Vitamin D and Cancer: Current Dilemmas/Future Needs

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In 2010, cancer will become the world’s leading cause of death.
By **2020**, cancer could kill **10.3 million** people per year unless we act.

Trends
The biggest cause of increase are in developing and newly industrialized countries.

The relative increase is smallest in some Western countries where populations are rejecting tobacco and adopting healthier lifestyles.

If Prevent Do Not Need to Treat!

Dr. Lee Jong-wook, Director General WHO
It has been estimated that about 1/3 of all cancer deaths may be attributable to dietary factors.
How Strong is the Evidence that vitamin D may have a role in cancer?
Age-Adjusted Prostate Cancer Mortality Rates (Whites) and Ultraviolet Radiation in 3073 U.S. Counties

Hanchette and Schwartz, Cancer 70:261-9, 1992
Cancer Mortality and Latitude

Dietary Vitamin D and Colorectal Cancer

Serum 25(OH)D and Colorectal Cancer Risk

Garland 1989
Braun
Tangrea 1996
Feskanich 2004
Wactawski-Wende 2006

Pooled odds ratio = 0.49
p < 0.0001

Serum 25(OH)D and Risk of Colorectal and Breast Cancer

Vitamin D and Cancer Incidence

1179 Healthy women, 66±7 yrs, 4 yr study, Calcium (1400 mg/d), Vitamin D$_3$ (1100 IU/d)

<table>
<thead>
<tr>
<th>Site</th>
<th>Placebo</th>
<th>Calcium</th>
<th>Calcium+D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Blood</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Uterus</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td><strong>15</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

Vitamin D Status and Mortality in Breast Cancer Patients

512 women, early stage breast cancer, Toronto, 11.6 year follow-up

Goodwin et al., J. Clin Oncol.23: 3755-3763, 2009
Serum 25(OH)D and Prostate Cancer Risk

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

Serum 25(OH)D and Pancreatic Cancer

200 cases and 400 controls from the ATBC study of Finnish Male Smokers

P<0.001

1\textsuperscript{-}α\,
Hydroxylase Activity is Reduced in Prostate Cancer

Expression of $1\alpha$-Hydroxylase and VDR in Human Colon Tissue

Matusiak et al. Cancer Epidemiol Biomark Prev 14:2370-2376, 2005
Vitamin D₃

Liver

Kidney

Prostate
Colon
Breast
Bones

Target cell nucleus

1α hydroxylase

25(OH)D₃

24,25(OH)₂D₃

Cyp 24

25(OH)D₃

1,25(OH)₂D₃

Retinoid X receptor

VDR

VDRE

Transcription
Effects of VDR ablation on chemically-induced carcinogenesis

DMBA:
- ↑ mammary hyperplasias in VDRKO mice
- ↑ hormone independent mammary carcinomas in VDRKO mice
- Skin papillomas developed in VDRKO but not WT mice
- ↑ Lymphomas in VDRKO mice
- Tumor incidence in ovary, liver, lung, uterus unaffected by VDR

AOM:
- ↑ aberrant crypt foci (ACF) in VDRKO mice

Effect of Dietary Vitamin D in VDR Knockout Animals

Serum 25(OH)D₃

Dietary vitamin D (IU/kg)

Tumor Development

Zinser & Welsh, personal communication
Single Nucleotide Polymorphisms in the VDR gene

Human VDR >470 reported SNPs
Distribution and frequency varies among ethnic groups
These polymorphisms may alter 1,25 Vitamin D function and thereby affect cancer risk
VDR FokI Polymorphism Affects Calcium Metabolism

Abrams et al. J. Bone Mineral Res. 20: 945-953, 2005
Dietary Calcium, VDR FokI Genotype and Colon Cancer Risk


**Dietary Calcium**
- <388 mg/day
- >388 mg/day

**P for trend = 0.004**
Vitamin D Status, VDR FokI Genotype and Prostate Cancer Risk

1,066 prostate cancer cases and 1,618 age-matched controls from the Physician’s Health Study

OR for Prostate Cancer

Serum 25(OH)D
- <24.4 ng/ml
- >24.4 ng/ml

p-value for interaction = 0.01

Haplotypes in the VDR Gene Influence Colon Cancer Risk

BsmI (b or B), poly (A) S or L, Fok I (f or F) and CDX2 (G or A); 1574 cases and 1970 controls

Haplotype frequencies varied by ethnic group

OR for colon cancer varied from 0.06 to 51.12 depending on haplotype

VDR Haplotypes and Bladder Cancer Risk in India

130 patients with bladder cancer and 346 controls in Northern India analyzed for Taq-1 and Fok-1 polymorphisms

Allele frequencies in India:
- Fok-1: FF 44%
  - Ff 49%
  - ff 7%
- Taq-1: TT 49%
  - Tt 40%
  - tt 11%

* p<0.001

One Size Does Not Fit All! Genetic Background May Determine Who Will Respond to Vitamin D for Cancer Prevention
Animal Models Are Providing Fundamental Clues About Vitamin D and Cancer Risk

"It would never work, Nichole; I'm in the experimental group and you're in the control."
Gene-Nutrient Interactions and Colon Cancer

Yang et al, Cancer Res. 61, 565, 2001
A Western-Style Diet Induces Malignant Neoplasms in the Colon of Normal Mice

Approximately 25% of the mice develop a single tumor …..this is a new mouse model of sporadic colon cancer, which represents the vast majority of human colon cancer

Supplementation with vitamin D and calcium inhibits tumor formation

Vitamin D and Calcium Modulate Wnt Signaling

Dietary Vitamin D and Calcium Modulate Cell Proliferation and Apoptosis in the Colon

Vitamin D Inhibits Cancer Cell Proliferation and Metastasis

Lewis Lung Carcinoma Cells

Nakagawa et al. Carcinogenesis, 26:429-440, 2005
Vitamin D Modifies Prostaglandin Metabolism

Vitamin D

CYP24

Vitamin D Degradation

PGE$_2$

DEGRADATION

15PGDH

AA

Expression

COX-2

Activity

PGE2

PG RECEPTORS

↓ Cell proliferation, ↑ Apoptosis, ↓ Metastasis, ↓ Angiogenesis

Vitamin D May Influence Genetic Events Associated with Several Cancer Processes

- Differentiation
- Apoptosis
- Carcinogen Metabolism
- Cell Proliferation
- Inflammatory Response
- Metastasis
Other Dietary components and Environmental Factors May Determine the Response to Vitamin D
Dietary Genistein Influences CYP24 and 1\alpha\textless Hydroxylase Expression in Mouse Colon

Cross HS et al. J. Nutrition 134: 1207s-1212s, 2004
Effect of Body Fat on Serum 25(OH)D Concentrations

Non-Hispanic White Women, aged 20-49, NHANES III Study

Effect of Physical Activity on Serum 25(OH)D Concentrations

Non-Hispanic White Women, aged 20-49, NHANES III Study

Selected activities quartiles (times/month)

0-1 2-9 10-29 30+

ng/mL

p= 0.0000

Colon Cancer Incidence

BMI

Physical Activity

↓ 25(OH)D

Colon Cancer Incidence
Fish Oil Enhances the Cell Growth Inhibition of 1,25 (OH)$_2$D in Liver Cancer Cells

Chiang KC et al. Anticancer Res. 29: 3591-3596, 2009
VITAL (VITamin D and OmegA-3 Trial)

Randomized, Double-Blind, Placebo Controlled Study

20,000 men, age ≥ 60 and women ≥ 65 years

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Vitamin D (2000 IU)</th>
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<tbody>
<tr>
<td>Fish Oil (1000 mg)</td>
<td>Vitamin D and Fish Oil</td>
</tr>
</tbody>
</table>

Principal Investigators: Drs. JoAnn Manson and Julie Buring
Research Needs: Better Biomarkers

Absorbed dose \rightarrow \text{Biologically effective dose} \rightarrow \text{Inactive metabolite} \rightarrow \text{MOLECULAR TARGET}

- Dietary Exposure
- Susceptibility Factors
- Early Biological Effect

\text{Health Effects} + and -

\text{Altered structure/function}
Just when I knew all of life’s answers,
They changed all the questions!!