Chemoprevention Strategies

~ M. Scott Lucia, MD

Chemoprevention Strategies for Prostate Cancer

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Chemoprevention

The use of specific natural or synthetic agents, dietary or pharmacological, to reverse, retard or prevent the development or progression of cancer

Sporn 1976

Multistep Carcinogenesis

Normal
Genetic
Promotion
Epigenetic
Premalignant
Genetic
Progression
Malignant
Metastatic
Characteristics of Prostate Cancer that support a role for chemoprevention

- Disease of aging (oxidative stress? Inflammation? epigenetic events)
- Long latency
- Putative precursor lesion
- Early dependence on androgen
- Susceptability to oxidative damage:
  - High prevalence of GSTP1 hypermethylation
  - Overexpression of COX-2
- Altered growth factor responsiveness


Early Events in Prostatic Carcinogenesis

Prostate Cancer – Risk Factors

- Age
- Family history
- Intact Androgen Axis
- Diet
  - High fat (oxidative stress? alteration of hormone balance? arachidonic acid?)
  - Low selenium/ antioxidants/ isoflavonoids
- Geographic locale
  - Western cultures (diet)
  - Low UV light exposure (vit D)
- Prostatitis (oxidative stress?)
- African-American ethnicity (androgens? vit D?)

Candidate Chemopreventive Agents for PCa

- Hormonal agents
  - 5α-reductase inhibitors (eg. Finasteride, Dutasteride)
  - Antiandrogens/ LHRH antagonists (eg. Flutamide, leuprolide)
  - SERMs (eg. Tamoxifen, raloxifene, bremiflene, SERM-3)
- Phytoestrogens and Protein Kinase Inhibitors
  - Isoflavonoids (eg. Genistein, silibinin)
  - Angiogenesis inhibitors (eg. SU-101)
- Antiproliferative or Differentiating Agents
  - Vitamin D analogs
  - Retinoids (eg. 4-HPR, 9cis-retinoic acid)
  - Polyamine inhibitors (eg. DFMO)
- Anti-inflammatory Agents
  - COX-2 inhibitors (eg. Celecoxib, sulindac sulfone)
  - Statins
- Antioxidants
  - Vitamin E (SELECT)
  - Selenium (SELECT)
  - Carotenoids (eg. Lycopene)
Candidate Chemopreventive Agents for PCa

- **Hormonal agents**
  - 5a-reductase inhibitors (eg. Finasteride, Dutasteride)
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- **Phytoestrogens and Protein Kinase Inhibitors**
  - Isoflavonoids (eg. Genistein, silibinin)
  - Angiogenesis inhibitors (eg. SU-101)

- **Antiproliferative or Differentiating Agents**
  - Androgens major regulator of growth and differentiation
  - Basis for androgen ablation therapy

- **Anti-inflammatory Agents**
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- **Antioxidants**
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**Hormonal Agents**

**Antiandrogens/ 5α-reductase inhibitors**

**Rationale**

- Androgen major regulator of growth and differentiation
- Basis for androgen ablation therapy
- Males castrated < 40 yrs age don’t get clinical prostate cancer¹
- Males with 5α-reductase deficiency don’t get prostate cancer²
- Racial differences in androgen metabolism³


**Hormonal Agents for Prostate Cancer Chemoprevention**

**Limitations**

- Side effects! (hot flashes, gynecomastia, sexual dysfunction, weakness, etc.)
- LHRH agonists
- Androgen receptor antagonists
- Candidates for prevention generally healthy with active physical & sexual lives
- Must maintain acceptable QOL
- 5α-reductase inhibitors (5ARI’s)
  - Favorable side effect profile
  - Treatment for BPH

**5ARI’s: Mechanism of Action**

[Diagram of 5ARI’s: Mechanism of Action]
Chemoprevention Trials for Prostate Cancer Using 5ARI’s

**Prostate Cancer Prevention Trial (PCPT)**

*Primary Endpoint:* To determine if **finasteride** administration for a period of seven years could reduce the period prevalence of prostate cancer.

**REDuction by DUtasteride of prostate Cancer Events (REDUCE)**

*Primary Endpoint:* To determine if **dutasteride** could reduce the likelihood of prostate cancer diagnosis on repeat biopsy after 2 and 4 years.

### Design comparison between PCPT and REDUCE

<table>
<thead>
<tr>
<th></th>
<th>PCPT</th>
<th>REDUCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test agent</td>
<td>Finasteride (5mg/day)</td>
<td>Dutasteride (0.5 mg/day)</td>
</tr>
<tr>
<td>n</td>
<td>18,800</td>
<td>8200</td>
</tr>
<tr>
<td>Age at randomization</td>
<td>55</td>
<td>50-75</td>
</tr>
<tr>
<td>PSA at randomization</td>
<td>≤3 ng/ml</td>
<td>&gt;2.5 and &lt;10 ng/ml</td>
</tr>
<tr>
<td>Negative DRE</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Negative baseline bx</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Scheduled biopsies</td>
<td>At 7 yrs</td>
<td>At 2 yrs and 4 yrs</td>
</tr>
<tr>
<td>Biopsy scheme</td>
<td>6 core (80%)</td>
<td>10 core</td>
</tr>
<tr>
<td>For-cause biopsies (PSA + DRE)</td>
<td>Many</td>
<td>Few</td>
</tr>
</tbody>
</table>

### Prostate Cancer Prevention Trial

- **Total Men Evaluated:**
  - Finasteride: 4368
  - Placebo: 4692
- **Men with For-Cause Biopsy/Procedure:**
  - Finasteride: 1639
  - Placebo: 1934
- **Men with End-of-Study Biopsy:**
  - Finasteride: 3652
  - Placebo: 3820

- **Number of Cancers:**
  - Total Cancers:
    - Finasteride: 1347
    - Placebo: 1147
  - For-Cause Cancers:
    - Finasteride: 436
    - Placebo: 438
  - End-of-Study Cancers:
    - Finasteride: 391
    - Placebo: 376

- **Thompson IM, et al. NEJM 2003.**

### Observed fractions of total subjects with low- and high-grade cancer in the PCPT

- **Cancer**
  - **RR:** 0.75 (0.60, 0.99)
  - **p < .001**

- **Gleason:**
  - **Gleason > 7**
  - **RR:** 1.27 (1.07, 1.50)
  - **p = .005**

- **Thompson IM, et al. NEJM 2003;349:211-20**
Grade 7-10 Cancers diagnosed in PCPT

Detection bias led to increased detection of high-grade cancer in PCPT
- Finasteride improved performance of PSA for cancer and high-grade cancer\(^1\)
- Finasteride increased sensitivity of DRE\(^2\)
- Finasteride increased sensitivity of prostate biopsy for detection of high grade cancer by reducing prostate volume\(^3\)

\(^3\) Lucia MS, et al. J Natl Cancer Inst. 2007;99:1375-83

Effect of finasteride on cancer detection

Estimated actual fractions of total subjects with low- and high-grade cancer after adjusting for bias

\[ RR_{70} = 0.70 \ (0.64, 0.76) \quad p < .0001 \]
\[ RR_{7} = 0.73 \ (0.56, 0.96) \quad p < .02 \]
\[ RR_{6} = 0.68 \ (0.57, 0.82) \quad p < .0001 \]

**REDUCE Primary Results**

![Graph showing REDUCE Primary Results](image)

Gleason 7-10: Placebo = 6.8%  
Dutasteride = 6.7%  
Andriole G. AUA 2009  
Used with permission

**Gleason score (GS) distribution by treatment group in REDUCE**

![Graph showing Gleason score distribution](image)

Andriole G. AUA 2009  
Used with permission

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**Future Directions for Prostate Cancer Chemoprevention: What next?**

- **Phytoestrogens (Phase II trials)**  
  - Inhibition of PKC, cell growth, angiogenesis
- **Anti-proliferative agents (Phase II trials)**  
  - Vit D analogues, retinoids, DFMO
- **Anti-inflammatory agents/ antioxidants**
- **Statins**  
  - Reduction of cholesterol  
  - Anti-inflammatory

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**Chemoprevention Strategies**

- **ROS/RNS**  
  - Peroxynitrite  
  - Lipid peroxidation  
  - Inactivation of DNA repair enzymes
- **NF-kB**  
  - COX-2  
  - VEGF  
  - PGE2
- **Angiogenesis**  
  - Fixation of Mutations  
  - Tumorigenesis  
  - Cell Proliferation  
  - Apoptosis

ROS=reactive oxygen species  
RNS=reactive nitrogen species  
COX-2=cyclooxygenase-2  
VEGF=vascular endothelial growth factor
Meta-analysis of effect of Non-steroidal anti-inflammatory drugs (NSAIDS) on prostate cancer risk


The Selenium and Vitamin E Cancer Prevention Trial (SELECT): Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group


How do we identify those men who would benefit most?

- Patient desire?
- Positive family history?
- The REDUCE model?
  - Elevated PSA and negative biopsy
- Risk calculator/ nomogram?
Chemoprevention Strategies

Prostate Cancer Risk Calculator based upon data from the placebo arm of the PCPT

http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp

Chemoprevention of Prostate Cancer
Challenges

- Candidates for chemoprevention
- Optimal dosages/combinations
- Impact on lifestyle
- Surrogate biomarkers
- Design of trials