Prostate Cancer: Screening

Charles Carter, MD, FAAFP

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Dr. Carter is a graduate of the University of South Carolina School of Medicine in Columbia. He completed his residency at Palmetto Health Richland in Columbia, and a fellowship at Georgetown University School of Medicine in Washington, DC. He practices in a residency teaching program and cares for mostly underserved patients. He has interests in diabetes, cardiovascular health, headache disorders, and urologic conditions. He feels family physicians are critical partners to help guide patients through complex evaluations and specialty care.

Learning Objectives

1. Counsel patients, using shared decision making resources, regarding the risks and benefits of prostate cancer screening.
2. Assess the value and limitations of the new ISUP Grade Group Classification System for risk stratification of prostate cancer.
3. Develop collaborative care plans, taking into account the risks and benefits of current evidence-based recommendations of pharmacologic, surgical, CAM, or watchful waiting treatment strategy.
4. Establish a coordinated care process with other health providers (e.g. urologists and oncologists) for men requiring prostate cancer surveillance, and possibly treatment.

Audience Engagement System
Prostate

- Walnut sized gland
- Surrounds urethra
- 70% glandular tissue surrounded by fibromuscular capsule
- Zones: transition, central, peripheral
- Most adenocarcinomas arise in peripheral zone

Prostate Cancer

- Leading cause of (non-skin) cancer in men
- 3rd leading cause of male cancer death behind lung, colorectal
- Estimated Cases - 2017
  - 161,360 new cases (9.6%)
  - 26,730 deaths (4.4%)
- Lifetime risk of diagnosis – 11.1%
  - 5 year survival – 98.6%
  - New case diagnoses down since 2007 with subsequent increase in death rate
  - Disparity: higher incidence and death rate for African-Americans

Prostate Cancer Risk Factors

- Age
  - Most cases in men over 60
- African-American race
  - 60% higher incidence than whites
- Family history of prostate cancer – first degree relatives
- Other possible factors (less significant)
  - Dietary – fats, procarcinogens, antioxidant use

AES Poll Question

- Which best describes your current clinical practice?
  1) I screen all men >50 annually with PSA as part of a standard annual lab set
  2) I offer PSA test to men >50 and screen those who accept
  3) I discuss risks/benefits/alternatives of PSA testing to men >50
  4) I only order PSA test in men who ask me for it
  5) I counsel my patients against PSA screening

The Prostate Cancer Conundrum

- Testing an asymptomatic population to detect disease at a preclinical phase
- Ideally:
  - A clinically important disease
  - With a test that is adequately sensitive, specific and with good population level predictive values
  - Where treating screened patients improves outcomes vs. finding the disease at clinical presentation
  - At a reasonable cost for benefit
  - With few harms

Screening

- Testing an asymptomatic population to detect disease at a preclinical phase
- Ideally:
  - A clinically important disease
  - With a test that is adequately sensitive, specific and with good population level predictive values
  - Where treating screened patients improves outcomes vs. finding the disease at clinical presentation
  - At a reasonable cost for benefit
  - With few harms
Do no harm

Find “clinically significant” cancer

Digital Rectal Exam

- Physical exam technique
- Abnormal exam may indicate tumor
- How does the test perform?
  - Depends on examiner
  - Imprecise
  - Poor inter-rater reliability
- Abnormal predicts Prostate Ca in 18-28% of cases
- 25% of biopsy-detected cancers after abnormal DRE occurred on opposite side of the abnormal “nodule”


Prostate Specific Antigen (PSA)

- A glycoprotein produced by prostatic epithelium
- A “tumor marker”
- Levels increase in:
  - Prostate adenocarcinoma
  - Prostatic hyperplasia
  - Inflammation/Infection (ex. prostatitis)
  - Intervention (procedures)
  - Ejaculation
  - Prostate massage (not clinical DRE)
- Widely available, cost varies

PSA

- More sensitive test than DRE
- In widespread use since mid 1980’s
- General clinical cutoff – 4.0 ng/mL
- Thus, PSA values are a metric of likelihood
  - A risk gradient
  - Not a +/- test
  - False positives and false negatives are a problem
- Most evidence prior to PLCO and ERSPC was observational, case-control, cohort, and/or focused on PrCa specific ends

“Normal” values

- Lower cutoffs have been proposed – 2.6 ng/mL.
- 15% of men with PSA <4.0 have prostate cancer
- 15% of those are high grade tumors
- Lower cutoffs would find more early cancer but increase false positive rate – ex. lowering to 2.5 would double abnormal tests in US
- There is no PSA value where you can tell a patient that they do not have cancer


Other methods of PSA testing

- Age-adjusted PSA
- PSA Velocity
- Free PSA
- Free/Total PSA ratio
- PSA Doubling Time
- Complexed PSA
- PSA Density
- None of these methods has shown improved screening outcomes

AES Poll Question

- Prostate cancer screening with PSA suffers from which type(s) of bias?
  a) Lead time bias
  b) Length time bias
  c) Neither
  d) Both

Lead Time Bias

Overestimation of improved survival among screen-detected cases vs. clinical detection. Not living longer, just living longer with disease.

Length Time Bias

- Overestimation of survival among screen-detected cases due to a relative excess of slowly progressing cases.
- The probability of detection is proportional to the time detectable
- i.e. slowly progressing disease = more opportunity to catch with screen

European Randomized Study of Screening for Prostate Cancer (ERSPC)

- Combination of European randomized trials
- 162,388 men ages 55-69
- PSA only, 4 year screening interval vs. no screening
- PSA cutoff of 3.0 ng/mL
- 29% relative reduction in prostate cancer mortality
- No reduction in all cause mortality

Prostate, Lung, Colorectal, and Ovary Trial (PLCO)

- U.S Screening Study – RCT
- 76,693 men ages 55-74
- annual serum PSA and DRE vs. “usual care”
- PSA cutoff of 4.0 ng/mL
- Cross contamination is an issue
- No reduction in prostate cancer mortality@ 15 years

Major Prostate Cancer Guidelines

- American Cancer Society
- American College of Physicians
- American Urological Association
- United States Preventive Services Task Force
American Cancer Society

- No “clear mandate” for or against screening
- Recommendation:
  - Asymptomatic men with a 10 year life expectancy should be allowed to make an informed decision on screening
  - After a discussion of risk, benefit, uncertainties
  - Elevated risk men at age 45
  - African-American, first degree relative with PrCa before 65
  - High risk men at age 40
  - Multiple family members with PrCa before age 65

American College of Physicians

- Informed decision about PSA test for men 50-69
- “limited potential benefits and substantial harms”
- Consider risk for Prostate CA, health status, life expectancy, and patient values.
- Don’t screen without a clear preference.
- Don’t screen in average-risk men under 50, men over 69, or men with a life expectancy of less than 10 to 15 years.

American Urological Association

- Recommendations:
  - Don’t screen under age 40
  - No recommendation to screen ages 40-54 at average risk. Individualize based on risk.
  - Shared decision to screen age 55-69
  - If screening, 2 year interval preferred
  - Don’t screen ≥70 or with less than 10 year life expectancy

United States Preventive Service TF

- 2012 Recommendation:
  - Against screening for prostate cancer in men using PSA test (USPSTF Grade D recommendation).
  - Recommendations based on
    - RCTs of prostate cancer screening;
    - cohort and cross-sectional studies of the psychological harms of false-positive prostate-specific antigen test results;
    - evidence on the natural history of PSA-detected prostate cancer
But wait, there’s more!

**USPSTF Draft Recommendation 2017**

For all men
Recommend against screening for prostate cancer in men using PSA test
- D Recommendation

For men ages 55 to 69
Individualized screening decisions. Inform about potential benefits and harms of PSA screening so patients can make an informed decision based on their values.
- C Recommendation
For men age 70 and older
Recommend against PSA-based screening
- D Recommendation

* Date for the final version is uncertain [https://screeningforprostatecancer.org/read-the-materials/](https://screeningforprostatecancer.org/read-the-materials/)

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So What/Why Has This Changed?

- NO - New data on screening that proves PSA improves mortality
- YES – Treatment trends away from aggressive treatment for low risk tumors

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One consistency…

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Universal Screening</th>
<th>Informed Screening</th>
<th>Limited Life Expectancy</th>
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<tr>
<td>AUA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>USPSTF</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

For PSA testing clinicians should engage patients in a discussion of:

- Risks
- Benefits
- Limitations
- Uncertainties

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![Image of shared decision making](https://screeningforprostatecancer.org/wp-content/uploads/2017/03/USPSTF_ProstateCancer_Infographic_April2017_Final_5081.pdf)

**Shared Decision Making**

- Often recommended, but evidence suggests physicians do an inadequate job with this
  - Occurs in minority of cancer screening discussions
  - Biased toward advantages of screening
  - Seems to increase testing
- Patient “education” i.e. knowledge likely inadequate
  - Patient empowerment equally/more important

Shared Decision Resources

- American Cancer Society
- Centers for Disease Control and Prevention
  http://www.cdc.gov/cancer/prostate/basic_info/infographic.htm
- National Cancer Institute
- U.S. Preventive Services Task Force
  https://screeningforprostatecancer.org/

AES Poll Question

John is a 63 y.o. African-American man who visits you after attending a health fair at his church. He has a lab result sheet that includes a PSA test. The result is 4.3. He has no FH of Prostate CA. His DRE reveals a smooth, slightly enlarged, non-tender prostate. He does endorse nocturia and some difficulty initiating urination. What would be your next step?

A. Treat him for prostatitis and retest his PSA in 3-6 months
B. Treat for BPH and retest PSA in 3-6 months
C. Recheck his PSA in 3-6 months
D. Refer him to urology

Can PSA testing detect clinically important prostate CA? Yes
Can PSA testing detect clinically insignificant prostate CA? Yes
Can PSA testing reliably differentiate these two? No
If you screen do fewer men die of prostate CA? Maybe
If you screen do men live longer? No
Can PSA differentiate which group your patient will be in? No
Can biopsy differentiate? Maybe
Does PSA testing leading to over detection and overtreatment? Yes
Does treatment carry harms? Yes
Do you have patients in whom PSA testing saved their lives? Yes
Do you have patients where it made no difference or harmed them? Yes
Can you easily tell the difference? No

Chemoprevention (?)

- finasteride study showed treatment reduced prostate cancer overall
  - However, if you did develop cancer it was higher grade
  - dutasteride also appears to yield similar results
- So, FDA rejected applications for approval of dutasteride and finasteride for chemoprevention
  - High grade disease risk seen as outweighing benefits
  - Not FDA approved

Harms

- Overdetection
  - Biopsy (12-13% risk accumulates with repeated testing)
  - Increased likelihood of finding clinically insignificant cancers
- Overdiagnosis as high as 50% in ERSPC
- Overtreatment
  - Surgery (risk of complications, death)
  - Radiation
  - Incontinence
  - Erectile dysfunction
  - Gastrointestinal
- Psychosocial
  - Labeling
  - Anxiety


CAM

- Selenium
  - Does not prevent
- Vitamin E
  - Does not prevent
  - Increases risk


AES Poll Question

- Warren is a 62-year-old man who you referred to Urology after finding a PSA of 5.6. He reports that he has prostate cancer and his surgeon is recommending radical prostatectomy. You obtain records and find that his Gleason score was 6, his ISUP Grade was 1, and his tumor is assessed to be localized to the prostate. He is generally healthy and has a normal life expectancy.
- Which one of the following is the recommended treatment?
  a) Radical prostatectomy
  b) High intensity focal ultrasound
  c) Watchful waiting
  d) Active surveillance
  e) Radical prostatectomy with androgen deprivation therapy

Treatment

- There are many assessment tools after diagnosis
- Tumor grade most important

Gleason Score

- Cancer scoring system based on prostate biopsy histology
  - Correlates with tumor aggressiveness
  - Cancer cell glandular architectural pattern (growth pattern and differentiation)
- Tumors graded 1 (least aggressive) to 5 (most aggressive)
- Biopsies have more than one pattern
- Gleason score sums the two most predominant types (range 2-10)
  - The first score is assigned to predominant pattern
  - Second to the next most common pattern
- A higher score indicates a greater likelihood of
  - Non–organ-confined disease
  - Poorer outcome after treatment for localized disease

New Grading System

- Intl Society of Urological Pathology (ISUP) system
- Uses Gleason Score to develop “risk groups”

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score</th>
<th>Glandular formation</th>
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<tbody>
<tr>
<td>1</td>
<td>4-6</td>
<td>Discrete, well-formed glands</td>
</tr>
<tr>
<td>2</td>
<td>3+4=7</td>
<td>Predominance of well-formed glands, lesser component poorly-differentiated</td>
</tr>
<tr>
<td>3</td>
<td>4+3=7</td>
<td>Predominantly poorly-differentiated glands, lesser component well-formed</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Poorly formed glands with some lacking glands</td>
</tr>
<tr>
<td>5</td>
<td>9-10</td>
<td>Lacking gland formation</td>
</tr>
</tbody>
</table>

- AUA treatment guidelines for localized prostate cancer
  - Emphasize shared decision making
  - Treating based on ISUP Grade
  - Favoring less aggressive treatment and workup options for very low and low risk disease

- Surgery
- Radiation
- Hormonal
- Cryosurgery
- Focal therapy
- High intensity focal ultrasound
- Watchful waiting
- Active surveillance
• Watchful waiting
  – Forgoes treatment and surveillance
  – Risk of treatment risk greater than benefit
  – Palliative care available if needed
• Active surveillance
  – Delays treatment
  – Monitoring/surveillance for progression over time
  – Treatment considered for disease progression
  – Routine PSA and periodic biopsy

For patients diagnosed with Prostate Ca
• There are decision aids regarding treatment
• Provide overview of options
• Consider multiple opinions
• Assist patients in defining core values
• Operative approach for localized cancer has uncertain benefit – no difference between radical prostatectomy and observation in RCT of men 65 and older.
• Similar to findings of another RCT showing no change in mortality at 10 years comparing active surveillance, prostatectomy, and radiation

Decision Tools for Localized Cancer
• Agency for Healthcare Research and Quality
  – http://www.effectivehealthcare.ahrq.gov/ehc/decisionaids/prostate-cancer/
• National Cancer Institute
• American Cancer Society
• American Urological Association
  – http://www.urologyhealth.org/educational-materials?product_format=466

Care planning and ongoing surveillance
• Who are the other members of the team?
  – Urology
  – Oncology/Radiation Oncology
• What is the plan during and after treatment?
• What is needed to coordinate care over time?
• What will be needed to address treatment complications?

Practice Recommendations
• Understand the risks, benefits and limitations of the PSA test
• Engage in shared decision making when using it
• Don't screen men with limited life expectancy
• Don't recommend finasteride, dutasteride, Vitamin E or Selenium for prostate cancer prevention
• Active surveillance is favored for very low and low risk patients diagnosed with prostate cancer

Questions
Thank you!

Resources:

American Cancer Society:
http://www.cancer.org/healthy/informationforhealthcareprofessionals/prostateandthrive/prostateinformationsource/index

American Urological Association:
http://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Specific-Antigen.pdf

National Cancer Institute: http://www.cancer.gov/cancertopics/hp/pbc/pbcpatypes

USPSTF: https://screeningforprostatecancer.org/