Vitamin D, Calcium and Prostate Cancer: The Good, the Bad, and the Dairy

Susan Steck, Ph.D., M.P.H., R.D.
Associate Professor
Department of Epidemiology and Biostatistics
Cancer Prevention and Control Program
Center for Research in Nutrition and Health Disparities
Arnold School of Public Health
University of South Carolina

ssteck@sc.edu
Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions

Racial Disparities
Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions
Prostate cancer incidence and mortality by race and ethnicity, U.S. 1999-2009

Incidence

Mortality

CDC, National Program of Cancer Registries and NCI, SEER
CDC National Center for Health Statistics
Risk Factors for Prostate Cancer

- Age
- Race
- Family history of prostate cancer

- possibly dairy products and/or calcium intake?
Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions
Production and metabolism of vitamin D

D2 (ergocalciferol) or D3 (cholecalciferol)

Prostate, breast, colon: VDR-mediated activity

Production and metabolism of vitamin D

Skin → ProD3 → PreD3 → Vitamin D3 → 25(OH)D → 1,25(OH)2D

Diet
Limited dietary sources of vitamin D:
- Fortified milk
- Fortified orange juice
- Salmon and other fatty fish
- Vitamin supplements

Liver → Kidney

Prostate, breast, colon: VDR-mediated activity

Increase calcium and phosphorus absorption
Mobilize calcium stores
Maintain serum calcium and phosphorus

Adapted from Hollis, B. W. et al. CMAJ 2006;174:1287-1290
Potential mechanisms for dairy/calcium association with increased risk of PrCA

- Marker of high fat diet
- Estrogen in milk
- Increased levels of insulin-like growth factor
- Suppression of production of 1,25(OH)₂D
- Increased inflammation

Krishnan and Feldman, Endocr Relat Cancer. 2010 Jan;17(1):R19-R38
Genomic mechanism of vitamin D activity

- **Mineral Homeostasis (bone, kidney, intestine)**
- **Differentiation of keratinocytes**
- **Inhibition of proliferation of breast, colon and prostate cancer cells and promyelocytic leukemia cells**
- **Modulation of immune system:**
  - Suppression of proliferation of activated T cells
  - Inhibition of cytokines (such as IL-2 and IFN-γ)
Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions
Prostate cancer incidence rates versus per capita milk intake among 38 countries

Butler et al. Cancer Res; 70(12) June 15, 2010 [adapted from Zhang and Kesteloot]
Meta-analysis: Relative risks of prostate cancer comparing the highest with the lowest dairy product intake categories

Study, year (reference)

Mills et al, 1989 (29)
Severson et al, 1989 (24)
Hsing et al, 1990 (10)
Le Marchand et al, 1994 (25)
Schuurman et al, 1999 (26)
Chan et al, 2000 (9)
Michaud et al, 2001 (27)
Chan et al, 2001 (14)
Rodriguez et al, 2003 (28)
Tseng et al, 2003 (23)

Pooled, Total
Pooled 1
Pooled 2

RR (95% CI)
Meta-analysis: Relative risks of prostate cancer comparing the highest with the lowest calcium intake categories


© The Author 2005. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.
Decreased cancer survival with high whole fat milk/dairy intake

- **Health Professional Follow-up Study (HPFS)**
  - Increased risk of lethal prostate cancer for those consuming whole milk >4 times/week compared to 0-3 times/month
  - Decreased risk of lethal prostate cancer for those consuming skim/low fat milk greater than once/day compared to 0-3 times/month
    - Pettersson et al. CEBP 2012

- **Life After Cancer Epidemiology (LACE)**
  - Higher risk of mortality after breast cancer diagnosis with high intake of high-fat dairy (but not low-fat dairy)
    - Kroenke et al. JNCI 2013
Objectives

- To examine the association between **dairy product** and **calcium** intake and **prostate cancer aggressiveness** among **African American** and **European American** men diagnosed with prostate cancer.

- To examine effect modification by **NSAIDs** use.
North Carolina-Louisiana Prostate Cancer Project (PCaP)
PI: Dr. James Mohler

Case-only study of prostate cancer among African American and European American men
Methods: PCaP

Eligibility criteria:
- Residents of NC and LA study areas with a first diagnosis of histologically confirmed adenocarcinoma of the prostate
- Between 40 and 80 years of age
- English-speaking
- Not institutionalized (nursing home)
- Not cognitively impaired or in a severely debilitated physical state
- Not under the influence of alcohol, severely medicated or apparently psychotic at the time of interview
- Could self-identify as either African American or Caucasian American
Methods (continued)

- In-person interviews by registered nurse
  - NCI Diet History Questionnaire
    - modified for use in Southern population
    - assessed diet in year prior to diagnosis
    - excluded participants with unreasonable energy intakes (<500 or >6000 kcals/d)
  - Other demographic and lifestyle questionnaires
- Blood draw at interview
- Medical record abstraction
- High aggressive cases:
  - Gleason sum ≥8, or PSA>20ng/ml, or Gleason sum=7 AND stage cT3-cT4
- Low aggressive cases:
  - Gleason sum <7 AND clinical stage cT1-cT2 AND PSA <10 ng/ml
- Intermediate aggressive cases:
  - All others
Methods (continued)

- Statistical Analyses:
  - Descriptive statistics
  - Logistic regression comparing low/intermediate to high aggressive
  - Potential confounders and effect modifiers:
    - Age
    - Race
    - Education
    - Marital status
    - Body mass index
    - Diabetes
    - Smoking status
    - PSA screening history
    - Energy intake
    - Alcohol intake
    - Physical activity
    - Family history of PrCA
    - NSAIDs
## Table 1. Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>Low/Intermediate Aggressive (n=1732)</th>
<th>High Aggressive (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ± SD)</td>
<td>63 ± 8</td>
<td>65 ± 8</td>
</tr>
<tr>
<td>Dairy, servings/d (mean ± SD)</td>
<td>1.4 ±1.2</td>
<td>1.5 ±1.2</td>
</tr>
<tr>
<td>Calcium, mg/d (mean ± SD)</td>
<td>872 ± 457</td>
<td>915 ± 480</td>
</tr>
<tr>
<td>Race</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>African American</td>
<td>817 (47%)</td>
<td>206 (56%)</td>
</tr>
<tr>
<td>European American</td>
<td>915 (53%)</td>
<td>164 (44%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some/Less than high school</td>
<td>324 (19%)</td>
<td>112 (30%)</td>
</tr>
<tr>
<td>High school grad/vo/tec</td>
<td>535 (31%)</td>
<td>102 (28%)</td>
</tr>
<tr>
<td>Some college/College grad</td>
<td>616 (36%)</td>
<td>121 (33%)</td>
</tr>
<tr>
<td>Grad school/prof. degree</td>
<td>256 (15%)</td>
<td>35 (9%)</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th></th>
<th>Low/Intermediate Aggressive (n=1732)</th>
<th>High Aggressive (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight &lt; 25</td>
<td>330 (19%)</td>
<td>60 (17%)</td>
</tr>
<tr>
<td>Overweight ≥25 - 30</td>
<td>750 (44%)</td>
<td>139 (39%)</td>
</tr>
<tr>
<td>Obese ≥30</td>
<td>641 (37%)</td>
<td>161 (45%)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>606 (35%)</td>
<td>99 (27%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>891 (51%)</td>
<td>194 (52%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>235 (14%)</td>
<td>77 (21%)</td>
</tr>
<tr>
<td><strong>NSAIDs use (Yes)</strong></td>
<td>1054 (61%)</td>
<td>228 (62%)</td>
</tr>
<tr>
<td>1st degree relative w/ prostate cancer</td>
<td>430 (27%)</td>
<td>77 (22%)</td>
</tr>
</tbody>
</table>
Table 2. Adjusted* ORs and 95%CIs for prostate cancer aggressiveness for dairy and calcium intake

<table>
<thead>
<tr>
<th></th>
<th>Low/Int Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dairy intake (servings/d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>794</td>
<td>162</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1 - ≤ 2</td>
<td>592</td>
<td>112</td>
<td>0.9</td>
<td>0.7, 1.2</td>
</tr>
<tr>
<td>&gt;2</td>
<td>334</td>
<td>86</td>
<td>1.1</td>
<td>0.8, 1.6</td>
</tr>
<tr>
<td><strong>Calcium from food (mg/d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 500</td>
<td>341</td>
<td>63</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>500 - ≤ 1000</td>
<td>854</td>
<td>167</td>
<td>1.0</td>
<td>0.8, 1.8</td>
</tr>
<tr>
<td>1000 - ≤ 1500</td>
<td>383</td>
<td>87</td>
<td>1.2</td>
<td>0.7, 1.8</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>142</td>
<td>43</td>
<td>1.5</td>
<td>0.8, 2.6</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, education, PSA screening history, body mass index, smoking status, and energy intake
Table 3. Adjusted ORs and 95% CI for prostate cancer aggressiveness for **calcium intake** stratified by NSAIDs use

<table>
<thead>
<tr>
<th>NSAIDs = Yes</th>
<th><strong>Calcium intake (mg/d)</strong></th>
<th>Low/Int Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 600</td>
<td>293</td>
<td>68</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>600 - ≤ 1000</td>
<td>409</td>
<td>79</td>
<td>0.9</td>
<td>0.5, 1.3</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>352</td>
<td>81</td>
<td>0.8</td>
<td>0.4, 1.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NSAIDs = No</th>
<th><strong>Calcium intake (mg/d)</strong></th>
<th>Low/Int Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 600</td>
<td>242</td>
<td>36</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>600 - ≤ 1000</td>
<td>253</td>
<td>55</td>
<td>1.8</td>
<td>1.0, 3.2</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>174</td>
<td>49</td>
<td>2.3</td>
<td>1.1, 4.9</td>
<td></td>
</tr>
</tbody>
</table>

P<0.05 for interaction
Table 4. Adjusted ORs and 95%CI for prostate cancer aggressiveness for dairy intake stratified by NSAIDs use

<table>
<thead>
<tr>
<th></th>
<th>Low/Int Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs = Yes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy (servings/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>440</td>
<td>104</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1 - ≤ 2</td>
<td>388</td>
<td>65</td>
<td>0.7</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>&gt;2</td>
<td>220</td>
<td>55</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td><strong>NSAIDs = No</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy (servings/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>350</td>
<td>56</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1 - ≤ 2</td>
<td>201</td>
<td>47</td>
<td>1.7</td>
<td>1.1, 2.7</td>
</tr>
<tr>
<td>&gt;2</td>
<td>113</td>
<td>31</td>
<td>1.7</td>
<td>0.9, 3.0</td>
</tr>
</tbody>
</table>

P<0.05 for interaction
No effect of other related dietary factors or supplements:

- Calcium supplements
- Vitamin D intake
- Vitamin D supplements
- Milk intake
Case-only study so cannot evaluate incidence of disease, only aggressiveness

Strengths:
- Large, population-based study, half of enrolled participants are African American
- Extensive questionnaires for evaluating potential confounders

Weaknesses:
- Association does not prove causation, cannot rule out the role of chance in findings
- Did not consider dose or type of NSAIDs
Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions
Using data from NASA on UV irradiance and data from SEER on cancer incidence, determined that prostate cancer incidence decreased with increasing levels of the UV index, and found a reduction in racial disparity in prostate cancer incidence in areas with moderately high UV indices compared to lower UV indices.

White, fairest skin in January
Black, darkest skin in January

White, fairest skin in July
Black, darkest skin in July
Potential mechanisms for dairy/calcium association with increased risk of PrCA

- Marker of high fat diet
- Estrogen in milk
- Increased levels of insulin-like growth factor
- Suppression of production of 1,25(OH)₂D
- Increased inflammation

Krishnan and Feldman, Endocr Relat Cancer. 2010 Jan;17(1):R19-R38
Production and metabolism of vitamin D

Production and metabolism of vitamin D involves several key steps:

1. **Solar exposure** leads to the production of vitamin D3 (cholecalciferol) in the skin.
2. **Liver** converts vitamin D3 to 25(OH)D.
3. **Kidney** further metabolizes 25(OH)D to 1,25(OH)2D.
4. **Intestines** and **bone** utilize 1,25(OH)2D to increase calcium and phosphorus absorption and mobilize calcium stores.
5. **Diet** can also provide vitamin D3 (cholecalciferol) or D2 (ergocalciferol) as limited dietary sources.

**Dietary Sources of Vitamin D**:
- Fortified milk
- Fortified orange juice
- Salmon and other fatty fish
- Vitamin supplements

**Breast, prostate, colon**: VDR-mediated activity

- **Increase calcium and phosphorus absorption**
- **Mobilize calcium stores**
- **Maintain serum calcium and phosphorus**

Adapted from Hollis, B. W. et al. CMAJ 2006;174:1287-1290
Meta-analysis of observational studies of 25(OH)D and prostate cancer

Gandini et al 2011 Int J Cancer
## Suggested cutpoints for circulating 25(OH)D

- Measured in ng/ml or nmol/L
- Conversion: 1 ng/ml = 2.5 nmol/L

<table>
<thead>
<tr>
<th></th>
<th>ng/ml</th>
<th>nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deficiency</strong></td>
<td>&lt; 8 - 20</td>
<td>&lt; 20 - 50</td>
</tr>
<tr>
<td><strong>Insufficiency</strong></td>
<td>20 - 30</td>
<td>50 - 75</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>&gt; 100 - 200</td>
<td>&gt;250 - 500</td>
</tr>
</tbody>
</table>
To examine the association between plasma 25(OH)D and prostate cancer aggressiveness among African American and European American men diagnosed with prostate cancer.

Measured plasma 25(OH)D by LC/MS/MS in 1200 PCaP participants.

High aggressive cases (n=414):
- Gleason sum ≥8, or PSA>20ng/ml, or Gleason sum=7 AND stage cT3-cT4, or Gleason sum=7 with primary pattern 4

Low aggressive cases (n=786):
- Gleason sum <7 AND clinical stage cT1-cT2 AND PSA <9 ng/ml
Figure 1. Plasma 25(OH)D by race and aggressiveness

Woloszynska-Read et al., presented at AACR 2013 Annual Meeting
Figure 2. Vitamin D sufficiency status by race and aggressiveness

Woloszynska-Read et al., presented at AACR 2013 Annual Meeting
### Table 5. Adjusted* ORs and 95%CIs for prostate cancer aggressiveness for plasma 25(OH)D (ng/ml) by race

<table>
<thead>
<tr>
<th></th>
<th>Low Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African Americans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 13.3</td>
<td>103</td>
<td>59</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>13.3 - &lt; 18.9</td>
<td>105</td>
<td>79</td>
<td>1.8</td>
<td>1.1, 3.0</td>
</tr>
<tr>
<td>≥ 18.9</td>
<td>104</td>
<td>87</td>
<td>1.6</td>
<td>1.0, 2.6</td>
</tr>
<tr>
<td><strong>European Americans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21.1</td>
<td>158</td>
<td>69</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>21.1 - &lt; 26.7</td>
<td>158</td>
<td>59</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>≥ 26.7</td>
<td>158</td>
<td>61</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
</tbody>
</table>

* Adjusted for age, BMI, education, smoking status, season of blood draw, PSA screening history, physical activity, energy intake, alcohol intake, NSAIDs use

Woloszynska-Read et al., presented at AACR 2013 Annual Meeting
Sensitivity Analyses

- No change in results or interpretation with:
  - Adjusting for weight change
  - Adjusting for time to blood processing
  - Excluding intermediate aggressive cases
  - Changing cutpoints for plasma 25(OH)D quantiles
Table 6. Adjusted* ORs and 95% CIs for prostate cancer aggressiveness for ratio of plasma 25(OH)D/1,25(OH)2D among African Americans

<table>
<thead>
<tr>
<th>Ratio of plasma 25(OH)D/1,25(OH)2D</th>
<th>Low Agg (n)</th>
<th>High Agg (n)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>35</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>27</td>
<td>0.9</td>
<td>0.5, 1.7</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>39</td>
<td>1.1</td>
<td>0.6, 2.1</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>69</td>
<td>2.2</td>
<td>1.2, 4.0</td>
</tr>
</tbody>
</table>

* Adjusted for age, BMI, education, smoking status, season of blood draw, PSA screening history, physical activity, energy intake, alcohol intake, NSAIDs use, study site
Issues to Consider

- Case-only study so cannot evaluate incidence of disease, only aggressiveness
- Temporality: Blood samples collected after diagnosis and at one point in time
  - Weight change?
  - Effects of therapy?
- Genetic differences in vitamin D binding protein affinity, vitamin D metabolism or VDR activity
**DBP polymorphism predicts differences in response to vitamin D supplementation**

Fig. 1. Response of 25(OH)D to supplementation by T436K genotype. (A) Association of serum 25(OH)D concentrations with genotypes at baseline and after 1 year vitamin D loading in low-dose (600 IU/d) and high-dose (4000 IU/d) groups. (B) Association between genotypes and percentage increase in 25(OH)D at one year. (C) Specific DBP binding capacity by genotype at baseline and after 1 year vitamin D loading. Error bars show mean ± SE.

Vitamin D metabolism and function

Diet

Sunlight

Vitamin D

DBP (GC)

25 (OH)D (major circulating form)

CYP27A1 (liver)

CYP27B1 (kidney & other target organs)

1,25 (OH)2D (active form)

CYP24A1

1,24,25 (OH)3D (metabolic degradation)

Target cells including Prostate

Vitamin D Response Element

VDR Target Genes

Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions
Observed significant interaction between calcium/dairy intakes and NSAIDs use
  - high calcium and dairy intakes among non-regular users of NSAIDs was positively associated with aggressive prostate cancer

Suggests moderation in dairy/calcium intake particularly among men not regularly using NSAIDs.
Higher plasma 25(OH)D was associated with increased odds of high aggressive prostate cancer among African Americans only.

Preliminary results suggest high 25(OH)D and low 1,25(OH)2D have highest odds of high aggressive prostate cancer.
Future Directions

- Vitamin D associations with cancer may vary by specific genotypes (e.g., VDR, CYP24A1, CYP27A1, CYP27B1, CYP2R1, and/or GC) and these associations may differ by race.

- Measurement of free 25(OH)D may help to explain racial differences observed.

- Analyses of whole fat milk vs. lowfat/skim milk, serum calcium, phosphorus, and PTH.
Kaplan-Meier plot of the prostate cancer-free status over time of men in the calcium and placebo groups.


Overall log rank p = 0.42
Randomized Controlled Trial: Vitamin D (1,100 IU) plus calcium (1400-1500mg) in 1,180 women in Nebraska

\[ P = 0.013 \]
Relative Risk = 0.40 (0.2, 0.8)

Kaplan-Meier estimates of the cumulative hazard ratio for invasive breast cancer with supplemental calcium (1000mg) plus vitamin D (400IU) as compared with placebo (WHI)
Effect Modification by Vitamin D Intake or by Personal Supplement Use: Calcium + Vitamin D and WHI Breast Cancer Outcome

<table>
<thead>
<tr>
<th>Baseline vitamin D intake</th>
<th>RR (95%CI)</th>
<th>Chlebowski et al. JNCI 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200IU</td>
<td>0.79 (0.65, 0.97)</td>
<td></td>
</tr>
<tr>
<td>200-&lt;400IU</td>
<td>0.97 (0.74, 1.26)</td>
<td></td>
</tr>
<tr>
<td>400-&lt;600IU</td>
<td>0.98 (0.77, 1.24)</td>
<td></td>
</tr>
<tr>
<td>600+IU</td>
<td>1.34 (1.01, 1.78)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal supplement use</th>
<th>RR (95%CI)</th>
<th>Bolland et al. AJCN 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplement use</td>
<td>0.82 (0.70, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Supplement use</td>
<td>1.08 (0.94, 1.24)</td>
<td></td>
</tr>
</tbody>
</table>
What is the VITAL study?
The *VIT*amin D and Omeg*A*-3 *TriaL* (VITAL) is a research study in 20,000 U.S. men and women investigating whether taking daily dietary supplements of vitamin D (about 2000 IU) or fish oil (about 1 gram of omega-3 fatty acids) reduces the risk of developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. Recruitment for the study began in January 2010.

Who is running the VITAL study?
The study is funded by the National Institutes of Health and is being run by Harvard Medical School and the Brigham and Women’s Hospital in Boston, MA. But you don’t have to travel to Boston to participate. All of the study materials—the study pills and the study forms—will be mailed directly to you and we are recruiting participants from every state in the country. Participation in the study does not require any clinic visits.

Who is eligible to participate in the VITAL study?
Both women and men can join the study. If you are a woman aged 65 or older or a man aged 60 or older and you have not previously had a heart attack, stroke or cancer (other than skin cancer), you may be eligible to participate in the VITAL study.

[www.vitalstudy.org](http://www.vitalstudy.org)
Acknowledgments

**Funding source**

- Department of Defense:
- PCaP: DAMD 17-03-2-0052
- Vitamin D Ancillary Study: DAMD 11-1-0568 (Prostate Cancer Health Disparity Research Award)
Collaborators

USC
- Angela Murphy
- Hongmei Zhang
- Rebecca George
- Amanda Ayers
- Sam Antwi
- Daria McMahon

Roswell Park
- James Mohier
- Candace Johnson
- Anna Woloszynska-Read
- Donald Trump
- Jeff Conroy
- Sean Glenn

PCaP
- Elizabeth Fontham
- Joseph Su
- Lenore Arab
- Jeannette Bensen
- John Adams, UCLA
- Laura Farnan
- Patricia Basta
- Paul Godley
- Merle Mishel
- Gary Smith

CANCER PREVENTION & CONTROL PROGRAM