Shedding Light on Vitamin D in Colorectal Cancer

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ISCO Spring 2017 Meeting
March 17, 2017
"Anything I can get you son?
 tea, coffee....vitamin D?"
Increase in Vitamin D Publications

Figure 4  Rate of growth of the number of peer-reviewed publications published each year, which have the term ‘vitamin D’ in their ‘title’
Outline

- *Colorectal Cancer*

- The Vitamin D Pathway

- Vitamin D and Colorectal Cancer
  - Biology
  - Risk
  - Survival

- Clinical Trials

- Conclusions
### Estimated New Cancer Cases* in the US in 2017

<table>
<thead>
<tr>
<th>Site</th>
<th>Males 836,150</th>
<th>Females 852,630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>23%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
### Estimated Cancer Deaths in the US in 2017

<table>
<thead>
<tr>
<th>Site</th>
<th>Males 318,420</th>
<th>Females 282,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Prostate</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>

- Breast: 14% for males, 14% for females
- Colon & rectum: 8% for males, 8% for females
- Lung & bronchus: 27% for males, 25% for females
- All other sites: 24% for males, 24% for females
Advances in Systemic Therapy for Colorectal Cancer


5-FU

Irinotecan
Capecitabine
Oxaliplatin
Bevacizumab
Cetuximab
Panitumumab
Aflibercept
Regorafenib
Ramucirumab
Trifluridine/Tipiracil

Targeted therapies

5-FU = 5-fluorouracil.
AJCC Stage and 5-Year Survival

Doc,

What should I eat?
Should I exercise?
What else can I do?
Diet and Cancer Risk

- The relationship between diet and cancer development has been a topic of great interest for over a century.


- Many studies report conflicting results.
## Risk Factors for Colorectal Cancer

<table>
<thead>
<tr>
<th>Decrease Risk</th>
<th>Increase Risk</th>
<th>Uncertain Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Family history</td>
<td>Statins</td>
</tr>
<tr>
<td>Exercise</td>
<td>IBD</td>
<td>Fiber</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Diabetes</td>
<td>Glycemic index</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Obesity</td>
<td>Fruits/Vegetables</td>
</tr>
<tr>
<td>Post-menopausal estrogen</td>
<td>Red meat</td>
<td>Folic Acid</td>
</tr>
<tr>
<td>Calcium</td>
<td>Western diet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>
Impact of Diet and Lifestyle Factors on Cancer Patients

- Many studies have evaluated the role of diet and lifestyle factors on the risk of developing colorectal cancer.

- Few studies have investigated whether these factors have an impact on patients already diagnosed with colorectal cancer:
  - Disease recurrence
  - Survival
  - Tolerance of chemotherapy
CALGB 89803: Clinical Trial of Adjuvant Chemotherapy in Stage III Colon Cancer

1264 patients enrolled between 1999 and 2001

No significant difference found between treatment arms

CALGB 89803: Diet and Lifestyle Companion Study

Patients enroll on adjuvant therapy trial

Complete **1st** questionnaire

0 2 4 6 8 10 12 14 16

Chemotherapy
every 3 month f/u

Complete **2nd** questionnaire

Included questions on:

- Diet and supplements
- Smoking
- Physical activity
- Medication use
- Other information
Emerging Data

- Decrease risk of recurrence / improve survival
  - Physical activity
  - Vitamin D
  - Aspirin or COX-2 inhibitor

- Increase risk of recurrence and mortality
  - Class III obesity (BMI ≥35 kg/m2)
  - Western pattern diet

- No association with recurrence or survival
  - Multivitamins
  - Change in weight
  - Obesity (BMI <35 kg/m2)
  - Statin use
Outline

- Colorectal Cancer

- **The Vitamin D Pathway**

- Vitamin D and Colorectal Cancer
  - Biology
  - Risk
  - Survival

- Clinical Trials

- Conclusions
The Vitamin D Pathway

Biological Actions of Vitamin D

- ↑ differentiation
- ↑ apoptosis
- ↓ proliferation
- ↓ invasiveness
- ↓ metastatic potential
- ↓ angiogenesis
- ↓ inflammation

Measurement of Vitamin D

- Diet accounts for only 20% of vitamin D in humans

- Plasma levels of vitamin D metabolites more accurate indicator of vitamin D status

- 1,25-dihydroxycholecalciferol [1,25(OH)₂D₃]
  - Physiologically active metabolite
  - Acts as hormone
  - Largely distributed intracellularly
  - Tightly regulated in circulation to ensure calcium homeostasis

- 25-hydroxyvitamin D₃ [25(OH)D]
  - Levels determined by sun exposure and dietary intake
  - The predominant circulating metabolite
  - Converted to 1,25(OH)₂D in kidney

Plasma Thresholds of 25(OH)D

<table>
<thead>
<tr>
<th>Result</th>
<th>Blood 25-OH-D Level</th>
<th>ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient*</td>
<td>&lt; 50</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Insufficient*</td>
<td>50 to &lt; 75</td>
<td>20 to &lt; 30</td>
</tr>
<tr>
<td>Sufficient*</td>
<td>75 to 375</td>
<td>30 to 150</td>
</tr>
<tr>
<td>Most advantageous†</td>
<td>90 to 100</td>
<td>36 to 40</td>
</tr>
<tr>
<td>Toxic‡</td>
<td>≥ 375</td>
<td>≥ 150</td>
</tr>
</tbody>
</table>

Abbreviation: 25-OH-D, 25-hydroxyvitamin D.

*These definitions were derived, in part, from provocative testing examining the physiologic impact of vitamin D supplementation on parathyroid hormone levels and calcium absorption in the gut.²²

†The advantageous range arose from a review of the association of 25-OH-D levels with a broad range of health outcomes that extended beyond bone and calcium metabolism.²¹

‡The toxic range has been associated with hypercalcemia and its complications.²²

### Institute of Medicine Recommendations

#### TABLE S-2 Vitamin D Dietary Reference Intakes by Life Stage (amount/day)

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>AI</th>
<th>EAR</th>
<th>RDA</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>—</td>
<td>1,000 IU (25 μg)</td>
</tr>
<tr>
<td>0 to 6 mo</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>—</td>
<td>1,500 IU (38 μg)</td>
</tr>
<tr>
<td>6 to 12 mo</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Children</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>2,500 IU (63 μg)</td>
</tr>
<tr>
<td>1–3 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>3,000 IU (75 μg)</td>
</tr>
<tr>
<td>4–8 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>3,000 IU (75 μg)</td>
</tr>
<tr>
<td>Males</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>9–13 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>51–70 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>800 IU (20 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>Females</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>9–13 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>51–70 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>800 IU (20 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>Lactation</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>400 IU (10 μg)</td>
<td>—</td>
<td>600 IU (15 μg)</td>
<td>4,000 IU (100 μg)</td>
</tr>
</tbody>
</table>

**NOTE:** AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

Outline

- Colorectal Cancer
- The Vitamin D Pathway
- Vitamin D and Colorectal Cancer
  - Biology
  - Risk
  - Survival
- Clinical Trials
- Conclusions
Vitamin D receptor (VDR) and 1-α-hydroxylase are expressed in colorectal cancer (CRC) cells

In vitro studies

– Well-differentiated CRC cell lines have high VDR levels
– Anti-proliferative effects of vitamin D are greatest in cell lines that express high levels of VDR

Animal studies:

– CRC-prone rats maintained on a high vitamin D diet develop fewer tumors and metastases than controls
– Treatment of $APC^{min}$ mice with vitamin D decreases tumor burden
– Adenoma numbers and size increase in VDR-null $APC^{min}$ mice

Plasma 25(OH)D and Risk of Colorectal Cancer

33% decrease in colorectal cancer with higher levels of vitamin D

WHI Trial of Vitamin D + Calcium

n = 36,282 healthy post-menopausal women

Vitamin D 400 IU/day + Calcium 1,000 mg/day

Placebo

Secondary outcome = colorectal cancer
Average treatment duration = 7 years

WHI Trial Results

**Figure 3.** Kaplan–Meier Estimates of the Cumulative Hazard for Invasive Colorectal Cancer with Supplemental Calcium plus Vitamin D, as Compared with Placebo.

CI denotes confidence interval. Two events in each group that occurred after year 8 are not shown.
Randomized Trial of Vitamin D + Calcium

n = 1,179 healthy post-menopausal women living in Nebraska

Vitamin D 1,100 IU/day + Calcium 1,500 mg/day

Calcium 1,500 mg/day

Placebo

Cancer-Free Survival

Ca+D Arm
RR = 0.23 (0.09–0.60)

P < 0.005
A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas

John A. Baron, M.D., Elizabeth L. Barry, Ph.D., Leila A. Mott, M.S.,
Judy R. Rees, B.M., B.Ch., Robert S. Sandler, M.D., Dale C. Snover, M.D.,
Robert M. Bostick, M.D., M.P.H., Anastasia Ivanova, Ph.D., Bernard F. Cole, Ph.D.,
Dennis J. Ahnen, M.D., Gerald J. Beck, Ph.D., Robert S. Bresalier, M.D.,
Carol A. Burke, M.D., Timothy R. Church, Ph.D., Marcia Cruz-Correa, M.D., Ph.D.,
Jane C. Figueiredo, Ph.D., Michael Goodman, M.D., M.P.H., Adam S. Kim, M.D.,
Douglas J. Robertson, M.D., Richard Rothstein, M.D., Aasma Shaukat, M.D., M.P.H.,
March E. Seabrook, M.D., and Robert W. Summers, M.D.
Polyp Trial: Study Schema

History of polyps removed at colonoscopy (n=2,259)

Vitamin D3 1,000 IU/d

Placebo

Calcium carbonate 1,200 mg/day

Placebo

Calcium carbonate 1,200 mg/day

Placebo

Polyps at 3-5 years

## Polyp Trial: Primary Results

### Table 2. Risk Ratios for Colorectal Adenoma Outcomes According to Treatment Assignment.*

<table>
<thead>
<tr>
<th>Treatment Assignment</th>
<th>One or More Adenomas†</th>
<th>One or More Advanced Adenomas‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients/Total No. (%)</td>
<td>Risk Ratio (95% CI)</td>
</tr>
<tr>
<td>Vitamin D vs. no vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vitamin D</td>
<td>442/1035 (42.7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>438/1024 (42.8)</td>
<td><strong>0.99 (0.89–1.09)</strong></td>
</tr>
<tr>
<td>Calcium vs. no calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No calcium</td>
<td>362/761 (47.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>Calcium</td>
<td>345/762 (45.3)</td>
<td>0.95 (0.85–1.06)</td>
</tr>
<tr>
<td>Calcium plus vitamin D vs. calcium alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>259/655 (39.5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Calcium plus vitamin D</td>
<td>259/643 (40.3)</td>
<td>1.01 (0.88–1.15)</td>
</tr>
<tr>
<td>Calcium plus vitamin D vs. neither agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither calcium nor vitamin D</td>
<td>183/380 (48.2)</td>
<td>Reference</td>
</tr>
<tr>
<td>Calcium plus vitamin D</td>
<td>174/381 (45.7)</td>
<td>0.93 (0.80–1.08)</td>
</tr>
</tbody>
</table>

## Polyp Trial: Analysis

### Strengths
- Assessed vitamin D and calcium individually and combined
- Well powered
- High compliance and adherence rates

### Weaknesses
- Clinical significance of recurrent diminutive polyp unclear
- Low dose of vitamin D
- Plasma 25(OH)D levels increased by only 7.83 ng/mL
- Insufficient duration of supplementation
VITamin D and OmegA-3 Trial: the VITAL Study

24,000 healthy individuals across the U.S. with oversampling for African-Americans
Vitamin D and Cancer Mortality

- Mortality rates for colon cancer are twice as high in the northeast U.S. compared to the southwest U.S. for both white and black Americans.¹

- Ecologic study of UV-B solar radiation found that insufficient exposure was associated with premature cancer death.¹

- Large observational study in Norway (n=115,456) demonstrated a >15% lower case fatality rate from breast, colon, and prostate cancer in cases diagnosed in the fall versus winter.²,³

¹ Grant WB. Cancer 2002; 94: 1867-75.
Plasma 25(OH)D and Survival in 304 Colorectal Cancer Patients (NHS/HPFS)

Plasma 25(OH)D (ng/mL)

Adjusted for age, gender, stage, grade, site, year of diagnosis, season of blood draw, BMI, and post-diagnosis physical activity

People with highest level of vitamin D have 48% improvement in outcome

Hazard Ratio for Death

P trend = 0.02

NCCTG N9741: Randomized Trial of Chemotherapy in Previously Untreated Stage IV Colorectal Cancer Patients

- FOLFOX
- IFL
- IROX

547 patients provided blood samples at study registration for use in future biomarker research

n = 1,691

Important Findings from N9741

Median plasma 25(OH)D = 20.0 ng/mL

Ng K et al. J Clin Oncol 2011; 29(12): 1599-1606.
Vitamin D Status and Survival of Metastatic Colorectal Cancer Patients: Results from CALGB/SWOG 80405 (Alliance)

Kimmie Ng¹, Alan P. Venook², Kaori Sato¹, Bruce W. Hollis³, Donna Niedzwiecki⁴, Cynthia Ye⁴, I-Wen Chang⁵, Bert H. O’Neil⁶, Federico Innocenti⁷, Heinz-Josef Lenz⁸, Charles D. Blanke⁹, Robert J. Mayer¹, Charles S. Fuchs¹, Jeffrey A. Meyerhardt¹

¹Dana-Farber Cancer Institute, ²University of California San Francisco, ³Medical University of South Carolina, ⁴Alliance Statistics and Data Center, ⁵Wayne Memorial Hospital, ⁶Indiana University Hospital, ⁷University of North Carolina at Chapel Hill, ⁸University of Southern California, ⁹Oregon Health and Science University
CALGB/SWOG 80405: Final Design

Original

mCRC 1st-line

KRAS wild type (codons 12, 13)

Strata:
- FOLFOX/FOLFIRI
- Prior adjuvant chemo
- Prior XRT

FOLFIRI or FOLFOX
MD choice

N = 1140

1° Endpoint: Overall Survival
Vitamin D Study Cohort

Randomized (n=2,334)

Bevacizumab (n=899)

- RAS WT (n=256)
- RAS mutant (n=167)
- Unknown (n=476)

Cetuximab (n=902)

- RAS WT (n=270)
- RAS mutant (n=180)
- Unknown (n=452)

Both (n=533)

- RAS WT (n=0)
- RAS mutant (n=124)
- Unknown (n=409)

Plasma 25(OH)D Available (n=1,043)

- n=172
- n=126
- n=123
- n=173
- n=121
- n=124
- n=0
- n=62
- n=142

Ng K et al. ASCO 2015.
# Overall Survival by Quintile of 25(OH)D

<table>
<thead>
<tr>
<th>Quintile</th>
<th>mOS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.5</td>
<td>21.7-28.6</td>
</tr>
<tr>
<td>2</td>
<td>30.0</td>
<td>25.8-32.2</td>
</tr>
<tr>
<td>3</td>
<td>28.4</td>
<td>24.2-31.0</td>
</tr>
<tr>
<td>4</td>
<td>27.2</td>
<td>25.0-31.5</td>
</tr>
<tr>
<td>5</td>
<td>32.6</td>
<td>27.7-36.9</td>
</tr>
</tbody>
</table>

Log-rank $P = 0.01$

**Quintiles 1 & 2**
- No. at Risk: 417, 328, 227, 117, 56, 27, 5, 1

**Quintiles 3 & 4**
- No. at Risk: 418, 332, 237, 125, 64, 34, 11, 2

**Quintile 5**
- No. at Risk: 208, 171, 137, 76, 41, 22, 1, 0

Ng K et al. ASCO 2015.
Progression-Free Survival by Quintile of 25(OH)D

<table>
<thead>
<tr>
<th>Quintile</th>
<th>mPFS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.1</td>
<td>9.2-11.3</td>
</tr>
<tr>
<td>2</td>
<td>10.9</td>
<td>9.6-11.6</td>
</tr>
<tr>
<td>3</td>
<td>11.4</td>
<td>9.7-12.9</td>
</tr>
<tr>
<td>4</td>
<td>12.7</td>
<td>11.1-13.6</td>
</tr>
<tr>
<td>5</td>
<td>12.2</td>
<td>10.8-14.2</td>
</tr>
</tbody>
</table>

Log-rank $P = 0.02$

Ng K et al. ASCO 2015.
Multivariate Analysis: Overall Survival

People with highest level of vitamin D have 35% improvement in overall survival

Hazard Ratio for Death

Plasma 25(OH)D (ng/mL)

<table>
<thead>
<tr>
<th>Plasma 25(OH)D (ng/mL)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 - 10.8</td>
<td>1.0</td>
<td>[0.66 - 1.03]</td>
</tr>
<tr>
<td>10.9 - 15.4</td>
<td>0.83</td>
<td>[0.65 - 1.02]</td>
</tr>
<tr>
<td>15.5 - 19.2</td>
<td>0.81</td>
<td>[0.63 - 1.00]</td>
</tr>
<tr>
<td>19.3 - 24.0</td>
<td>0.79</td>
<td>[0.51 - 0.83]</td>
</tr>
<tr>
<td>&gt; 24.1</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, stage, race, ECOG PS, chemo backbone, previous adjuvant therapy, assigned biologic, RAS mutation status, season of blood draw, geographic region, BMI, and physical activity.

Ng K et al. ASCO 2015.
* Adjusted for age, sex, stage, race, ECOG PS, chemo backbone, previous adjuvant therapy, assigned biologic, RAS mutation status, season of blood draw, geographic region, BMI, and physical activity.

Ng K et al. ASCO 2015.
Outline

- Colorectal Cancer
- The Vitamin D Pathway
- Vitamin D and Colorectal Cancer
  - Biology
  - Risk
  - Survival
- Clinical Trials
- Conclusions
Challenges

- Willingness to accept randomization to placebo or lower dose of vitamin D
- High baseline use of vitamin D supplements and multivitamin supplements
- Compliance
- Contamination
- Funding
Vitamin D Deficiency in Blacks

- 60% of African-Americans are vitamin D deficient
  - Blacks have approximately half the levels of 25(OH)D compared to Whites

- Mechanism thought to be lower synthesis in skin with greater melanin content, which blocks UV-B penetration
  - Reduced rate of conversion of cholecalciferol to 25(OH)D may also contribute
  - Dark-skinned individuals require 5x the amount of UV-B radiation to produce a similar amount of vitamin D cutaneously

- Could hypovitaminosis D in Blacks account for disparities in colorectal cancer incidence and mortality?
  - 19% higher incidence
  - 40% higher mortality

Defining Optimal Doses of Vitamin D for Chemoprevention in Blacks

R A N D O M I Z A T I O N

During winter months

n=80
Blood drawn at baseline, 3 months, and 6 months for 25(OH)D levels

1,000 IU vitamin D3
Placebo

n=80
Primary endpoint = dose level needed to achieve a 25(OH)D level of 33 ng/mL in 80% or more of participants

2,000 IU vitamin D3

n=80
Correlative studies on effect of germline genetic variation, and impact on inflammatory markers, PSA, and HTN

4,000 IU vitamin D3

n=80
Daily x 3 months
Study Results

Median baseline 25(OH)D = 15.3 ng/mL

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Placebo</th>
<th>1,000 IU vitamin D3</th>
<th>2,000 IU vitamin D3</th>
<th>4,000 IU vitamin D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20th Percentile 25(OH)D, ng/mL</td>
<td>6.7</td>
<td>22.6</td>
<td>26.8</td>
<td>37.2</td>
</tr>
</tbody>
</table>
Determining the RDA of Vitamin D

- 2011 IOM report recommends target plasma 25(OH)D = 20 ng/mL

- RDA = daily intake needed to achieve 20 ng/mL in 97.5% of population

- Current RDA per IOM = 600 IU/day (ages 19-70)

- Based on data in this trial of 328 African-Americans:

  **RDA of Vitamin D = 1,640 IU/day**
SUNSHINE: Randomized Phase II Trial of Vitamin D Supplementation in Metastatic CRC

R A N D O M I Z A T I O N

1:1

n=140

FOLFOX-bevacizumab + Vitamin D3 8,000 IU/day x 2 weeks (loading dose), followed by Vitamin D3 4,000 IU/day (maintenance dose)

FOLFOX-bevacizumab + Vitamin D3 400 IU/day

- Bank blood at serial intervals for 25(OH)D assays
- Restaging scans and CEA every 4 cycles
- Treat until disease progression
- Primary end point = PFS

Participating Sites:
DFCI, MGH, BIDMC, DF/HCC satellites & affiliates, Northwestern, Vanderbilt, MSTI
Randomized Trial of Preoperative Vitamin D: Determining Transcriptional Targets

Stage I-III colon cancer or resectable colorectal cancer liver metastases undergoing surgical resection

Randomize

Arm A: Higher-dose vitamin D3 orally once daily 50,000 IU/day x 7 days, then 10,000 IU/day

Follow-up blood draw for 25(OH)D*

Arm B: Placebo orally once daily days

Surgery

Harvest malignant and adjacent benign tissue for mechanistic laboratory studies

Co-investigators:
Surgical oncology: Thomas Clancy, MD
Colorectal surgery: Ronald Bleday, MD; Joel Goldberg, MD
Pathology: Jason Hornick, MD, PhD

n=48
Subset of VDR Binding Sites Gained in Tumors Compared to Normal Colon

3,369 VDR binding sites

VDR high in tumor

PoolT_VDR PoolN_VDR

Scale 0-15

Tumor Normal
Outline

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Conclusions & Future Directions

- Colorectal cancer has the most consistent data for modifiable diet and lifestyle factors impacting risk of disease
- There is now emerging data that these factors may also impact risk of cancer recurrence and survival among established colorectal cancer patients and survivors
- Higher plasma levels of 25(OH)D are associated with decreased risk of colorectal cancer and improved survival among colorectal cancer patients
- Metastatic colorectal cancer patients and Blacks have high rates of vitamin D deficiency and insufficiency, and may require higher doses of supplementation
- Randomized clinical trials are ongoing
- Efforts to decipher target genes from integrated ChIP-seq and RNA-seq analysis of vitamin D-treated patients are promising and ongoing
- Precision medicine analyses of the effect of vitamin D are ongoing
Vitamin D Receptor-Mediated Stromal Reprogramming Suppresses Pancreatitis and Enhances Pancreatic Cancer Therapy


Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status

Mingyang Song, Reiko Nishihara, Molin Wang, Andrew T Chan, Zhi Rong Qian, Kentaro Inamura, Xuehong Zhang, Kimmie Ng, Sun A Kim, Kosuke Mima, Yasutaka Sukawa, Katsuhiro Nosho, Charles S Fuchs, Edward L Giovannucci, Kana Wu and Shuji Ogino

Gut 2016 65: 296-304 originally published online January 15, 2015
doi: 10.1136/gutjnl-2014-308852
Evidence is imperfect

Discuss risks and benefits

Correlative but not causal

Other health benefits to maintaining sufficient levels of vitamin D

Monitor plasma 25(OH)D levels and titrate to ≥ 30ng/mL

Most patients require vitamin D3 1,000-2,000 IU/day
Acknowledgments

- Dana-Farber Cancer Institute
  - Charles Fuchs
  - Ramesh Shivdasani
  - Paloma Cejas
  - Ewa Sicinska
  - Shuji Ogino
  - Jeffrey Meyerhardt
  - Kaori Sato
  - Chen Yuan
  - Michele Vincitore
  - Christopher Mackintosh
  - Christine Ganser
  - Andrew McAward

- Harvard School of Public Health
  - Edward Giovannucci
  - Walter Willett

- Massachusetts General Hospital
  - Andrew Chan
  - Hui Zheng

- Medical University of South Carolina
  - Bruce Hollis

- NCCTG and Alliance
  - Alan Venook
  - Daniel Sargent
  - Lindsay Renfro
  - Donna Niedzwiecki

- Participants of NHS and HPFS
- Our clinical trial patients & staff

- Pharmavite, LLC