Prostate and Bladder Cancer: 2012
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  – Oncogenex
  – Imclone
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  – Novartis
  – GlaxoSmithkline
  – Imclone

Cancer Incidence Rates Among Men, US, 1975-2008

Cancer Death Rates Among Men, US, 1930-2008

U.S. Cancer Statistics: Prostate Cancer 2012
• Leading cause of cancer in men
  – 241,740 cases
• Second leading cause of cancer death in men, after lung
  – 28170 deaths
• 2 million men alive who have had prostate cancer
• Cancer-specific survival estimates
  – 5 years: ~100%
  – 10 years: 95%
  – 15 years: 82%

Known Risk Factors
• Age
  – Strong association with aging
• Race/Geographic Origin
  – Increased risk in African Americans
• Family History/Genetics
  – New intriguing genetic links (8q24)
    – BRCA2
• Diet
• Obesity
Family History And Risk Of Prostate Cancer

<table>
<thead>
<tr>
<th># of Affected First-Degree Relatives</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2 (1.4-3.5)</td>
</tr>
<tr>
<td>2</td>
<td>4.9 (2.0-12.3)</td>
</tr>
<tr>
<td>3</td>
<td>10.9 (2.7-43.1)</td>
</tr>
</tbody>
</table>

Dietary Factors

- Fat
- Soy Protein
- Lycopene
- Vitamin E
- Selenium
- Vitamin D/Calcium

Vitamin E/Selenium

- Two large randomized trials evaluated chemoprevention for lung, skin cancer
- Secondary endpoint of prostate cancer
  - Vitamin E decreased risk by 32%
  - Selenium decreased risk by 60%
- Prospective trial: SELECT (2001-2004)
  - 35,533 men
  - 2 x 2 factorial design
    - Vitamin E (400 IU/d) vs placebo
    - Selenium (200 ug/d) vs placebo
  - Endpoint: prostate cancer incidence

SELECT: No Difference in Prostate Cancer Rates

Dihydrotestosterone is most biologically active form of testosterone

- 5-alpha reductase inhibitors can decrease DHT levels
- Tested in two large trials:
  - PCPT: finasteride: 18,882 men
  - REDUCE: dutasteride: 6729 men

PCPT: Finasteride Reduces Risk Of Prostate Cancer By 25%

REDUCE: Dutasteride Reduces Risk Of Prostate Cancer By 23%
**Interpretation: PCPT and REDUCE**

- More high-grade cancers found in patients treated with 5-alpha reductase inhibitors
- Decreased prostate volume and selective inhibition of low-grade cancers may have increased detection of high-grade cancers
- 5-alpha reductase inhibitors prevent low-grade cancers that may not need treatment
- Long-term data awaited

**Chemoprevention Conclusions**

- Finasteride and dutasteride reduce prostate cancer risk
  - Reduces anxiety, diagnosis, treatment
  - Increased risk of high-grade cancer not clear
  - Prevention of high-grade cancer not proven
  - No clear recommendation
- No role for selenium or vitamin E based on SELECT trial

**Screening**

- DRE
- Prostate-specific antigen (PSA)
- Many false positives
  - Benign Prostatic Hyperplasia (BPH)
  - Prostatitis

**Clear Impact Of Screening (positive and negative)**

**Pro:**
- Diagnosis made 5-6 years earlier
- Average age at diagnosis has fallen
- Fewer advanced cases at diagnosis
- Proportion of “good risk” patients at diagnosis has increased

**Con:**
- Only modest reduction in mortality rates in US
- Screening can lead to invasive tests and treatments which may have permanent harms without proven benefits

<table>
<thead>
<tr>
<th></th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>76,693</td>
<td>182,000</td>
</tr>
<tr>
<td>Age</td>
<td>55-74 yrs</td>
<td>50-74 yrs</td>
</tr>
<tr>
<td>Sites</td>
<td>10 US sites</td>
<td>7 Euro nations</td>
</tr>
<tr>
<td>% Screened</td>
<td>85% (52% controls)</td>
<td>82%</td>
</tr>
<tr>
<td>Median f/u</td>
<td>7 yrs</td>
<td>9 yrs</td>
</tr>
<tr>
<td>Cancer detection rates</td>
<td>7.4 vs 6.0%</td>
<td>8.2% vs 4.8%</td>
</tr>
<tr>
<td>Rate ratio death</td>
<td>1.13 (p=NS)</td>
<td>0.80 (p=0.04)</td>
</tr>
</tbody>
</table>

**PLCO Screening Study: No decrease in cancer death**

Cancer Incidence vs Cancer Death

European Randomized Screening for Prostate Cancer (ERSPC): Decreased prostate cancer specific mortality


- In order to prevent a single prostate cancer death over 10 yrs:
  - You need to screen 1410 men
  - Of those, you need to treat 48 patients who are diagnosed with prostate cancer

- Is this worth the morbidity and cost?

Conclusions of Randomized Screening Studies in 2012

- 2 large randomized trials
- Relatively short follow up
- Significant contamination in control arm of US study
- Morbidity from testing and treatment of indolent cancers
- Modest prostate cancer specific survival benefit to screening in one (higher quality) study- ERSPC

US Preventive Services Task Force

- Draft statement:
  - The USPSTF concludes that there is moderate certainty that the harms of PSA-based screening for prostate cancer outweigh the benefits.
  - USPSTF now recommends against PSA-based screening for prostate cancer in all age groups.

Screening: Summary

- Randomized data do not show definite evidence of benefit for PSA and DRE screening
- PSA screening results in earlier diagnosis
- % free PSA and PSA velocity may improve accuracy of diagnosing cancer
  - Other tests are coming
- However, there is no true “PSA cutoff” separating cancer from no cancer
- Recommendations for screening are in flux
  - Do not screen men over 75 years old
  - Consider screening for high risk (FamHx, AA)
  - USPTF may recommend against any screening

Diagnosis

- Findings suggesting evaluation
  - Abnormal PSA
  - Abnormal DRE
  - Cancer detected on TURP (rare)
- Biopsy
  - TRUS guidance
  - 6-18 cores by spring-loaded biopsy gun
- Pathology
  - Gleason score assigned based on differentiation from 2 (well) to 10 (poorly)
Clinical Risk Groups Predict Cancer Specific Survival

Low: T1c-T2a, PSA <10, and Gleason ≤ 6
Intermediate: T2b or PSA ≥ 10 but ≤ 20 or Gleason 7
High: T2c or greater, or PSA > 20 or Gleason ≥ 8

D'Amico JCO 2002

Treatment Options

- Watchful waiting
- Radical prostatectomy
  - Open vs laparoscopic vs robotic
- External beam radiotherapy
  - 3D conformal
  - IMRT
- Seed implants (brachytherapy)
- Cryosurgery
- Androgen deprivation therapy (ADT)

Watchful Waiting

- 767 patients in Connecticut
- Mean age: 68 years
- Mean f/u: 15.4 years
- Diagnosis: TURP (60%), needle bx (26%)
- Stage: 21% had no bone scan
- Death certificates, path reviewed

Albertson JAMA 2005

Prostate Cancer-Specific Death Rates At 20 Years

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Mortality Rate (95% CI) Per 1000 person-yrs</th>
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</thead>
<tbody>
<tr>
<td>2-4</td>
<td>6 (2-11)</td>
</tr>
<tr>
<td>5</td>
<td>12 (6-19)</td>
</tr>
<tr>
<td>6</td>
<td>30 (23-37)</td>
</tr>
<tr>
<td>7</td>
<td>65 (49-83)</td>
</tr>
<tr>
<td>8-10</td>
<td>121 (90-156)</td>
</tr>
</tbody>
</table>

Randomized Study: Surgery Versus Watchful Waiting

- 695 Scandinavian men, 1989-1999
- Median f/u 8.2 years
- Mean age: 64.7 years
- Mean PSA: 12.8 ng/ml
- Stage T1b (12%), T1c (11%), T2 (76%)
- Gleason: 2-6 (61%), 7 (23%), 8-10 (5%)

Bill-Axelson NEJM 2005

Overall Survival

Overall Survival Graph
**Prostatectomy vs. Watchful Waiting**

- Radical local treatment in a non-screened population with localized cancer leads to improved OS, PFS, decreased distant metastases and local progression
- The absolute benefit is small, requiring 17 RPs for 1 life saved (in 8 yrs)
- Benefit most significant in men < 65 yrs old

**Treatment for Localized Prostate Cancer: Conclusions**

- Reasonable to consider surgery, external radiation, or brachytherapy seed implants in younger, healthier men
- Reasonable to consider watchful waiting (active surveillance) in older men with low grade disease and decreased life expectancy
- Options depend on risk group

**Failure Of Local Therapy**

- Two-thirds of men treated for localized prostate cancer are cured
- As many as a third recur, usually manifested initially as a rising PSA alone
- Little is known about optimal management of rising PSA patients

**Natural History Of Rising PSA**

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

<table>
<thead>
<tr>
<th>Event</th>
<th>RP</th>
<th>8 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Rise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone scan (+)</td>
<td></td>
<td></td>
<td>Death</td>
</tr>
</tbody>
</table>

Pound JAMA 1999

**Hormonal Therapy**

- Highly effective treatment at palliating metastatic disease
- Often used early in the setting of a rising PSA alone without evidence of metastases (unclear benefit)
- Average response to hormones 1-2 years for metastatic disease
- Rapidly rising PSA (aka shorter doubling time) indicates population at high risk of death from prostate cancer

**Castration Induces Selection Of Androgen-Independent Clones**
Prostate Cancer: Evolving Standards: 2012

Localized Rx

Androgen Deprivation Therapy

Secondary Hormones

Docetaxel

Abiraterone

Enzalutamide

Cabazitaxel

Sipuleucel T

Radium, Zoledronic Acid, Denosumab

CRPC: castration resistant prostate cancer
ASX: asymptomatic; Visc: visceral metastasis

Chemotherapy: Improved Survival

Median survival Hazard ratio P-value

Docetaxel 3 wky: 18.9 0.76 0.009
Mitoxantrone 16.4 – –

Probability of Surviving

0 6 12 18 24 30

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Immunotherapy for prostate cancer: Sipuleucel-T

Sipuleucel-T (n = 341)

Median Survival: 25.8 mo.
36 mo. survival: 31.7%

Placebo (n = 171)

Median Survival: 21.7 mo.
36 mo. survival: 23.0%

No. at Risk

Sipuleucel 341 274 129 49 14 1

Placebo 171 123 55 19 4 1

34.1 mo median f/u
HR = 0.775 (95% CI: 0.614, 0.979)
pp = 0.032 (Cox model)
Median Survival Benefit = 4.1 months

Novel hormonal agents are active in castration resistant disease

African-Americans have worse prognosis, stage for stage

Bladder Cancer 2012

- 73,501 estimated new cases (75% male), 14,880 deaths
- Fourth most common cancer in men
- In the US, vast majority are transitional cell carcinomas (aka urothelial carcinoma)
- African-Americans have worse prognosis, stage for stage

Bladder Cancer
Risk Factors for Bladder Cancer

• Cigarette smoking
• Industrial exposure - aromatic amines
• Schistosoma hematobium (Nile)
• Chronic cyclophosphamide use
• Decreased fluid intake

Clinical Presentation and Diagnosis

• Gross hematuria in 80%
  – Hematuria in a smoker/former smoker requires bladder cancer workup
• Bladder irritation in 20%
• Diagnosed by cystoscopy
• IVP useful, CT/MR urogram preferred
• Transurethral resection of bladder tumors (TURBT) for biopsy and treatment if tumors identified

Clinical Presentation and Diagnosis

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Prognosis is Predicted by Depth of Cancer Invasion

<table>
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<tr>
<th>T Stage</th>
<th>5 Year Survival</th>
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<tbody>
<tr>
<td>T1</td>
<td>90%</td>
</tr>
<tr>
<td>T2a</td>
<td>80%</td>
</tr>
<tr>
<td>T2b</td>
<td>60%</td>
</tr>
<tr>
<td>T3</td>
<td>40%</td>
</tr>
<tr>
<td>T4</td>
<td>20%</td>
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Superficial Bladder Cancer

• 2/3 of all cases
• Multifocal disease in >50%
• Recurrences in >50%
• Progression in <5%
• Risk of progression:
  – Stage T1 > Ta
  – Grade 3 > Grade 1 or 2 (or high > low)

Superficial Bladder Cancer: Management

• TURBT as diagnostic and therapeutic maneuver
• Adjuvant intravesical chemotherapy or immunotherapy to reduce risk of recurrence
  – BCG, mitomycin
• Cystectomy for very high risk or refractory cases

Muscle Invasive Bladder Cancer: Management

• Radical cystectomy
  – Men: cystectomy, prostatectomy
  – Women: cystectomy, TAH/BSO
• Bladder-sparing
  – TURBT + Radiation
  – TURBT + Chemotherapy + Radiation
• Chemotherapy before surgery improves survival
Treatment for Metastatic Disease

• Chemotherapy is highly active but not curative
• Many active combinations with response rates of up to 70%
• However median survival is still only 14 months
• Best regimens:
  – MVAC
  – Gemcitabine/cisplatin
  – Dose intensified MVAC

Bladder Cancer: Summary

• Transitional cell carcinoma is the most common histology
• Superficial bladder cancer comprises 2/3 of cases
• Superficial bladder cancer recurs frequently, but rarely progresses to more aggressive disease
• Muscle invasive disease requires more radical therapies such as cystectomy or radiation therapy
• Combination chemotherapy is used for advanced disease

Prostate Cancer: Summary

• Screening remains very controversial
  – Benefits modest, harms real
  – Strongly consider for high-risk men
  – USPSTF likely will recommend against it
• Radical prostatectomy improves survival in an unscreened population
• Still the second-most common cancer killer among men
• Better screening strategies are needed
• Good news is that improved treatments are here

Question

Which of the following has not been linked to prostate cancer risk?

1. Family history
2. Diet
3. Cigarette smoking
4. Race
5. Age

Answer

Cigarette smoking has not been consistently shown to be associated with risk of prostate cancer. Dietary factors such as fat intake, age, family history and race have all been linked strongly to risk of prostate cancer.

Question

Which of the following is NOT associated with increased risk of dying from bladder cancer?

1. Grade 3 disease
2. T3 muscle invasive cancer
3. African American race
4. Use of chemotherapy prior to surgery in locally advanced disease
Answer

High grade disease, high stage disease and African American race are all associated with increased mortality from bladder cancer. Using chemotherapy prior to surgery is associated with a decreased risk of death.

Disclosures

• Consulting
  – Boehringer Ingelheim
  – Oncogenex
  – Imclone

• Research Funding
  – Novartis
  – GlaxoSmithkline
  – Imclone

References: Prostate

• Andriole GL, et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. NEJM 2009 360:1310-1319.
• Schroder FH, et al. Screening and Prostate-Cancer Mortality in a Randomized European Study. NEJM 2009 360:1320-1328

References: Bladder