Chemoprevention of Prostate Cancer

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Methods to Reduce Cancer Morbidity and Mortality

- Screening
- Improved Therapy
- Prevention
Chemoprevention

- Pharmacologic approach to arrest or reverse carcinogenesis

Sporn

- Does not specify whether prevention is
  - normal → cancer
  - premalignant → cancer
  - occult → clinically apparent cancer
Goals of Chemoprevention

- Decrease number of cases
  - Reduce rx-related morbidity
- Decrease mortality
Primary Prevention

Secondary Prevention (Screening & Early Detection)

Tertiary Prevention

Normal

Preinvasive lesions

Occult cancer

Clinically apparent and localized

Locally advanced

Metastatic

Hormone refractory
Unfavorable Environment (North America)

? Modified Environment (Prevention)

Favorable Environment (Asia)
## Large Scale 1° Prevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Risk Group</th>
<th>Molecular Target</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPT</td>
<td>Low</td>
<td>Type II 5AR</td>
<td>Reported</td>
</tr>
<tr>
<td>REDUCE</td>
<td>Intermediate</td>
<td>Types I and II 5AR</td>
<td>2008</td>
</tr>
<tr>
<td>Toremifene</td>
<td>High</td>
<td>Estrogen Receptor</td>
<td>2008</td>
</tr>
<tr>
<td>SWOG/Se</td>
<td>High</td>
<td>Se-mediated effects</td>
<td>2009</td>
</tr>
<tr>
<td>SELECT</td>
<td>Low</td>
<td>Oxidative Stress</td>
<td>2012</td>
</tr>
</tbody>
</table>

### Statins and Prostate Cancer Risk

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Px Cancer</td>
<td>1.09</td>
</tr>
<tr>
<td>Advanced Px Cancer</td>
<td></td>
</tr>
<tr>
<td>Any use</td>
<td>0.51</td>
</tr>
<tr>
<td>Use &lt; 5 yrs</td>
<td>0.60</td>
</tr>
<tr>
<td>Use &gt; 5 yrs</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Health Professionals Follow-up Study, N = 34,989

Prostate Cancer
Diet & Exercise Risk Factors

- May **Increase** Risk
  - Fat / Red Meat
  - Cooking methods
  - Dairy/Calcium
  - Smoking
  - Total Calories, Body size

- May **Decrease** Risk
  - Plant-based Foods/Vegetables
    - Tomatoes
    - Cruciferous
    - Soy/Legumes
  - Specific Nutrients
    - Selenium
    - Vitamin E
    - Carotenoids/Lycopene
    - Total Antioxidants
  - *Fish / Marine Omega 3 Fatty acids*
  - *Moderate to Vigorous Exercise*
The Molecular Effects of Nutrition Supplements Study (MENS)

- Carroll PR, Haqq C, Chan JM et al (*Funding: NCI/NIH*)
- n=114 watchful waiters, low risk CaP
- Intervention=tomato, fish oil supplement, or placebo
- Outcome = gene expression changes in bx @ 3 mths

Men with low-burden CaP, Biopsy

Re-biopsy 3 months. Examine changes in gene expression
Low risk prostate cancer

Endpoint: 50% reduction in definitive therapy
The Prostate Cancer Prevention Trial

Enrollment

Randomization

Placebo

End of Study Biopsy

F/U q3mo x 7yr
Annual DRE & PSA
Biopsy for cause

Finasteride

End of Study Biopsy
PCPT Results

- 6.4% reduction (RR = 0.75) in prevalence of prostate cancer
- 1.3% increase (RR = 1.27) in high grade disease

<table>
<thead>
<tr>
<th>Gleason Sum</th>
<th>Observed Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 6$</td>
<td>Decreased</td>
</tr>
<tr>
<td>7</td>
<td>Unchanged</td>
</tr>
<tr>
<td>$\geq 8$</td>
<td>Increased*</td>
</tr>
</tbody>
</table>

* For cause biopsies only
Needle misses high grade cancer (red) due to increased ratio of benign tissue/cancer

With shrinkage of benign prostate tissue relative to high grade cancer, there is an increased likelihood of sampling high grade cancer.
Pathological Features at RP

![Bar chart showing the percentage distribution of stages T2a, T2b, T2x, T3a, T3b, and Tx for Finasteride (222) and Placebo (306).]
Finasteride Reduces the Incidence of HG PIN

RR = .85
RR = .69
RR = .79

 Courtesy I. Thompson
Effect of Finasteride on Sexual Function

Moinpour et al, JNCI, 2007
Finasteride as a Preventative

**Benefits**
- 25% reduction in cancer detection
- 21% reduction in high grade PIN
- Fewer urinary symptoms & lower risk of AUR/TURP
- Improves diagnostic accuracy of PSA
- Avoids “burden of cure”

**Costs**
- Increased risk of high grade disease
  - More aggressive rx
  - ? Excess mortality
- Sexual side effects
- Cost of finasteride
• 17% lifetime risk of being diagnosed with prostate cancer (US men)

• With finasteride, the risk is reduced to 13%

• 250,000-360,000 person-years saved over 10 years in the U.S. (Unger)
Infections and Cancer

- 17.8% of all cancers world-wide
  - 1.9 million cases

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Pylori</td>
<td>Gastric (63%)</td>
</tr>
<tr>
<td>HPV</td>
<td>Cervical, anal, genital (100%)</td>
</tr>
<tr>
<td>HBV, HCV</td>
<td>Hepatic (86%)</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi’s sarcoma (100%)</td>
</tr>
<tr>
<td>EBV</td>
<td>Burkitt’s lymphoma, Nasopharyngeal</td>
</tr>
<tr>
<td>HIV</td>
<td>KS, lymphoma, cervical</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>T cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Schistosomes</td>
<td>Bladder</td>
</tr>
<tr>
<td>Liver flukes</td>
<td>Bile duct</td>
</tr>
</tbody>
</table>

American Cancer Society, 2006
WASHINGTON, June 8 — Federal drug officials announced today that they had approved a vaccine against cervical cancer that could eventually save thousands of lives in the United States each year and hundreds of thousands in the rest of the world.

Called Gardasil, the vaccine is the culmination of a 15-year scientific effort that began at the National Cancer Institute and a research center in Australia, and it may one day be seen as one of the major health advances of the early 21st century.
Is Prostate Cancer an Infectious Disease?

Epidemiologic Data

- Increased Risk of Prostate Cancer with
  - STI OR 1.44 Dennis et al, Epidemiology 2002; 13:72
  - Prostatitis OR 1.60 Dennis et al, Urology 2002; 60:78
  - T. Vaginalis OR 1.43 Sutcliffe et al, CEBP 2006; 15:939
  - HHV8 OR 4.67 Hoffman et al, JID 2004; 189:15
Is Prostate Cancer an Infectious Disease?

Genetic Data

- Variants in *RNaseL*, *MSR1*, & *TLR4* associated with increased risk for
  - Infections in animals
  - Prostate cancer in humans
XMRV Integration Sites

Dong et al, PNAS Jan 15, 2007
“Prevention is so much better than cure because it saves the labor of being sick.”

Thomas Adams, 1618