Prostate Cancer Screening and Early Detection

What is the best approach?
radical prostatectomy specimen

transition zone

prostate cancer

urethra

peripheral zone
Early Diagnosis of Prostate Cancer in Asymptomatic Men

• Screening/primary testing
  – digital rectal examination (DRE)
  – serum prostate-specific antigen (PSA)

• Diagnostic testing
  – transrectal ultrasound (TRUS)-directed needle biopsy
Prostate-Specific Antigen (PSA) is a protease secreted into the ejaculate.

*http://www.spendloveresearch.org/images/s_psaimage.gif

**Peyromaure M et al., Med Hypoth, 64: 92-5, 2005
### Unsuspected Prostate Cancers in Healthy Men Over Age 55 Years: Results of the Prostate Cancer Prevention Trial (PCPT)*

<table>
<thead>
<tr>
<th>serum PSA level (at study entry)</th>
<th>number of men biopsied from the placebo group</th>
<th>number of men with prostate cancer&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 – 1.0 ng/mL</td>
<td>2196</td>
<td>357 (16.3%)</td>
</tr>
<tr>
<td>1.1 – 2.0 ng/mL</td>
<td>1647</td>
<td>457 (27.7%)</td>
</tr>
<tr>
<td>2.1 – 3.0 ng/mL</td>
<td>848</td>
<td>332 (29.3%)</td>
</tr>
<tr>
<td>3.1 – 4.0 ng/mL</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>63% of prostate cancer diagnoses made at end-of-study biopsy.

Decline in Prostate Cancer Mortality: Result of PSA Screening?

- Prostate cancer mortality rates since 1995 are below those for 1986 when serum PSA testing was rare

- Mortality decline is attributable to a decrease in the incidence of advanced/metastatic prostate cancer (Chu KC et al., Cancer, 97: 1507-16, 2003)

- Mortality rates are lowest in areas where the rates of advanced stage prostate cancer are lowest, and advanced stage prostate cancer is lowest in areas with highest PSA utilization (Jemal A et al., Cancer Epidemiol Biomarkers Prev, 14: 590-5, 2005)
AUA Practice Guidelines: Serum PSA Best Practice Policy*

“…Early detection of prostate cancer should be offered to asymptomatic men 50 years of age or older with an estimated life expectancy of more than 10 years. It is reasonable to offer testing at an earlier age to men with defined risk factors, including men with a first-degree relative who has prostate cancer and African-American men…”

*www.auanet.org/guidelines/
A Single Serum PSA Determination and Prostate Cancer Detection

• Highest predictive value for prostate cancer when compared to other tests

• Leads to detection of early stage cancers

• Pathologic features of prostate cancers detected by serum PSA screening more favorable compared to DRE detected cancers

• Cutoff values miss significant cancers

• Limited ability to distinguish life-threatening from indolent prostate cancer
Prevalence of Prostate Cancer at Autopsy in Wayne County, Michigan, USA (n = 249 cases)

At What Age Should Prostate Cancer Screening Start?

- PSA is a more specific test in young men

- Baseline PSA in men age 40-50 yrs is predictive of prostate cancer risk over 3 decades:
  - 4X risk of prostate cancer if PSA >median (0.6 ng/mL) vs < median (Baltimore Longitudinal Study of Aging 2001)

- Younger men are more likely to have curable cancer when compared to older men (Carter HB, Urology, 58: 639-41, 2001)

- Infrequent testing beginning at age 40 yrs reduces prostate cancer deaths and costs of screening, when compared to annual testing beginning at age 50 yrs (Ross KS et al., JAMA, 284: 1399-405, 2000)
Prostate Cancer is Common in High Risk Young Men (Age 40-49 Years)

<table>
<thead>
<tr>
<th>Screen Findings</th>
<th>Black</th>
<th>Risk Group Family History</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with suspicious screen</td>
<td>8</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>% of men with suspicious screen that had cancer at biopsy</td>
<td>54</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

*Catalona WJ et al., J Urol, 168: 1980-3, 2002*
Population Distribution of Serum PSA Values

- 10,248 men
- ≤2.5ng/ml: 78%
- 2.6-4.0ng/ml: 12%
- 4.1-9.9ng/ml: 8%
- >10ng/ml: 2%

Smith DA et al., JAMA, 276: 1309-15, 1996
PSA Thresholds have Limitations in Predicting Presence and Significance of Prostate Cancer*

<table>
<thead>
<tr>
<th>PSA (ng/ml)</th>
<th>Gleason grade ≥7 vs Gleason grade &lt;7 or no cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>1.1</td>
<td>93</td>
</tr>
<tr>
<td>1.6</td>
<td>84</td>
</tr>
<tr>
<td>2.1</td>
<td>76</td>
</tr>
<tr>
<td>2.6</td>
<td>67</td>
</tr>
<tr>
<td>3.1</td>
<td>58</td>
</tr>
</tbody>
</table>

*Thompson IM et al., JAMA, 294: 66-70, 2005
PSA Velocity (PSAV) Predicts Death From Prostate Cancer a Year Before Diagnosis

An annual PSA velocity of > 2 ng/mL in the year before prostate cancer diagnosis was associated with a significantly shorter time-to-death from prostate cancer after surgery or radiation therapy (D’Amico AV et al., N Engl J Med, 351: 125-35, 2004; D’Amico AV et al., JAMA, 294: 440-7, 2005)

Is there a PSA velocity cut-point that can predict death from prostate cancer at a time when cure is still possible?
PSA Kinetics Predict Life-Threatening Prostate Cancer when Cure may be Possible*

*data from Baltimore Longitudinal Study of Aging (2005)
PSA Velocity Identifies Men With Life-Threatening Prostate Cancer*

*data from Baltimore Longitudinal Study of Aging (2005)
Core Needle Biopsies of the Prostate
Random Sampling of the Peripheral Zone

biopsy #1: “positive” for cancer
biopsy #2: “negative” for cancer
Cumulative Cancer Detection With Sextant Biopsies*

*Roehl KA et al., J Urol, 167: 2435-9, 2002
Molecular Profiling of Prostate Cancer: New Prostate Cancer Biomarker Discovery

Anti-AMACR and Anti-p63 for Prostate Cancer Diagnosis: Rapid Translation Using Tissue Microarray Core

Appearance of Prostate Cancer Cell DNA, RNA, or Protein in Prostate Secretions/Urine
Summary

• Cumulative data after the onset of serum PSA screening suggests that earlier detection of prostate cancer has led to lower prostate cancer mortality

• If serum PSA is an effective screening test, screening that begins early in life is more likely to improve outcomes than lowering PSA thresholds

• Accumulation of a PSA history beginning early in life and evaluating changes in PSA (velocity) can lead to detection of life-threatening disease

• New molecular biomarkers, including various PSA molecular forms, will aid to the sensitivity and specificity of prostate cancer screening, early detection, and diagnosis

• New approaches to prostate imaging are desperately needed
Prostate Cancer Screening: The Johns Hopkins Approach

Age 40-50 yrs
PSA < median (0.6 ng/mL): re-screen at ages 45 and 50 yrs
PSA > 0.6 ng/mL: screen every 2 yrs
Suspect prostate cancer if PSA velocity > 0.2 ng/mL per yr and screen annually
Biopsy if PSA above 2-2.5 ng/mL and/or abnormal DRE

Age 50-70 yrs
PSA < 2.0 ng/mL and stable: screen at 2 yr intervals
PSA > 2.0 ng/mL: screen annually
Suspect cancer if PSA velocity > 0.2 ng/mL per yr when
PSA < 4; or if PSA velocity > 0.75ng/ml per yr when
PSA > 4
Biopsy if PSA > 3-4 ng/mL depending on risk, abnormal DRE
## Etiologies of the World’s Leading Cancers*

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Infection</th>
<th>Inflammation</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/Bronchus</td>
<td>probably</td>
<td></td>
<td>smoking</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td>sex steroids</td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>definitely</td>
<td></td>
<td>diet</td>
</tr>
<tr>
<td>Stomach</td>
<td>$H. pylori$</td>
<td>definitely</td>
<td>diet</td>
</tr>
<tr>
<td>Liver</td>
<td>Hep. viruses</td>
<td>definitely</td>
<td>aflatoxin $B_1$</td>
</tr>
<tr>
<td>Prostate</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>HPV</td>
<td>probably</td>
<td>smoking</td>
</tr>
<tr>
<td>Esophagus</td>
<td>$S. haematobium$</td>
<td>maybe</td>
<td>smoking, diet</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>maybe</td>
<td>smoking</td>
</tr>
</tbody>
</table>

| All sites         | often          | almost always| almost always    |
| (excluding skin)  |                |              |                  |

*Ordered by incidence as reported by the World Health Organization International Agency for Research on Cancer (IARC); see [www.iarc.fr](http://www.iarc.fr)
Inflammation as a Cause of Prostate Cancer

Epidemiology of Inflammation and Prostate Cancer: Meta-Analyses of Association Studies

Association of prostate cancer and prostatitis\(^1\)
- Population case-control studies-pooled: 1.8
- All studies-pooled: 1.6

Association of prostate cancer and sexually transmitted infections\(^2\)
- Population case-control studies-pooled: 1.51
- All studies-pooled: 1.44

\(^1\)Dennis LK et al., Urology 60: 78-3 (2002).
\(^2\)Dennis LK and Dawson DV. Epidemiology 13: 72-9 (2002).
Familial Clusters of Prostate Cancer Attributable to Genetic Factors*

*Steinberg GD et al., The Prostate 17: 337-47 (1990);
*Carter BS et al., Proc Natl Acad Sci USA 89: 3367-71 (1992);
A Genome-Wide Screen for Genetic Linkage to Prostate Cancer

Identification of Inherited Prostate Cancer Susceptibility Genes*

Inherited Prostate Cancer Susceptibility Genes*

RNASEL (aliases: HPC1, RNS4, PRCA1) encodes 2',5'-oligoisoadenylate synthetase-dependent ribonuclease activated by interferon chromosome 1q25

MSR1 (aliases: SR-A, phSR1, phSR2, SCARA1) encodes subunits of trimeric integral membrane receptor expressed by macrophages chromosome 8p22

Variants of Inflammatory Genes and Prostate Cancer*


**GDF15** (aliases: *MIC-1, PDF, PLAB, NAG-1, PTGFB, GDF-15*)
encodes macrophage inhibitory cytokine-1
chromosome 19p13.1-13.2

**TLR4** (aliases: *TOLL, hToll*)
encodes pathogen binding toll-like receptor in macrophages
chromosome 9q32-33

**IL8** (aliases: *K60, NAF, GCP1, LECT, LUCT, NAP1, 3-10C, CXCL8, GCP-1, LYNAP, MDNCF, MONAP, NAP-1, SCYB8, TSG-1, AMCF-I, b-ENAP*)
encodes interleukin-8, a mediator of inflammation
chromosome 4q13-21

**IL10** (aliases: *CSIF, TGIF, IL-10, IL10A*)
encodes interleukin-10, a mediator of inflammation
chromosome 1q31-32
Proliferative Inflammatory Atrophy
May be a Precursor to Prostate Cancer*

Increases in Serum PSA Caused by Infections in Young Men*

*for men age 16-47 years (median 28 years) from STI Transmission and Acquisition (TRAC) Study, Baltimore City 1990-1992; Sutcliffe S et al., J Urol, In press, 2005

25-30% of men with exudative STIs exhibit increases in serum PSA values
Reduction of Inflammation Leads to Less Prostate Cancer: Epidemiology Findings

Leitzmann MF et al. JAMA 291: 1578-86 (2004);
Platz EA et al. Cancer Epid Biom Prev 14: 390-6 (2005);
# Etiologies of the World’s Leading Cancers

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Infection</th>
<th>Inflammation</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/Bronchus</td>
<td></td>
<td><strong>probably</strong></td>
<td>smoking</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td><strong>definitely</strong></td>
<td><strong>sex steroids</strong></td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td></td>
<td><strong>definitely</strong></td>
<td>diet</td>
</tr>
<tr>
<td>Stomach</td>
<td><em>H. pylori</em></td>
<td><strong>definitely</strong></td>
<td>diet</td>
</tr>
<tr>
<td>Liver</td>
<td>Hep. viruses</td>
<td><strong>definitely</strong></td>
<td>aflatoxin B₁</td>
</tr>
<tr>
<td>Prostate</td>
<td><strong>maybe</strong></td>
<td><strong>probably</strong></td>
<td><strong>diet</strong></td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>HPV</td>
<td><strong>probably</strong></td>
<td>smoking</td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td><strong>maybe</strong></td>
<td>smoking, diet</td>
</tr>
<tr>
<td>Bladder</td>
<td><em>S. haematobium</em></td>
<td><strong>maybe</strong></td>
<td>smoking</td>
</tr>
<tr>
<td>All sites (excluding skin)</td>
<td>often</td>
<td>almost always</td>
<td>almost always</td>
</tr>
</tbody>
</table>