assure potency.

Semiannually
- Supplement compliance
- Review of medical status & meds.
  Cancer cases were validated by medical records.

Baseline and end of study
- Dietary assessment
Adherence

- Mean adherence (defined as $\geq 80\%$ of assigned doses)
  - 86\% for vitamin D
- 74\% for calcium.

Of the 1179 women enrolled, 1024 (86.8\%) completed the study.
## Subject Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Calcium</th>
<th>Calcium/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=288</td>
<td>N=445</td>
<td>N=446</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66.1±6.8</td>
<td>66.5±7.2</td>
<td>67.3±7.7</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63±0.06</td>
<td>1.63±0.06</td>
<td>1.62±0.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.2±14.7</td>
<td>77.7±16.0</td>
<td>75.8±15.0</td>
</tr>
<tr>
<td>Body mass index (wt/ht²)</td>
<td>28.8±5.5</td>
<td>29.4±5.9</td>
<td>28.8±5.5</td>
</tr>
<tr>
<td>Diet calcium intake (mg/d)</td>
<td>699±415</td>
<td>692±388</td>
<td>662±397</td>
</tr>
<tr>
<td>Total calcium intake (mg/d)</td>
<td>1062±588</td>
<td>1058±597</td>
<td>1020±559</td>
</tr>
</tbody>
</table>
## Baseline and 12-month Serum 25OHD (nmol/L - ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± S.D)</th>
<th>12 months (mean ± S.D)</th>
<th>Change (mean ± S.D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>72.1 ± 20.7</td>
<td>71.1 ± 19.8</td>
<td>-0.23 ±14.7</td>
</tr>
<tr>
<td></td>
<td>28.8 ± 8.3</td>
<td>28.4 ± 7.9</td>
<td>-0.09 ± 5.9</td>
</tr>
<tr>
<td>Calcium only</td>
<td>71.6 ± 20.5</td>
<td>71.0 ± 20.3</td>
<td>-0.74 ±13.0</td>
</tr>
<tr>
<td></td>
<td>28.6 ± 8.2</td>
<td>28.4 ± 8.1</td>
<td>-0.30 ± 5.2</td>
</tr>
<tr>
<td>Calcium plus D</td>
<td>71.8 ± 20.0</td>
<td>96.0 ± 21.4</td>
<td>+23.9 ± 17.8</td>
</tr>
<tr>
<td></td>
<td>28.7 ± 8.0</td>
<td>38.4 ± 8.6</td>
<td>9.6 ± 7.1</td>
</tr>
</tbody>
</table>
25(OH)D in Older Women in Nebraska at Baseline

- women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU

Lappe et al., JACN 2006

~65%
25(OH)D in Older Women in Nebraska at Baseline

- women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU

Lappe et al., JACN 2006
Cancer Occurrence

Over the 4 years of study 50 women were diagnosed with cancer, 13 in the first year and 37 thereafter.
## Number of Cancers by Site and Treatment Group

<table>
<thead>
<tr>
<th>Anatomical Site</th>
<th>Placebo n = 288</th>
<th>Calcium n = 445</th>
<th>Vitamin D plus Calcium n = 446</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lymph/Leukemia/Myeloma</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Uterus</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>20 (6.9%)</td>
<td>17 (3.8%)</td>
<td>13 (2.9%)</td>
</tr>
</tbody>
</table>
Kaplan-Meier survival curves (i.e., free of cancer) for the 3 treatment groups in the entire cohort of 1,179 women.

- Calcium and Vitamin D: P < 0.01, Relative Risk = 0.40
- Calcium only
- Placebo

Kaplan-Meier survival curves for the 3 treatment groups in the cohort of women free of cancer at 1 year of intervention (n = 1,085).

- Calcium and Vitamin D
  - $P < 0.01$
  - Relative Risk = 0.23

- Calcium only

- Placebo

Logistic regression models were developed to explore determinants of cancer incidence.

- 12-month 25OHD (P < 0.002)
- Baseline 25OHD (P < 0.03)

- Treatment and 12 month 25OHD level - only 25OHD was a significant predictor ($R^2 = 0.037; P < 0.05$)

- Treatment and baseline 25OHD - both were significant predictors ($R^2 = 0.055; P < 0.05$).

- Neither age or BMI was a significant predictor.
Study Limitations/Strengths

- Primary outcome was antifracture efficacy
- Small sample size compared to many cancer studies

+ Population-based study with few exclusion criteria
+ Rigorous design (double-blind, randomized, placebo-control)
+ High adherence to supplement regimen
+ Low dropout rate
Our study is the first to report the effects of vitamin D status on all-cancer incidence.

It is also the first randomized clinical trial that used a vitamin D intervention sufficient to raise serum 25OHD to optimum levels and that targeted a cancer outcome.
“The statistical analysis of the Nebraska trial was not correct.

• For instance, subjects that received (Ca only) had a decrease in cancer risk of similar magnitude to subjects receiving (Ca + D). Thus a correct intent to *threat* analysis comparing the (Ca + D) group with (Ca only pooled with placebo) shows no significant decrease in cancer risk.

• In contrast, an intent to *threat* analysis of (Ca + D pooled with Ca only) versus placebo shows a significant reduced cancer risk due to calcium supplements.

• The methodology and statistical analysis of this trial have been much criticised (Sood *et al.*, 2007; Bolland *et al.*, 2007; Ojha *et al.*, 2007; Shabas *et al.*, 2008). For instance, the cancer incidence was unusually high in the placebo group, a bias that undermined the trial’s findings (Shabas *et al.*, 2008). In conclusion, the design of the Nebraska trial was biased, and its results were negative for vitamin D.”

Summary

- A variety of research designs, other than randomized clinical trials, provide evidence that vitamin D decreases risk of cancer.

- One randomized controlled trial with all-type cancer as a secondary outcome reported a 60% reduction in cancer incidence in older women.

- However, many members of the scientific community, including the International Agency for Research on Cancer, find the data lacking support for a causative effect.

- In addition, there are concerns about safety of consistently “high” levels of 25(OH)D over a long period of time.

- Two randomized trials, funded by the NIH, are currently in progress - designed to run 4 and 7 years, respectively.
Vitamin D: The Sunshine Vitamin