Vitamin D and Prostate Cancer

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The next slide locates the highest and lowest (age-adjusted) incidences of 21 common cancers. The figures are striking:

- The rate of prostate cancer among blacks in Atlanta is 70 times higher than in Tianjin, China. That’s 7,000 % higher.

- The rate of lung cancer among blacks in New Orleans is 19 times higher than in Madras, India. That’s 1,900 % higher.

- The rate of colon cancer among whites in Connecticut is 19 times higher than the rate in Madras, India.
TABLE 23–1 Variation Between Countries in the Incidence of Some Common Cancers

<table>
<thead>
<tr>
<th>SITE OF ORIGIN OF CANCER</th>
<th>HIGH-INCIDENCE POPULATION</th>
<th>LOW-INCIDENCE POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOCATION</td>
<td>INCIDENCE*</td>
</tr>
<tr>
<td>Lung</td>
<td>USA (New Orleans, blacks)</td>
<td>110</td>
</tr>
<tr>
<td>Breast</td>
<td>Hawai (Hawaiians)</td>
<td>94</td>
</tr>
<tr>
<td>Prostate</td>
<td>USA (Atlanta, blacks)</td>
<td>91</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Brazil (Recife)</td>
<td>83</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan (Nagasaki)</td>
<td>82</td>
</tr>
<tr>
<td>Liver</td>
<td>China (Shanghai)</td>
<td>34</td>
</tr>
<tr>
<td>Colon</td>
<td>USA (Connecticut, whites)</td>
<td>34</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Australia (Queensland)</td>
<td>31</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Hong Kong</td>
<td>30</td>
</tr>
<tr>
<td>Esophagus</td>
<td>France (Calvados)</td>
<td>30</td>
</tr>
<tr>
<td>Bladder</td>
<td>Switzerland (Basal)</td>
<td>28</td>
</tr>
<tr>
<td>Uterus</td>
<td>USA (San Francisco Bay Area, whites)</td>
<td>26</td>
</tr>
<tr>
<td>Ovary</td>
<td>New Zealand (Polynesian Islanders)</td>
<td>26</td>
</tr>
<tr>
<td>Rectum</td>
<td>Israel (European and USA born)</td>
<td>23</td>
</tr>
<tr>
<td>Larynx</td>
<td>Brazil (São Paulo)</td>
<td>18</td>
</tr>
<tr>
<td>Pancreas</td>
<td>USA (Los Angeles, Koreans)</td>
<td>16</td>
</tr>
<tr>
<td>Lip</td>
<td>Canada (Newfoundland)</td>
<td>15</td>
</tr>
<tr>
<td>Kidney</td>
<td>Canada (NWT and Yukon)</td>
<td>15</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>France (Bas-Rhin)</td>
<td>14</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Canada (Ontario)</td>
<td>12</td>
</tr>
<tr>
<td>Testis</td>
<td>Switzerland (urban Vaud)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Incidence = number of new cases per year per 100,000 population, adjusted for standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, uterine cervix, uterus, and ovary are for women; other figures are for men. (Adapted from V.T. DeVita, S. Hellman, and S.A. Rosenberg (eds.), Cancer: Principles and Practice of Oncology, 4th edn. Philadelphia: Lippincott, 1993; based on data from C. Muir et al., Cancer Incidence in Five Continents, Vol. 5. Lyon: International Agency for Research on Cancer, 1987.)
What causes these very different cancer rates? Sunlight, diet, exercise, genetics, reporting errors?

In 1937, Peller and Stephenson (1) suggested, and in 1941, Apperly (2) showed a relation between low sunlight and high cancer mortality. Later, Garland et al. and Schwartz et al. linked poor vitamin D status to the higher risks of colon (3), breast (4), ovarian (5), and prostate (6; 7) cancers seen at higher latitudes (8). Low serum levels of vitamin D in winter may cause Seasonal Affective Disorder (SAD) (9).

Diet: the low cancer rates of India and East Asia may be due to low intakes of mammal meat and high intakes of curcumin and soy, respectively. After discussing vitamin D, I’ll briefly comment on soy and curcumin.

The next slide shows the incidence of colon cancer.
How much vitamin D should a normal person take per day to reduce the risk of cancer?

Holick (10) advises an adult to take at least 1400 IU of vitamin D$_3$ (cholecalciferol) each day.

Referring to the work of Heaney (11) et al., Giovannucci et al. (8) suggest that an adult take at least 1500 IU per day of vitamin D$_3$.

Hollis (12; 13) suggests that an adult take more than 2000 IU of vitamin D$_3$ per day, and that a pregnant woman take 6000 IU per day.
Vitamin D

UVB photons (300 nm) break the B ring of the steroid 7-dehydrocholesterol, which is the last intermediate in the biosynthesis of cholesterol. In the lipid bilayer, the resulting pre-vitamin D₃ isomerizes to vitamin D₃, which enters the bloodstream.

Liver cells add a hydroxyl group to the 25th carbon atom. This molecule 25(OH)D₃ is the dominant form of vitamin D in the blood. It lasts for days.

In kidney cells and other cells, including prostate cells, 1-OHase adds a hydroxyl group to the 1st carbon atom of 25(OH)D₃, making 1,25(OH)₂D₃, calcitriol, which is the active form of vitamin D. This (seco)steroid hormone lasts for hours.
Both 25(OH)D₃ and 1,25(OH)₂D₃ use carrier proteins to travel through the blood stream. But being hydrophobic, they easily slip through cell membranes.

Most human cells, including those of the prostate gland, have in their nuclei vitamin-D receptors (VDR’s) which are members of the nuclear-receptor superfamily. When 1,25(OH)₂D₃ binds to the ligand-binding region of the VDR, the VDR frees itself from its inhibitory proteins and dimerizes with the retinoid X receptor (RXR) \(^{(14)}\).

The VDR-RXR heterodimer then binds to DNA sequences known as vitamin D response elements (VDREs) in the promoter regions of target genes and recruits coactivator proteins that stimulate the transcription of the target genes \(^{(14)}\).
A VDR’s ligand-binding domain traps a vitamin D$_3$ molecule:
A VDR-RXR complex binds to a VDRE (RXR not shown):

The 30 min response to the (seco)steroid vitamin D₃:

![Diagram of early primary response to steroid hormone](image)

- Early primary response to steroid hormone:
  - Steroid hormone interacts with steroid hormone receptor.
  - Steroid-hormone-receptor complexes activate primary-response genes.
  - Induced synthesis of a few different proteins in the primary response.

Figure 15–14 part 1 of 2. Molecular Biology of the Cell, 4th Edition.
The delayed, secondary response to vitamin D₃:

(B) DELAYED SECONDARY RESPONSE TO STEROID HORMONE

secondary-response proteins

DNA

a primary-response protein shuts off primary-response genes

a primary-response protein turns on secondary-response genes

Calcitriol (1,25(OH)$_2$D$_3$), the active form of vitamin D$_3$, regulates calcium homeostasis and bone mineralization by its effects in intestine, bone, kidney, and parathyroid glands (15). It also reduces proliferation and increases differentiation in many malignancies including prostate cancer (PCa) (14).

Calcitriol increases the expression of the cyclin-dependent protein-kinase inhibitors p21 and p27 and so induces cell-cycle arrest in the G$_1$/G$_0$ phase. It down-regulates the expression of anti-apoptotic genes such as bcl-2. It regulates growth-factor action by modulating the expression of genes such as the insulin-like growth-factor-binding protein-3 (IGFBP-3) and the transforming growth factor $\beta$ (TGF$\beta$) (14).
Calcitriol reduces inflammation by inhibiting the prostaglandin pathway (14). Prostaglandins (PGs) are long-chain oxygenated fatty acids derived from arachidonic acid (AA). Cyclooxygenase-2 (COX-2) helps turn AA into the PG precursor PGH₂, which specific synthases convert to various PGs. The NAD⁺-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH) converts biologically active PGs into inactive ketoderivatives.

Calcitriol down-regulates the COX-2 gene and up-regulates the 15-PGDH gene: it doubly inhibits the prostaglandin pathway. COX-2 may induce cell proliferation, angiogenesis, and tumor invasiveness, and may decrease apoptosis and immune surveillance (14). NSAIDs, which also inhibit COX-2, have been shown to reduce PCa growth in cells and animals (16).
PGE2, a COX-2 product, activates COX-2 expression and helps human cancer cells grow \(^{(17; 18)}\).

PGs act thru G-protein-coupled membrane receptors, which activate signal-transduction pathways, such as those that induce the immediate-early gene \(c-fos\) and stimulate PCa growth \(^{(19)}\). Calcitriol reduces the secretion of PGE2 by PCa cells \(^{(14)}\). It also decreases mRNA expression of the PGE2 and PGF\(_{2\alpha}\) G-protein-coupled membrane-receptor subtypes EP2 and FP \(^{(19)}\). It also up-regulates the mitogen-activated protein kinase phosphatase 5 (MKP5) in primary prostatic adenocarcinoma cells (but not in cells derived from metastases) \(^{(20)}\). MKP5 dephosphorylates & inactivates the stress-activated protein kinase p38, which up-regulates the pleiotropic, inflammatory cytokine interleukin 6.
Thus calcitriol reduces PCa-promoting inflammation in at least four ways:

- By down-regulating COX-2, it slows the synthesis of prostaglandins.
- By up-regulating 15-PGDH, it catabolizes prostaglandins.
- By down-regulating the PGE$_2$ and PGF$_{2\alpha}$ prostaglandin receptors, it reduces the bio-activity of these prostaglandins.
- By up-regulating MKP5, it inactivates p38 and reduces IL-6 expression.
NSAIDs and Curcumin

NSAIDs are designed to reduce inflammation. They retard prostate cancer by inhibiting COX-1 and COX-2 in ways that are somewhat similar to the actions of calcitriol.

But while calcitriol upregulates 15-PGDH, some COX inhibitors, especially ciglitazone and curcumin, downregulate it (21). The mechanism of chemoprevention by these compounds may be that their inhibition of 15-PGDH leads to less production of highly reactive $\alpha,\beta$-unsaturated aldehydes and ketones in the tissues (21).

Curcumin is a spice used in curry; it may account for the minimal cancer rates of eight cities in India, although the Indian sunshine may have a bigger effect.
Soy

The lowest rate of prostate cancer is in Tianjin, a city on the coast of China at 39° 08’ north latitude. Soybeans and tofu are a large part of the diet in China and East Asia. In a study of 59 countries, soy was found to be the food most associated with a low rate of mortality from prostate cancer (22).

Plasma and urinary levels of phytoestrogens are much higher in countries with lower incidences of breast and prostate cancer than in countries with high incidences (23).

Of the phytoestrogens, the isoflavones genistein and daidzein, and the coumestan coumestrol seem to protect against PCa (23).
Per 100 g: soybeans contain 26.4 mg of genistein and 17.1 mg of daidzein; tofu has 16.2 and 7.4; and pinto beans have 1.3 mg of coumestrol (24).

Fig. 1. Structure of the isoflavonoids genistein (a), daidzein (b) and glycitein (c).

Fig. 3. Structure of the coumestan coumestrol.
Of the phytoestrogens, the isoflavones genistein and daidzein have received the most attention.

Genistein inhibits cell growth in prostate, breast, and lung cancer cell lines ([25; 26]).

It inhibits tyrosine kinases, topoisomerase II, $5\alpha$-reductase, and angiogenesis ([26]).

It induces G$_2$/M cell-cycle arrest and modulates the protein expression levels of at least two cell-cycle regulating proteins: it downregulates cyclin B, and upregulates p21$^{\text{WAF1}}$ ([25]).

Nuclear factor-$\kappa$B (NF-$\kappa$B) is a transcription factor that opposes apoptosis. Genistein inhibits NF-$\kappa$B and promotes apoptotic signaling mechanisms in androgen-sensitive (LNCaP) and androgen-insensitive (PC3) PCa cell lines ([25]).
Clinical Applications

NSAIDs and calcitriol inhibit prostate cancer in similar ways. Both are FDA-approved generic drugs. Aspirin and naproxen seem to be the most heart-friendly of the NSAIDs. In high doses, the long-term use of calcitriol can cause hypercalcemia; this seems to be its only side-effect. NSAIDs and calcitriol are synergistic: they inhibit PCa cell growth at dosages that are 2 to 10 times lower when used together than when used separately (19). They should be used together at safe dosages (27).

Soy is a food; curcumin is a spice. They should be used liberally.
Calcitriol Dosage

In a pilot study of eight men, the tolerated dose of calcitriol was 1.5 µg per day, based on maintaining calciuria at less than 350 mg daily (28). The calcitriol was taken at bedtime to minimize calcemic effects; no subject became hypercalcemic during the study (28).

In this study, calcitriol therapy significantly decreased the rate of PSA rise in 6 of 7 patients; the deceleration in the 7th man was not statistically significant (28).
Celecoxib Dosage

In a pilot study, 12 men who had biochemical relapse after RP or RT were given 200 mg of the COX-2 selective NSAID celecoxib (Celebrex) twice daily for one year. After 3 months, the PSA level declined in 5 patients, stayed constant in 3, and rose more slowly in 4 (29).
In a more recent placebo-controlled study (30), 78 men with rising PSAs after RP or RT were given 400 mg of celecoxib twice daily. The PSA doubling times more than tripled in 20% of the placebo group and in 40% of the celecoxib group. Mean PSA velocity increased by 3% in the placebo group and decreased by 3.4% in the celecoxib group. Due to the Vioxx nightmare, the study was terminated early.

Celecoxib inhibits COX-2 about 10 times more than it inhibits COX-1; it is 10 times less selective than rofecoxib (Vioxx). So celecoxib is safer than rofecoxib.

If celecoxib is used, the dosage is between 200 and 400 mg twice daily.
Dosage for Aspirin and Naproxen

The safest NSAIDs may be aspirin and naproxen, which inhibit COX-1 and COX-2 without prejudice. One 325 mg aspirin tablet per day may reduce the risk of heart disease. Suitable dosage for naproxen is between 200 and 800 mg thrice daily. The use of 10 mg of famotidine twice daily should avoid too much stomach acid.
Statins, Androgens, & Vitamin D

Many PCa patients take statins. Statins inhibit the action of HMG-CoA reductase, which is the essential control point in the synthesis of cholesterol from acetyl coA. Cholesterol is the precursor of the steroid hormones, including the androgens. Thus statins offer some protection against PCa by reducing the levels of cholesterol and testosterone to normal values.

But vitamin D is made from the steroid 7-dehydrocholesterol, which is the last intermediate in the biosynthesis of cholesterol. Thus patients on statins may be less able to synthesize their own vitamin D.
PGs & Hypercalcemia

Calcitriol and COX inhibitors inhibit the synthesis of prostaglandins.

PGs cause hypercalcemia (31; 32).

The worrisome side-effect of high doses of calcitriol is hypercalcemia.

So NSAIDs and curcumin may protect against this side-effect by reducing PG levels.
Acknowledgments

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*References*


