PROSTATE CANCER PREVENTION: FROM THE UNKNOWN TO THE DOABLE?

Neil Fleshner MD MPH FRCSC

Professor of Surgery

University of Toronto

Head, Division of Urology

University Health Network

Head, Genitourinary Cancer Program

Princess Margaret Hospital

Co-Director

Canadian Prostate Cancer BioNetwork
PROSTATE CANCER 2008

• Most common malignancy in man (17.7% lifetime risk)
• 2nd most common cause of cancer deaths in men
• Potential for overdetection/overtreatment
• Treatments for early disease has associated morbidity
PROSTATE CANCER: WHY ENVIRONMENT?

- International incidence/death rates
- Latent (‘autopsy) prostate cancers are stable worldwide
- Migration studies: adopt incidence of host nation
- Autopsy data \(\rightarrow\) PCA starts in 4\(^{th}\) decade
Age-standardized Incidence and Mortality Rates for Prostate Cancer

# LATENT vs CLINICAL CANCERS

<table>
<thead>
<tr>
<th>PATHOLOGIC FEATURES</th>
<th>LATENT</th>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Grade</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Foci</td>
<td>Few</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
PROSTATE CANCER: WHY ENVIRONMENT?

• International incidence/death rates
• Latent (‘autopsy’) prostate cancers are stable worldwide
• Migration studies: adopt incidence of host nation
• Autopsy data → PCA starts in 4th decade
MIGRATION STUDIES

Japanese/American

SIR

Chinese/American

Native

Immigrant

US

Princess Margaret Hospital
PROSTATE CANCER: WHY ENVIRONMENT?

- International incidence/death rates
- Latent (‘autopsy) prostate cancers are stable worldwide
- Migration studies: adopt incidence of host nation
- Autopsy data ➔ PCA starts in 4th decade
# Prostate Cancer: Early Onset

(Sakr et al)

<table>
<thead>
<tr>
<th>Decade</th>
<th>Isolated PIN</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>9%</td>
<td>---</td>
</tr>
<tr>
<td>30-39</td>
<td>16%</td>
<td>31%</td>
</tr>
<tr>
<td>40-49</td>
<td>26%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Princess Margaret Hospital
Unfavorable Environment (USA/Canada)

? Modified Environment (Complementary)

Favorable Environment (China/Japan)
The Influence of Finasteride on the Development of Prostate Cancer

PCPT Schema

Enrollment

18,882 Men Randomized

9,423 Placebo
End-of-Study Biopsy

9,459 Finasteride
Annual PSA and Digital Rectal Exam for 7 Years
End-of-Study Biopsy

5 mg/day
PCPT Results

• 25% reduction in px ca on finasteride
  – 24.4% vs. 18.4%

• Slight increase in Gl 7 – 10
  – 6.4% vs. 5.1%

• Equal # deaths

• Most cancers detected by EOS bx

• 98% clinically localized

Princess Margaret Hospital
Gleason Score
Total Number of Cancers

Not graded: Finasteride n=46, Placebo n=79

Princess Margaret Hospital
PCPT: PERSONAL VIEW

• Significant reduction in period prevalence is real
• Impact on Gleason scoring needs to be sorted out
  – Pathological Artifact
  – Real biological change
  – Biopsy artifact
• Conclusion:
  – Use for BPH if needed
  – Await results of pivotal studies
DIETARY FAT AND PROSTATE CANCER

CASE-CONTROL/ COHORT STUDIES

- 5/9 cohort and 12/19 case control studies suggest association b/w dietary fat and PCA
- More consistent that dietary fat and breast/colon cancer
- Recent incidence studies not consistent
  - ? Difference between cases/controls
DIETARY FAT AND PROSTATE CANCER: BIOLOGIC PLAUSIBILITY

- Dietary fat increases circulating androgen levels
  - Hill: low fat dietary intervention ↓ T
  - Bishop: co-twin with higher intake ↑ T
- Pesticide
- Oxidative Stress
EFFECT OF DIETARY FAT ON LNCAP

Wang et al, JNCI 1996
EXPERIMENTAL APPROACH

• Lady-TRAMP mouse
  – Develops spontaneous PCA ~14-30 weeks
• Assessing Role of Diet on this Tumor System
PROSTATE CANCER PROGRESSION AND FAT INTAKE
Meyer et al, Cancer Causes & Control, 1999, 10:241

- Cohort of 384 men with advanced CaP
- Follow up 5.2 yrs
- Highest tertile of saturated fat
  - Adjusted RR of 3.1 (1.3-7.7) for death
- Adjusted for stage/grade/treatment etc..

Princess Margaret Hospital
OBESITY

• Increasingly being recognized as a risk factor for disease progression
• Androgen metabolism/dietary promoters
• Confounded by race (higher in AA-s)
• Technical difficulty with surgery/XRT planning
  – Positive margin rates are higher
Freedland et al- SEARCH Dataset

- Dataset from 5 centres (1250 RP’s) of which 731 had OC disease
- Adjusted HR for biochemical failure (P<0.05)

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.56</td>
</tr>
<tr>
<td>Mild</td>
<td>1.20</td>
</tr>
<tr>
<td>Mod &amp; Severe</td>
<td>4.09</td>
</tr>
</tbody>
</table>
Hypothesis

Hyperinsulinemia resulting from high-carbohydrate intake would lead to more rapid growth of the well characterized LNCaP prostate cancer xenografts.
Methodology

- LNCaP Xenografts in Swiss Athymic nude mice

- Animals with palpable tumors were randomized to either of the isocaloric diets:
  - Low carbohydrate-high fat diet (HC-HF)
  - High carbohydrate-high fat diet (LC-HF)

- Outcome:
  - Body weight
  - Tumor volume
  - Histology
  - Serum Insulin
  - Serum IGF-1
  - Tumor Tissue
  - Proliferative Marker (Ki67)
  - Akt
  - Insulin Receptor
  - In Vitro Mitogenicity
<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Carbohydrate</th>
<th>High-Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition of diet (% weight)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>11.4</td>
<td>47.5</td>
</tr>
<tr>
<td>Fat</td>
<td>22.8</td>
<td>23.8</td>
</tr>
<tr>
<td>Protein</td>
<td>51.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Others (Minerals)</td>
<td>14.3</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Energy Contribution (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Fat</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Protein</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td><strong>Average grams of food consumed/day/ animal</strong></td>
<td>4.83</td>
<td>4.77</td>
</tr>
<tr>
<td>* Total Energy Value of diets /gm (Kcals/gm)</td>
<td>4.58</td>
<td>4.76</td>
</tr>
<tr>
<td>** Total energy consumed / day / animal**</td>
<td>22.12</td>
<td>22.7</td>
</tr>
<tr>
<td>*** Grams Consumed / day / animal of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>0.55</td>
<td>2.27</td>
</tr>
<tr>
<td>Fat</td>
<td>1.1</td>
<td>1.14</td>
</tr>
<tr>
<td>Protein</td>
<td>2.49</td>
<td>0.85</td>
</tr>
<tr>
<td>**** Kcal energy from.../ day / animal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>2.2</td>
<td>9.08</td>
</tr>
<tr>
<td>Fat</td>
<td>9.9</td>
<td>10.17</td>
</tr>
<tr>
<td>Protein</td>
<td>9.96</td>
<td>3.4</td>
</tr>
</tbody>
</table>

* Values provided in the specification sheet of the respective diets
** Total energy value X gms of diet consumed
*** Composition X gms consumed / 100
**** Grams of diet consumed / day / animal X physiological fuel value (Carbohydrate, Fat and Protein is 4, 9, 4 Kcal/gm respectively).
Increased tumor volume and wet weight in animals on a high-carbohydrate diet

Diets commenced

* $P \leq 0.05$

** $P \leq 0.01$
Significant increase in the number of positive stained nuclei (Ki67) in the prostate tumor tissue of animals on the high-carbohydrate diet.

High Carbohydrate-High Fat: (>25%)

Low Carbohydrate-High Fat: (<5%)
Increased levels of serum insulin and IGF-I in animals administered a high-carbohydrate diet.

![Bar graph showing increased serum insulin](image1)

![Bar graph showing increased serum IGF-I](image2)
Conclusion

- Increasing carbohydrate intake (without altering fat intake or total calories) augmented the growth rate of prostate cancer xenografts.

- Added simple sugars are predominant sources of carbohydrate in modern American diets, and are high in glycemic index and thus evoke high insulin surges.

- Insulin is a candidate mediator of the effect of our high-carbohydrate diet on prostate cancer behavior.
**ALPHA TOCOPHEROL BETA CAROTENE CANCER PREVENTION TRIAL**

![Bar chart showing the number of cases for different cancer types with and without Vitamin E.]

- **Lung**
  - No Vitamin E: 400 cases
  - Vitamin E: 451 cases
  - *p < 0.05*

- **Prostate**
  - No Vitamin E: 99 cases
  - Vitamin E: 151 cases

- **Bladder**
  - No Vitamin E: 75 cases
  - Vitamin E: 120 cases

- **Colorectal**
  - No Vitamin E: 200 cases
  - Vitamin E: 300 cases

- **Gastric**
  - No Vitamin E: 50 cases
  - Vitamin E: 75 cases

- **Other**
  - No Vitamin E: 300 cases
  - Vitamin E: 400 cases

---

Princess Margaret Hospital
RESULTS: TUMOR GROWTH

![Graph showing tumor growth over weeks with different fat and vitamin E treatments.](image)

- Red line: 40% FAT
- Yellow line: 40% FAT + E
- Green line: 20% FAT
- Cyan line: 20% FAT + E

P < 0.05

Princess Margaret Hospital
FACS analysis of Vitamin E Treated Cells

LNCaP

PC3

% Cells

Hours

0 24 48 72

0 24 48 72

0 10 20 30 40 50 60 70

% Cells

G1 S G2/M

Princess Margaret Hospital
Cyclin E Immune Complexes (LNCaP)

<table>
<thead>
<tr>
<th>Vit E</th>
<th>Time (h)</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- Cyclin E
- cdk2
- p27
- β Actin

Graph showing % Max over Hours from 0 to 100 with peaks at 48 hours.
VITAMIN E: SAFETY

• Decades long history of megadosing
• Vitamin E considered to be safe in doses up to 1500IU’s per day
  – Short term toxicity studies
• But never assessed at high doses in a long term study
• ATBC—50 IU’s
  – Slight higher (NS) incidence of stroke (hemorrhagic)
META ANALYSIS
Miller AIM;142:2005

- 135,967 pts in 19 clinical trials
  - 9 vitamin E alone (10 combinations)
- 11 trials of “high dose” (≥ 400 IU’S) vitamin E
  - 9 increased risk of all cause mortality
  - 39/10,000 (95%CI 3-74) P=0.035
- 8 trials of low dose--NS
HOPE TRIAL
JAMA 293; 2005

• RCT in 9541 patients
  – Vitamin E/Ramipril
• Hope II– 7 yr extension data
• 12% higher incidence of CHF (AR ~1%)
SELENIUM

• Trace micronutrient
• Co-factor for Glutathione-S-transferase
• Dietary sources: inconsistent
• Canada-low selenium area
• Epidemiological data—higher cancer incidence in low selenium areas
SELENIUM INTERVENTION STUDY

• 1312 pts with NMSC
• Placebo-controlled RCT
• Multicenter
• Selenomethionine (200 microgram/day)
• 10 yr follow up
  – RR 0.29
In vitro growth curves of LNCaP cells after selenium treatment.

- Control
- 100 µM
- 150 µM
- 200 µM

Cells/Well vs. Time (Hours)
Gene Globe
Gene-specific products for human, mouse, rat and other species

Products for KCNMA1

Instructions
Choose from the following options:
- Click "View details" to see further information about the product.
- Add products to your cart by selecting the "Add to cart" checkbox and clicking the "Add to cart" button.
- If you did not find what you were looking for, go back to the search results or start a new search.

<table>
<thead>
<tr>
<th>Gene Description</th>
<th>Gene Symbol</th>
<th>Species</th>
<th>Entrez Gene ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>potassium large conductance calcium-activated channel, subfamily M, alpha member 1</td>
<td>KCNMA1</td>
<td>Human</td>
<td>3778</td>
</tr>
</tbody>
</table>

Orthology genes: KCNMA1 (Human), KCNMA1 (Mouse), KCNMA1 (Rat), KCNMA1 (Chicken), LOC100808 (Chicken), etc. (fruit fly)

Display all 12 sRNA(s) per gene

Products available for this gene

<table>
<thead>
<tr>
<th>Add to Cart?</th>
<th>Product type</th>
<th>Product name [Help]</th>
<th>Cat. No.</th>
<th>List Price</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HP GenomeWide sRNA</td>
<td>Hs_KCNMA1_1 HP siRNA (NM_00104797, NM_002497)</td>
<td>SI00035070</td>
<td>$89.001</td>
</tr>
<tr>
<td></td>
<td>HP GenomeWide sRNA</td>
<td>Hs_KCNMA1_5 HP siRNA (NM_00104797, NM_002497)</td>
<td>SI00344455</td>
<td>$89.001</td>
</tr>
<tr>
<td></td>
<td>HP GenomeWide sRNA</td>
<td>Hs_KCNMA1_6 HP siRNA (NM_00104797, NM_002497)</td>
<td>SI00360239</td>
<td>$89.001</td>
</tr>
<tr>
<td></td>
<td>HP GenomeWide sRNA</td>
<td>Hs_KCNMA1_7 HP siRNA (NM_00104797, NM_002497)</td>
<td>SI00370683</td>
<td>$89.001</td>
</tr>
<tr>
<td></td>
<td>QuantiTect Primer Assay</td>
<td>Hs_KCNMA1_5_3G QuantiTect Primer Assay (200) (NM_002497)</td>
<td>QT00024157</td>
<td>$70.00</td>
</tr>
</tbody>
</table>

Add to Cart
Select all 1 Order minimum is 4 FlexTube siRNAs

Note: No LiquiChip assay kits currently available.
Si RNA of SCGD and KCNMA1 on PC3 cells: Response to Selenium

Control

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>S1</th>
<th>S1+Se</th>
<th>S2</th>
<th>S2+Se</th>
<th>S3</th>
<th>S3+Se</th>
<th>K1</th>
<th>K1+Se</th>
<th>K5</th>
<th>K5+Se</th>
<th>K6</th>
<th>K6+Se</th>
<th>K7</th>
<th>K7+Se</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>1.0</td>
<td>0.4</td>
<td>0.6</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K6, K7, P = 0.05
LYCOPENE

- Carotenoid
- Potent antioxidant
- Sources: tomato/guava/watermelon
- Epidemiological Data
  - Tomato consumption associated with protection from cancer mortality
GIOVANNUCCI et al
JNCI 1995; 87:1767

- Men > 10 servings of tomato products per week
- 35% reduced rate of prostate cancer
- Particular benefit for advanced disease
VITAMIN E/SELENIUM/LYCOPENE COMBINATION

LARGE PROSTATE TUMOR

VIRTUALLY NO PROSTATE
PRE-OP STUDY: METHODS

- Randomized trial of men with prostate cancer for radical prostatectomy
- N=50
- 5 groups (n=10 per group)
  - Control
  - Vitamin E (800IU)
  - Selenium
  - Lycopene
  - All 3
Ki-67

- Staining
- Control Vitamin E Selenium Lycopene All 3

Princess Margaret Hospital
P27 Nuclear Staining

Counts for different interventions:
- Control (n=8)
- Vitamin E (n=8)
- Selenium (n=8)
- Lycopene (n=6)
- E + S + L (n=9)

Legend:
- 0
- 1
- 2
- 3
- 4

* indicates a significant difference.
Immunohistochemical analysis of cell cycle inhibitory protein p27 on tumor tissue of patients administered micronutrients

Control (C 1+ / N 0)  E+S+L (C 4 / N 4)

Vitamin E (C 0 / N 0)  Selenium (C 2 / N 0)  Lycopene (C 3 / N 0)
CHEMOPREVENTION TRIALS

- SELECT
- PIN – CANADA
- PIN-SWOG
- PIN-SERM
- GSK-REDUCE
NCIC – PRP1

• RCT of Soy, Vitamin E, Selenium among Pts with HGPIN (2 biopsies)
• Endpoint: Invasive cancer @ 3 years
• 40gm Soy Protein
• Vitamin E 800 IU
• Selenium 200 micrograms
PROPOSED TRIAL

- RCT of selenium and vitamin E among good risk PCA post radical prostatectomy
- 2:1 stratify
- N=650
- Endpoint: PSA failure
CONCLUSIONS

• Evidence suggests that PCA is preventable
• Studies needed (underway) to assess these agents as complements to traditional therapies
• Real definitive answers within next 5 years
ACKNOWLEDGEMENTS:

- Fleshner/Klotz Lab
  - Vasundara Venkateswarran
  - Ahmed Haddad
  - Mireilla Musqueira

- CPC-Bionet
- NCIC
- CIHR
- OICR