Prostate Cancer Early Detection: Update 2010

Prostate Cancer

Disease Burden

The most common non-skin cancer, and the second leading cause of cancer death among U.S. men

It is estimated that:

- 1 in 6 men in the U.S. will be diagnosed with prostate cancer in their lifetime
- 1 in 36 men will die of the disease

Source: American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta, GA: American Cancer Society; 2010.

Prostate Cancer

Disease Burden

In 2010 in the United States:

- 217,730 new cases
- 32,050 deaths
- 2.2 million men living with active disease or a previous diagnosis

Source: American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta, GA: American Cancer Society; 2010.

Who's At Risk for Prostate Cancer?

Age, Race and Family History define risk

- Most cases are in men over age 50
  - The older the man, the higher the risk
- Race/Ethnicity
  - Increased risk in African Americans
  - Lower risk among Hispanic, Asian, and Native Americans
  - Reasons for these racial/ethnic differences are not yet known
- Family History
  - Increased risk if first degree relative with prostate ca
  - Higher risk if multiple relatives affected
  - Many men with prostate cancer <u>do not</u> have a family history of the disease

Can We Prevent Prostate Cancer?

New Prevention Findings

SELECT trial (Selenium and Vitamin E Cancer Prevention Trial)

- Results were reported in late 2008
- After 5½ years of follow up
  - No decrease in prostate cancer seen with Selenium and Vitamin E, alone or in combination
  - Slight increase in prostate cancer (vitamin E) and diabetes (selenium)

Can We Prevent Prostate Cancer?

New Prevention Findings

Finasteride and dutasteride (5-alpha reductase inhibitors or 5-ARIs) may decrease the chance of prostate cancer by as much as 25% in some men

*However, the ACS does not currently recommend for or against using these drugs because:

- Although these drugs may prevent some cases of prostate cancer, there is no evidence thus far that they can lower deaths from prostate cancer
- In the largest studies of these drugs some prostate cancers were prevented, but
  - Men who took 5-ARIs were more likely to be diagnosed with high-grade cancer
  - There were more cardiovascular complications with dutasteride

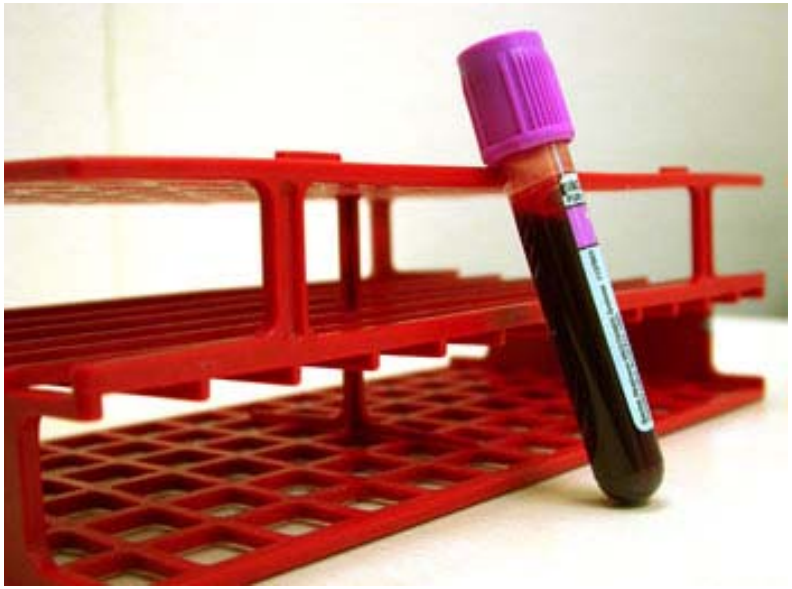
Can We Prevent Prostate Cancer?

Other Prevention Possibilities

Researchers are looking at a number of other possibilities

- Low-fat diet
- Soy-based diet
- Lycopene (found in tomatoes, watermelon, other fruits)

Testing for Early Prostate Cancer Detection



Tests for Prostate Cancer

Types of Tests

Diagnostic tests - tests done because of an identified problem (disease is suspected or known); may be used for disease management or follow-up

Screening tests -tests done on people who have no symptoms of disease

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There is general agreement on the use of PSA and DRE to detect prostate cancer in symptomatic men (i.e. as diagnostic tests)

Screening for prostate cancer in asymptomatic men is much more controversial

Criteria for Use of a Screening Test

- Significant burden of disease in population
- Preclinical stage is detectable and prevalent
- Screening tests are acceptable to population, inexpensive, and *relatively accurate**
- Effective treatment is available for detected disease
- *Early detection improves outcome (mortality) with acceptable morbidity**

****Controversy related to prostate cancer screening revolves primarily around these points***

Source: Smith RA, Duffy SW, Eyre HJ. Screening and Early Detection. In Holland JF, Frei E, Bast RC, Kufe DW, Pollock RE, Weichselbaum RR (eds.). *Cancer Medicine* (7th edition); B.C. Decker; Ontario, 2006.

Tests for Prostate Cancer

- **Digital Rectal Exam**
- **PSA blood test** (Prostate Specific Antigen)
  - Measures protein made by prostate cells
  - Increased PSA levels in blood are usually <u>not</u> due to cancer. Common causes include:
    - Benign Prostatic Hypertrophy (BPH)
    - Prostatitis
    - Post-biopsy/surgery

Both tests can be used to screen asymptomatic men or for diagnostic evaluation of men with symptoms.

Does screening for prostate cancer save lives?

Key Questions

- Does screening extend men's lives (are there benefits)?
- Does screening lead to health problems (are there harms)?
- Do the benefits outweigh the harms?

Surveillance Data

Five-year Relative Survival (%)* during Three Time Periods by Cancer Site

Site	1975-1977	1984-1986	1996-2002
•All sites	50	54	68
•Breast (female)	75	79	90
•Colon	52	59	66
•Lung and bronchus	13	13	16
•Melanoma	82	87	93
•Non-Hodgkin lymphoma	48	53	69
•Ovary	37	40	46
•Pancreas	3	3	6
•**Prostate**	**69**	**76**	**100**
•Rectum	49	57	69
•Urinary bladder	74	78	82

*5-year relative survival rates based on follow up of patients through 2006.

Source: Surveillance, Epidemiology, and End Results Program, 1975-2006, Division of Cancer Control and Population Sciences, National Cancer Institute, 2009.

Does screening for prostate cancer save lives?

New Findings in Screening

Results from 3 major, long-term, randomized controlled trials (RCTs) were recently reported:

- European Randomized Study of Prostate Cancer (ERSPC)
- Göteborg (Swedish) Trial
- Prostate, Lung, Colon and Ovarian Trial (PLCO)

European Randomized Study of Prostate Cancer (ERSPC)

- Began in 1991 in 7 European countries
- 162,000 men aged 55 to 69 randomized to screening vs. usual care
- Median follow-up about 9 years

ERSPC

Findings

- 162,000 men enrolled
- More cancers detected with screening
  - 5990 cancers in screening group vs. 4307 cancers in control arm
- Fewer prostate cancer deaths in screening group
  - 261 deaths in screening group vs. 363 deaths in control arm

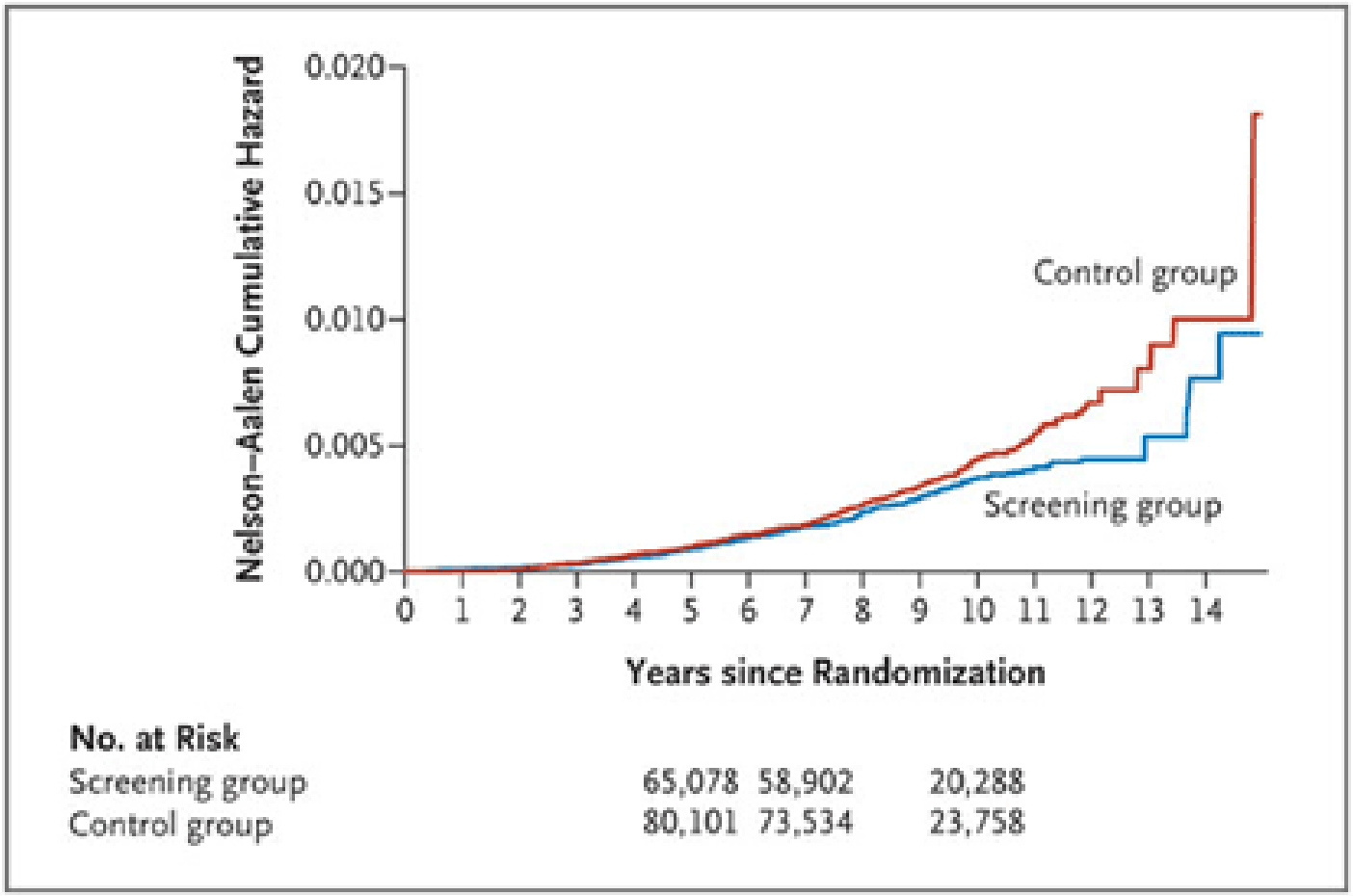
Conclusion: 20% lower risk of prostate cancer death in the group invited to screening

ERSPC

Caveats

- Screening every 4 years, with PSA threshold of 3 ng/ml was associated with a decreased chance of prostate cancer death
  - Unclear how this correlates to current U.S. pattern of annual screening with different PSA “triggers” (2.5 – 4.0 ng/ml)
- Benefit first seen 8-9 years after randomization

ERSPC



Cumulative Risk of Death From Prostate Cancer

Source: Schroeder, et al. NEJM 2009;360:1320

ERSPC

Questions/concerns with study

- To prevent one prostate cancer death
  - 1410 men screened
  - 48 men treated (with attendant risks, side-effects, complications)
    - Both figures are likely overestimates and are expected to improve with longer follow up
- Variation in screening and follow-up protocols
- Minimal to no participation of men of African origin and limited participation of men with family history
  - Relevance of findings to high risk men is unclear

Göteborg (Swedish) Trial

- Began in 1995 in the Swedish city of Göteborg
- 20,000 men aged 50 to 64 randomized to screening (PSA q2 years) vs. usual care
  - Findings from 11,850 of these men were included in ERSPC data
- Median follow-up 14 years

Göteborg Trial

Findings

- 20,000 men enrolled
- More cancers detected with screening
  - 1138 cancers in screening group vs. 718 cancers in control arm
- Fewer prostate cancer deaths in screening group
  - 44 deaths in screening group vs. 78 deaths in control arm

Conclusion: 40% lower risk of prostate cancer death in the group invited to screening

Göteborg Trial

Other findings

- No difference in overall mortality
  - 1981 deaths in screening arm vs. 1982 in controls
- Like ERSPC, prostate cancer mortality benefit not seen until 7-8 years after randomization
- To prevent one prostate cancer death
  - 293 men screened
  - 12 men treated
    - Both figures are significantly lower than those reported for the total ERSPC cohort
- 40% of men with screen detected cancer chose active surveillance over curative treatment

Göteborg Trial

Questions/issues with study

- Low PSA threshold for biopsy
  - Initially 3.0 ng/ml, later dropped to 2.5 ng/ml
  - Nearly 1 of every 3 men who were screened underwent biopsy at some point during the study
- No information on quality of life issues, side effects of treatment, etc.
- No information on family history; no participation of men of African origin
  - Relevance of findings to high risk men is unclear

PLCO

- Began in 1993 in 10 U.S. Centers
- 73,000 men aged 55 to 74 randomized to screening annually vs. routine follow-up
- Median follow-up about 10 years

PLCO

Findings

- At 7 years, screening found more cases of cancer
  - 2820 prostate cancers in annual screening group
  - 2332 cases in “usual care” group
- More prostate cancer deaths in screening arm
  - 7 years: 50 deaths among those in the annual screening compared with 44 in usual care group
  - 10 years: 92 deaths in screening group vs. 82 in usual care

Conclusion: No mortality benefit among those invited to screening

PLCO

Questions/concerns with study

- 44% of men had at least one PSA test prior to study
  - May have excluded more aggressive prevalent cancers
  - Selectively included men with prostate cancers not detected by PSA screening (bias against showing a screening effect)
- Many men in the “usual care” group were screened during the course of the study
  - PSA screening in control group: 40% first year; 52% year 6
- Less than half of those with a positive screen result had a biopsy

PLCO

Questions/concerns with study (cont.)

- Insufficient African American participation (< 5%) or men with family history of prostate cancer (~7%) to allow analyses of outcomes in these groups
  - Relevance of findings to high risk men is unclear
- Longer follow up is needed

Bottom line – no difference in death rates at 10 years between intensively screened and less-intensively screened men

Does screening for prostate cancer save lives?

- There is a higher rate of early stage detection, and prostate cancer death rates have fallen during the PSA era – but it is not clear that this is primarily due to screening
- Other possible reasons for this decline:
  - *Disease is found earlier because of increased awareness and use of diagnostic PSA testing*
  - *There have been substantial improvements in treatment for prostate cancer over the past 2 decades*

Is screening for prostate cancer associated with any harms?

Limitations of Screening

- False negative results
- False positive results
- Overdiagnosis
- Overtreatment

Limitations of Screening

False negative results

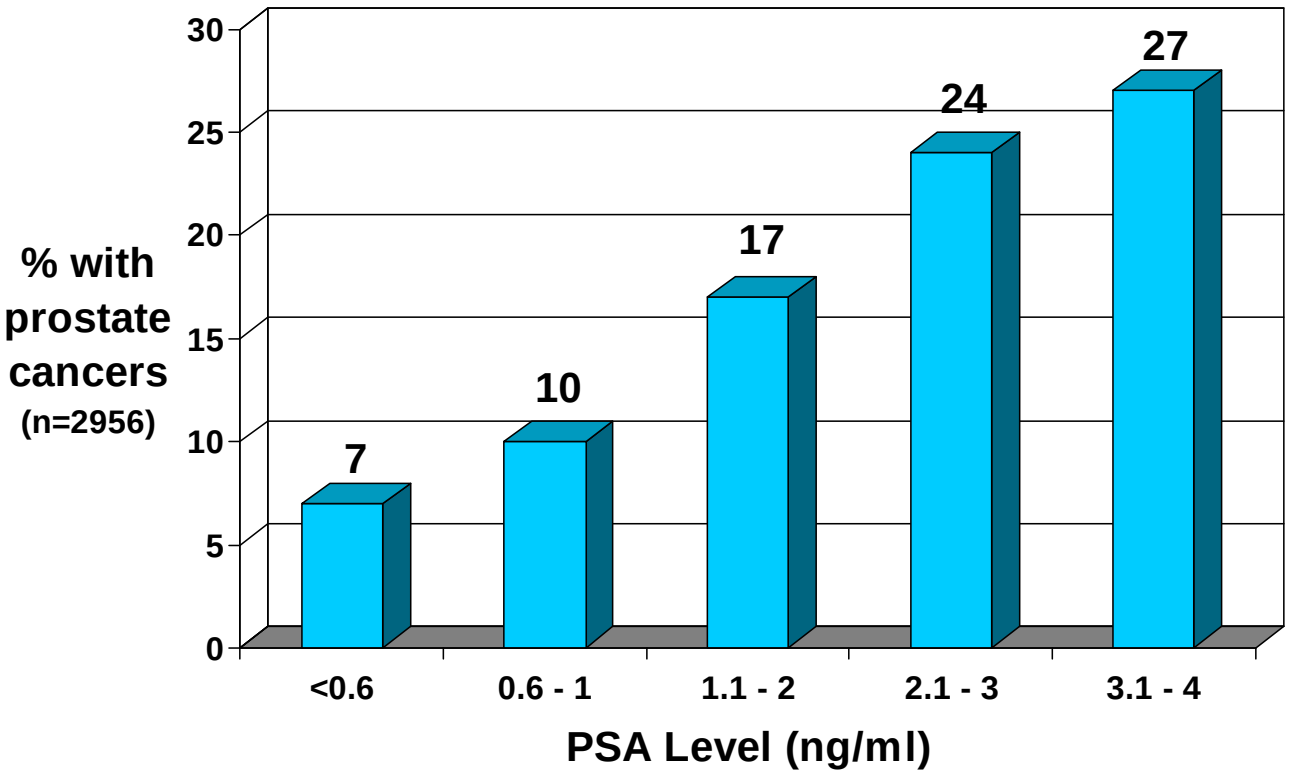
- PSA and DRE “normal”, but cancer is present
- May lead to false reassurance and delayed diagnosis

Research has shown that no cut-off value of PSA is completely reliable to rule-out cancer

- End of study biopsies in the Prostate Cancer Prevention Trial found cancer in some men with PSA less than 1.0 ng/ml

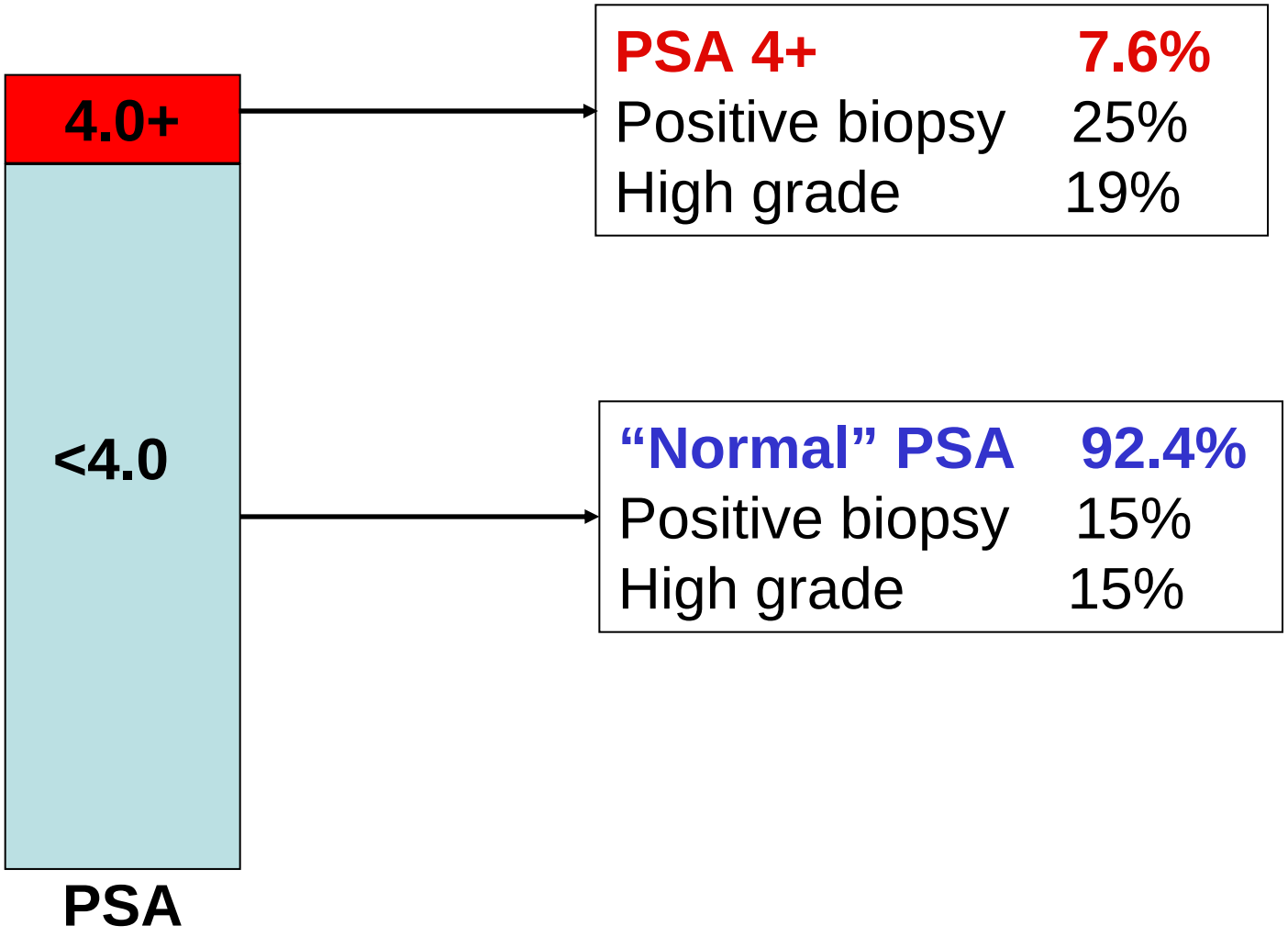
False Negative Results

Prostate Cancer in Men with PSA < 4.0ng/ml in the Prostate Cancer Prevention Trial



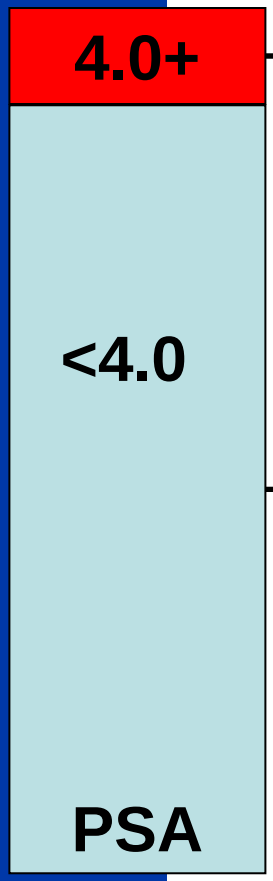
Adapted from Thompson I. *N Engl J Med*. 2004;350:2239-46.

Population Screening with PSA



Sources: SEER, PCAW, Prostate Cancer Prevention Trial Data

Population Screening with PSA



PSA 4+	**7.6%**
Positive biopsy	25%
High grade	19%

“Normal” PSA	**92.4%**
Positive biopsy	15%
High grade	15%

Screen 10,000 Men

PSA 4+	**760**
Cancer	190
High grade	36

PSA <4	**9240**
Cancer	1386
High grade	208

Sources: SEER, PCAW, Prostate Cancer Prevention Trial Data

Limitations of Screening

False positive results

- PSA and/or DRE abnormal, but no cancer found
- Can lead to worry, additional tests and increased utilization of health care services and resources

False Positive Results

If 100 men in each age group are tested:

Age (in years)	# With PSA > 4.0	# With Cancer	# False Positives
50s	5	1–2	3–4
60s	15	3–5	10–12
70s	27	9	18

Limitations of Screening

Overdiagnosis

- Some cancers found by screening grow very slowly and will never cause problems

Risk of Prostate Cancer Diagnosis by Age and by Race/Ethnicity

	Risk during the next 15 years (per 1000 men)	
Race/Ethnicity	At age 50	At age 65
All	50	117
African American	76	163
White	44	113
Hispanic	29	94
Asian & Pacific Islanders	18	84
American Indian & Alaska Native	14	35

Risk of Death From Prostate Cancer by Age and by Race/Ethnicity

	Risk during the next 15 years (per 1,000 men)	
Race/Ethnicity	At age 50	At age 65
All	2	16
African American	5	34
White	2	14
Hispanic	1	12
Asian & Pacific Islanders	1	7
American Indian & Alaska Native	2	9

Limitations of Screening

Overdiagnosis

- Estimates of screening-related overdiagnosis in the U.S.
  - Whites: 23 – 29%
  - African Americans: 34 – 44%

Sources: Etzioni 2002; Telasca 2008

Limitations of Screening

Overtreatment

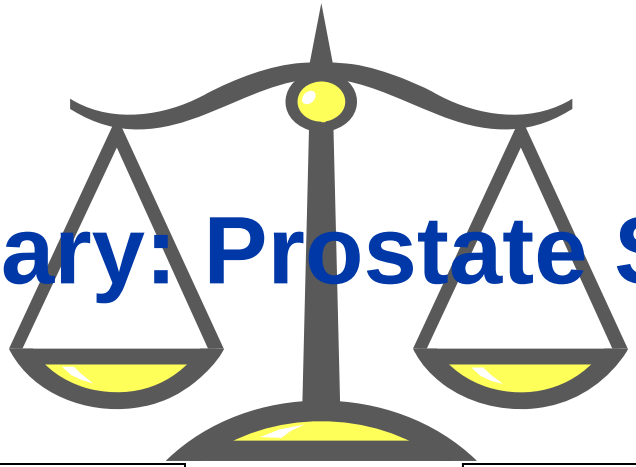
- Overdiagnosis leads to overtreatment
  - Definition - treatment of cancer that, if undetected, would never cause harm
  - Estimates range from 20 – 40% in U.S.
- Treatment of prostate cancer can have life-altering complications and side effects

Frequency of Side Effects

Treatment	Side Effect	Frequency
Radical prostatectomy	• Erectile dysfunction	20–70%
	• Urinary incontinence	15–50%
External beam radiation therapy	• Erectile dysfunction	20–45%
	• Urinary incontinence	2–16%
Androgen deprivation therapy	• Sexual dysfunction	20–70%
	• Hot flashes	50–60%
	• Cardiovascular Dz	?
	• Diabetes	?

These complications may be a worthwhile trade-off for men whose lives are saved by treatment, but it is not clear how many men fall into this category.

Summary: Prostate Screening



Potential Benefits

- PSA screening detects cancers earlier.
- Treating PSA-detected cancers may be more effective, but this is uncertain.
- PSA may contribute to the declining death rate, but the extent is unclear

Potential Harms

- False negatives and false positives are common.
- Overdiagnosis and overtreatment are problems, but the magnitude is uncertain.
- Treatment-related complications and side effects can be significant.

Bottom line: Uncertainty about degree of benefits and magnitude of harms

2010 ACS Guideline for the Early Detection of Prostate Cancer

The American Cancer Society recommends that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening.

Source: Wolf, et al. *CA*, 2010.

Informed Decision Making is Recommended by all Major Organizations

	Recommendation
NCCN (2010)	*"Start risk and benefit discussion AND offer baseline DRE and PSA at age 40."* *"There are advantages and disadvantages to having a PSA test, and there is no 'right' answer about PSA testing for everyone. Each man should make an informed decision about whether the PSA test is right for him."*
AUA (2009)	*"The AUA is recommending PSA screening … for well-informed men who wish to pursue early diagnosis."* *"Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of over-detection and overtreatment should be included in this discussion."*
USPSTF (2008)	*"Clinicians should discuss the potential benefits and known harms of PSA screening with their patients younger than age 75 years. Men in this age group should be informed of the gaps in the evidence, and their personal preferences should guide the decision of whether to order the test."* *"Do not screen for prostate cancer in men age 75 years or older."*

2010 ACS Guideline for the Early Detection of Prostate Cancer

The informed decision making discussion should begin:

- At age 50 for men who are at average risk of getting prostate cancer and have at least a 10-year life expectancy
- At age 45 for men at high risk of developing prostate cancer
  - African American men
  - Men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65)
- At age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age)

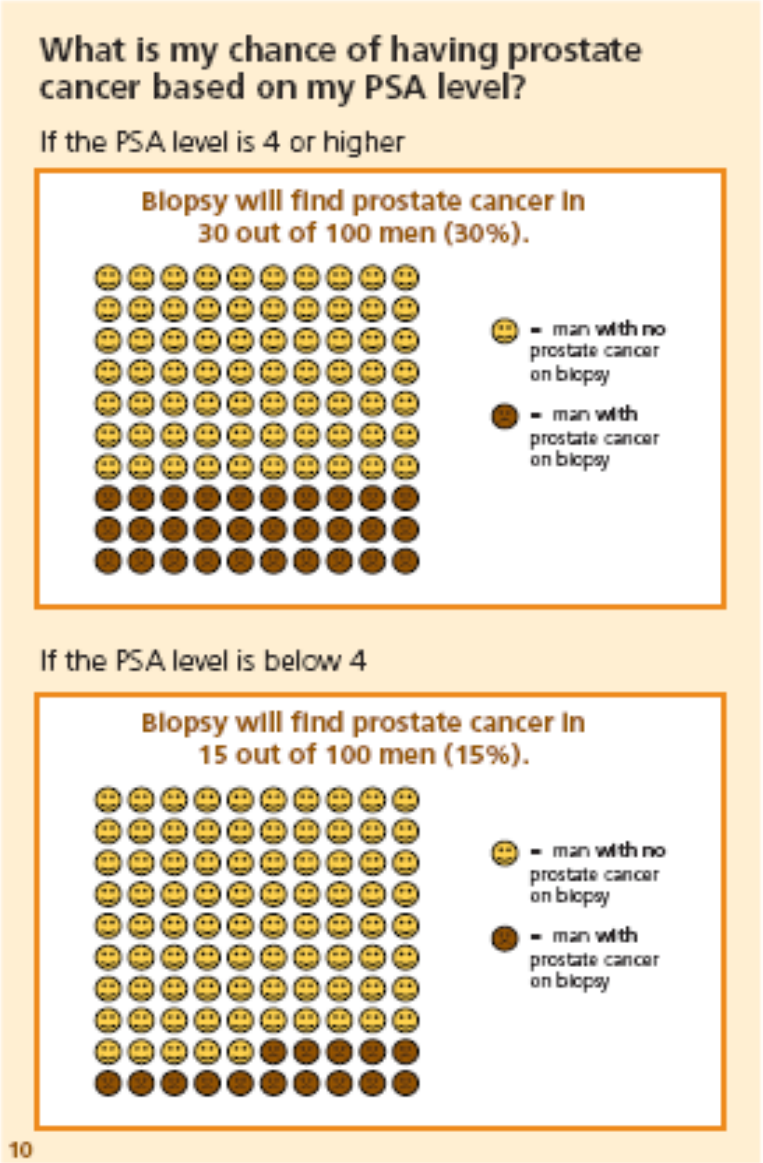
2010 ACS Guideline for the Early Detection of Prostate Cancer

- Screening should not occur without an informed decision making process.
- Asymptomatic men who have less than a 10-year life expectancy based on age and health status should <u>not</u> be offered prostate cancer screening.

2010 ACS Guideline for the Early Detection of Prostate Cancer

- Men should weigh this information against their personal values and preferences when making a screening decision.
- Patient decision aids are helpful in preparing men to make a decision whether to be tested, and their use is encouraged.

2010 ACS Guideline: Decision Aids



Decision Aids: Values and Preferences

What is important to you?

There are many reasons men decide to be tested or to not be tested for prostate cancer. Some reasons are listed below. Place a check by the reasons that are important to you.

Some reasons to be tested

Check what's Important to you	✔
I will have peace of mind when I know the test results.	
I will know if I have prostate cancer or not.	
I will have a better chance of getting cancer treatment if a cancer is found early.	

Other reasons important to you (list them here):

over

Cut out and take to your doctor.

What is important to you?

Some reasons not to be tested

Check what's Important to you	✔
I will worry about the test results.	
I might find a prostate cancer that never would have caused me problems or shortened my life.	
I will have to deal with treatment and its side effects.	

Other reasons important to you (list them here):

Which way are you leaning about being tested?

Want to be tested — Not sure — Do not want to be tested

2010 ACS Guideline: Decision Aids

Supporting Organization	Type of Decision Aid	Title & On-line Access
American Cancer Society	Downloadable Document (PDF)	"Should I Be Tested for Prostate Cancer" Available at: www.cancer.org/prostatemd
Foundation for Informed Medical Decision Making	Video and On-Line Interactive Resource	"Is a PSA Test Right For You?" Available through Health Dialog at: www.healthdialog.com
Centers for Disease Control and Prevention	Downloadable Document (PDF)	"Prostate Cancer Screening: A Decision Guide" Available at: www.cdc.gov/cancer/prostate/pdf/prosguide.pdf "Prostate Cancer Screening: A Decision Guide for African Americans" Available at: www.cdc.gov/cancer/prostate/pdf/aaprosguide.pdf "La Detección del Cáncer de Próstata: Una Guía para Hispanos en los Estados Unidos" Available at: www.cdc.gov/cancer/prostate/pdf/prostate_cancer_spanish.pdf
Mayo Clinic.com	On-Line Resource	"Prostate Cancer Screening: Should you get a PSA test?" Available at : www.mayoclinic.com/health/prostate-cancer/HQ01273
University of Cardiff, U.K.	On-Line Interactive Resource	"PROSDEX: A PSA Decision Aid" Available at: www.prosdex.com

Source: Wolf , et al. *CA,* 2010.

2010 ACS Guideline for the Early Detection of Prostate Cancer

Guideline also includes:

- Core elements of a decision making discussion
- Guidance regarding community-based screening events
- Recommendations for men who choose to be screened
- Individualized risk assessment

For Men Who Choose to be Screened

After learning about the potential benefits and known limitations of screening for prostate cancer, if a man decides to be screened:

- Screening should be done using the PSA blood test
- DRE is optional (at the discretion of the man and his clinician)

For Men Who Choose to be Screened

Rescreening intervals are based on the PSA result:

- < 2.5 ng/ml repeat screening can be safely extended to every 2 years
- 2.5 to 3.9 ng/ml rescreen annually; consider DRE; perform individualized risk assessment
- ≥ 4.0 ng/ml consider referral for further evaluation and/or biopsy

Individualized Risk Assessment for Men with PSA Levels of 2.5 – 4.0 ng/ml

- Factors that influence the risk of prostate cancer:
  - African American race
  - Family history of prostate cancer
  - Increasing age
  - Abnormal digital rectal exam
  - Prior negative prostate biopsy lowers risk
- A Web-based risk assessment tool merges this information to estimate a man's overall risk of prostate cancer and, more specifically, his risk of high-grade prostate cancer.
  - This tool is available on-line at http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp

Research Needs

New screening and diagnostic tools that:

- Detect cancers, but not benign disease
  - Serum, tissue, and urine markers are all under evaluation
- Distinguish aggressive, dangerous prostate cancers from slow-growing, low risk forms.

Treatment enhancements:

- New treatments with lower morbidity
- Better application of existing treatment modalities resulting in enhanced quality of care and more uniform outcomes

Bottom Line

Clinicians should:

- ✓ Educate men regarding uncertainties, risks, and potential benefits of screening and treatment.
- ✓ Provide decision aids, or refer men to appropriate aids.
- ✓ Recognize and inform those men who are at increased risk of a prostate cancer diagnosis (particularly high-grade disease).
- ✓ Recognize men who are not likely to benefit from prostate cancer early detection, and who should therefore not be screened.
- ✓ Ensure appropriate follow up and management for their patients.

2010 ACS Guideline: Supporting Materials and Information

Updated materials for clinicians and patients are available at www.cancer.org/prostatemd

- Patient decision aid: “Should I Be Tested for Prostate Cancer”
- Brochure: “What You Should Know About Prostate Cancer Testing”
- Prostate Cancer Fact Sheet
- Cancer Facts for Men
- Cancer screening exam room wall chart
- Links to decision aids from other organizations
- Link to ACS guidelines article and evidence review

Thank You!