PSA Screening for Prostate Cancer

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Goals

• Review the history, rationale and evidence for PSA screening for Prostate Cancer (PCa)
• Review the limitations of PSA screening
• Discuss the guidelines
• Complications of metastatic prostate cancer
Disclosures

None
Prostate cancer screening

• Who?
  – Men age 40-75

• Why?
  – Detect early and prevent prostate cancer death
  – Prevent need for testosterone ablation
  – Prevent morbidity of metastases

• How?
  – Screen Smarter, biopsy judiciously
  – Observe clinically insignificant disease
  – Treat significant disease in younger patients
Who should have a PSA?

• Actually a complicated question
Who should have a PSA?

- Actually a complicated question
- Several answers immediately come to mind:
Who should have a PSA?

• Actually a complicated question

• Several answers immediately come to mind:
  – I don’t know
Who should have a PSA?

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- Several answers immediately come to mind:
  - I don’t know
  - Whoever wants one
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  – I don’t know
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  – Anyone with a prostate
Who should have a PSA?

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  – I don’t know
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  – Anyone with a prostate
  – Whoever will benefit from it
Who should have a PSA?

• Actually a complicated question

• Several answers immediately come to mind:
  – I don’t know
  – Whoever wants one
  – Anyone with a prostate
  – Whoever will benefit from it
  – No one at all
Outline

• History of PCa screening
• What is PSA?
• What is the normal PSA threshold?
• Limitations of PSA
• Current recommendations
Prostate Cancer (PCa)

- Most common noncutaneous cancer in US men
- 2014: 233,000 new cases
- 2014: 29,480 deaths (#2 behind lung cancer)
- Represents 25% of male cancers and 9% of all male cancer deaths
CaP

- 1 man in 36 will die of their disease
- 1 in 7 men will be diagnosed with the disease
- Average age of diagnosis is 66
Risk factors for CaP

• Age
  – Rare under 40
  – 6 out of 10 are diagnosed over 65

• Race
  – African American men
  – Caribbean men of African ancestry

• Nationality
  – Most common in North America, Northwestern Europe, Australia, and Caribbean islands
Risk factors of CaP

- Family history
- Diet
  - Higher fat?
  - Higher calcium?
- Obesity?! (more aggressive types of CaP)
- Vasectomy?!
Data supporting this theory

- Obesity is associated with increased risk of biochemical recurrence after RRP

- Obesity associated with an increased risk of prostate cancer death.

- Obese men have higher-grade and larger tumors: an analysis of the Duke prostate center database.
Prostate Cancer

- Testing has doubled the diagnosis
  - In 1980, it was 1 in 11 for white men
- But deaths have dropped in the last 20 years
- Not necessarily a significant drop?
- Tumor biology trumps stage
Prostate Cancer (PCa)

• Heterogeneous natural history
  – Some men have slow-growing, local tumors
  – Others have rapidly growing

• Goal is early detection with tailored therapy
History of PCa screening

• Before the discovery of PSA, healthcare providers relied on digital rectal examination (DRE), transrectal ultrasonography (TRUS), and measurement of serum prostatic acid phosphatase (PAP) to screen for PCa.

• DRE had an estimated 1-2% cancer detection rate in self-referred screening populations and 48-85% of men whose PCa is detected with DRE have non-organ-confined disease.

• PAP was discovered in 1938 and serum levels were found to be elevated in men with metastatic PCa.
Outline

• History of PCa screening
• What is PSA?
• What is the normal PSA threshold?
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• Current recommendations
• At OUI
What is PSA?

• Prostate-specific antigen (PSA) was first isolated in seminal fluid in 1966 and was used for the identification of semen in sexual assault cases
• In 1979, Wang et al isolated PSA from normal prostatic tissue, as well as cells from benign prostatic hyperplasia (BPH) and PCa, but not other tissue from the body
• PSA is a serine protease secreted by prostatic epithelial cells which lyses the clotted ejaculate to enhance sperm motility
What is PSA?

- PSA is prostate specific, but not PCa specific
- PSA is a screening tool, but not a perfect test
- PSA levels can be altered with BPH, infection (prostatitis or UTI), catheterization, cystoscopy, prostatic massage, pt physiologic factors, medications and supplements
- PCa cells actually produce lower levels of PSA than do BPH cells, but release a greater amount of PSA into the bloodstream
- The majority of PSA in serum is complexed to alpha 1-antichymotrypsin, and the remaining free PSA is composed of 3 isoforms
We'd love to handle your package.
Outline

• History of PCa screening
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• Current recommendations
• At OUI
What is a normal PSA?

• Threshold of 4.0 ng/mL was accepted from early studies without significant evidence.

• In 1997, Catalona et al examined a PSA threshold of 2.5 ng/mL.

• PCa detected in 22% of men with PSA of 2.5 to 4.0 ng/mL, with 80% organ-confined, compared to 70% using a cutoff of 4.0 ng/mL.

• Detected cancers were considered clinically significant based on volume and Gleason score.
What is a normal PSA?

• In 2004, results from the Prostate Cancer Prevention Trial (PCPT) revealed the prevalence of PCa in men with a PSA <4.0 ng/mL
• 2950 men with a PSA <4.0 ng/mL and normal DRE underwent prostate biopsy at the end of the study
• PCa was detected in 15% of these men, and 15% of the cancers detected had a Gleason score ≥7
• If a woman has a positive mammogram, her risk of having breast cancer is ~16%. If a man has an elevated PSA, his risk of having prostate cancer is 20-35%
What is a normal PSA?
What is a normal PSA?

Table 3. Sensitivity and Specificity for Prostate Cancer and High-Grade Disease, by Cutpoints of Prostate-Specific Antigen (PSA) and by Age.

<table>
<thead>
<tr>
<th>PSA, ng/mL</th>
<th>Any Cancer (n = 1225) vs No Cancer (n = 4392)</th>
<th>Gleason Grade ≥7 (n = 250) vs Gleason Grade &lt;7 or No Cancer (n = 5325)</th>
<th>Gleason Grade ≥8 (n = 57) vs Gleason Grade &lt;8 or No Cancer (n = 6518)</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
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What is a normal PSA?

- There is no cutpoint of PSA with simultaneous high sensitivity and high specificity but rather a continuum of prostate cancer risk at all values of PSA.
- Age-specific ranges have been proposed to increase cancer detection (increase sensitivity) in younger men and decrease unnecessary biopsies (improve specificity) in older men.
- Race-specific reference ranges have also been suggested but the data on different thresholds have been inconsistent.
- Both of these concepts remain controversial.
Outline

- History of PCa screening
- What is PSA?
- What is the normal PSA threshold?
- When should screening begin and stop?
- Limitations of PSA
- Current recommendations
Should he get a PSA?

“You’re late.”
When should screening begin?

- Age 50 has traditionally been the age for starting PCa screening
- High-risk groups such as African American men and men with a family history of PCa may benefit from earlier initiation of screening
- In 2001, Fang et al showed that the median PSA for men in their 40’s was 0.6 ng/mL and for men in their 50’s was 0.7 ng/mL
- Demonstrated a 3-fold higher risk of PCa within 10-25 yrs if a man’s PSA was greater than the median for his age
When should screening begin?

- Autopsy studies have shown that histological evidence of PCa is present in approximately 25% of men in the fourth decade of life.
- Epidemiology studies show that PCa deaths begin to appear in men in their 30’s.
- Accordingly, many in the recent past have advocated that screening for PCa should begin earlier than age 50.
When should screening begin?

- Found that a single PSA of >1 at age 44-50 was associated with an increase in odds of cancer of 3.69.
- 80% of advanced cancers in 1999 (T3, T4 or metastatic at diagnosis) occurred in men with PSA levels above the median at age 44–50 years.

When should screening stop?

• Traditionally, PSA screening has been performed for men with at least a 10 yr life expectancy
• This has been interpreted by many as meaning that men over 70 yo do not require screening
• Recent research suggests that a PSA of $\leq 3.0$ ng/mL in men $\geq 75$ yo is associated with very low risk of PCa death
• What about preventing metastatic disease?
Should he get a PSA?
Outline

• History of PCa screening
• What is PSA?
• What is the normal PSA threshold?
• When should screening begin and stop?
• Limitations of PSA
• Current recommendations
Limitations of PSA

• Prostate-specific, not PCa-specific
• Not very useful for distinguishing nonaggressive versus aggressive PCa
• Relatively high rate of “false-positive” results, i.e. poor specificity
• No specific cutoff or normal range
• Levels are variable and can be influenced by a number of factors
  • Size of gland
  • Thiazide diuretics
• Cost-effective?
Consequences of PSA

- Worry about an elevated PSA – who should have a biopsy?
- Invasive, stressful, expensive or time-consuming follow-up tests
- False reassurance from a low PSA
- Stress or anxiety associated with active surveillance
- Deciding to have surgery, radiation or other treatments that can cause side effects that are potentially more harmful than untreated cancer
No good RCTs evaluating PSA screening

However, in the U.S., there has been a steady decline in PCa mortality of approximately 30% which began soon after the introduction of PSA

Whereas 19.2% of pts presented with locally advanced disease in 1988, this decreased to 4.4% a decade later

Since PSA screening began, there has been a 70% reduction in the proportion of men presenting with metastatic disease
Outline

• History of PCa screening
• What is PSA?
• Use of PSA and PSA derivatives in PCa detection
• What is the normal PSA threshold?
• When should screening begin and stop?
• Limitations of PSA
• Latest studies – PLCO and ERSPC
• Current recommendations
Guidelines: EAU

• EAU Guidelines on Prostate Cancer 2013
• The decision to undergo early PSA testing should be a shared decision between the patient and his physician
• PSA testing and digital rectal examination should be offered from the age of 40-45 years to men with a life expectancy of at least 10 years
• The most recent research suggests further PSA testing is unnecessary in men ≥ 75 years and a PSA level ≤ 3 ng/mL at their first screening visit
EAU guidelines 2013

• Early detection of CaP reduces
  – CaP mortality
  – The incidence of advanced and metastatic CaP
Guidelines 2013: AUA

• In men < 40 – NOT recommended
• Routing screening between ages of 40-54 at average risk – NOT recommended
• Between the ages of 55-69, weigh the benefits of screening of preventing 1 in 1000 CaP deaths over a decade against the known potential harms associated with screening and treatment.
• To reduce screening harm, a routine screening interval of two years or more MAY be preferred
• Routine PSA screening is NOT recommended in men over the age of 70 OR any man with less than a 10-15 year survival
Guidelines: AUA, cont’d

• A physician should assess the individual patient’s health status to determine the appropriateness of PSA testing at any given age

• Diagnosis of prostate cancer in men >75 yo may be informative for a man’s overall health but may never require treatment beyond active surveillance

• Men with aggressive prostate cancer in this age group should not be denied the opportunity for the diagnosis and treatment which could affect their length and quality of life
Guidelines: ACS

• American Cancer Society Statement (from website)
  “The ACS does not support routine testing for prostate cancer at this time. ACS does believe that health care professionals should discuss the potential benefits and limitations of prostate cancer early detection testing with men before any testing begins.”

• This discussion should include an offer for testing with PSA and DRE yearly, beginning at age 50, to men who are at average risk of prostate cancer and have at least a 10-year life expectancy
• This discussion should take place starting at age 45 for men at high risk of developing PCa, e.g. African American men and men who have a first-degree relative diagnosed with PCa at an early age (<65)
• This discussion should take place at age 40 for men at even higher risk (those with several first-degree relatives who had PCa at an early age)
• If, after this discussion, a man asks his health care professional to make the decision for him, he should be tested (unless there is a specific reason not to test)
Guidelines: USPSTF

- US Preventive Services Task Force Recommendation on Screening for Prostate Cancer (August 2012)
  
- “The USPSTF recommends against PSA screening for prostate cancer”
Complications of metastatic prostate cancer

- Erectile dysfunction
- Incontinence
  - Overactive bladder
- Lumbar compression
  - New onset back pain
  - Weakness
- Leptomeningeal carcinomatosis
  - New onset headache
  - Seizures
- Death

- Autonomic dysfunction
- Sensory changes
- Altered mental status
- Motor deficits
Complications of metastatic prostate cancer

- Bladder outlet obstruction with potential renal failure
- Gross hematuria with clot retention
- Pathologic fractures causing intractable pain
  - Either at the time of diagnosis
  - Or treatment with androgen ablation from MCap causing pathologic fractures
    - Due to bone loss (up to 4% a year)
So, what does it all mean???
Is PSA . . .?

- anxiety
- surgery
- incontinence

- biopsy
- radiation
- impotence
Is PSA ... ?
At Oregon Urology Institute

• Biopsies
  – Overzealous biopsies result in lower cancer Dx%
  – National average is 35-40% positive
  – At OUI over two years 55-60% positive
• Management of a positive biopsy
  – 27% active surveillance (Nat’l ave. ?15-20%)
  – 29% radiation therapy (Nat’l Ave. 34-35%)
  – 40-45% surgery (nat’l ave. 40%)
• More patients will be on active surveillance
• Difficulty for patients to watch cancer
Food for Thought
Can we prevent CaP

- Eat at least 2.5 cups of vegetables and fruit a day
- Be physically active
- Stay a healthy weight
- Take your vitamins
  - Especially selenium and vitamin E
- 5 alpha reductase inhibitors
  - (but NOT FDA approved to treat CaP)

American Cancer Society
Conclusions

• Who needs a PSA? - That’s debatable. But:
  – Ignorance is not always bliss
  – What you don’t know can sometimes hurt you
  – PCa is curable if detected early but potentially lethal when advanced

• Screening can be initiated after the pt is well-informed of the consequences

• Screening should likely start with a baseline PSA and DRE at 40-50 years of age

• Routine screening is likely not advisable in most patients after the age of 75
Conclusions

• What would you do, Doctor?
• “Treatment or non-treatment decisions can be made once a cancer is found but not knowing about it in the first place surely burns bridges.” - Dr. Joseph Smith
THANK YOU