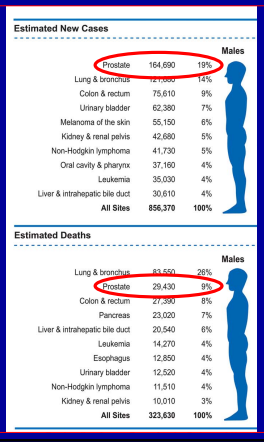
BREAKTHROUGHS IN THE DETECTION OF PROSTATE CANCER

Carolyn M. Fronczak M.D., M.S.P.H.
Urologic Surgery
303-647-9129

Prostate cancer is a VERY COMMON DISEASE

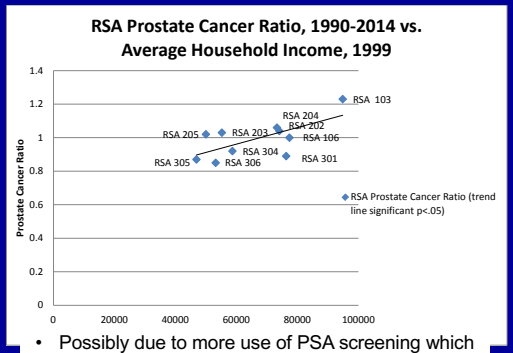
#1 cancer

#2 killer



Ca Cancer J Clin 2018;68:7–30

Boulder has higher rate of prostate cancer compared to other areas surrounding Rocky Flats



- Possibly due to more use of PSA screening which is often seen in higher income areas

Source: 2000 U.S. Census and Colorado Central Cancer Registry, Colorado Department of Public Health and Environment

Boulder has a higher incidence of prostate cancer compared to other areas surrounding Rocky Flats

Table 2a - "Boulder City - Periphery" Regional Statistical Area (RSA 103) 1990-2014, Ratios of Observed to Expected Counts of Cancers, All Cancers Combined (All Ages and Children 0-14) and Ten Selected Cancers (All Ages) - Males

	Cancers Diagnosed	Cancers Expected	Diagnosed/ Expected Ratio	95% C.I. for Ratio
All Cancers – All Ages	1339	1381.488	0.97	0.92-1.02
All Cancers – Age 0-14	8	8.825	0.91	0.39-1.79
Esophagus	6	18.772	0.32**	0.11-0.70
Stomach	16	19.629	0.82	0.47-1.32
Colon and Rectum	115	121.181	0.95	0.78-1.14
Liver	10	21.230	0.47*	0.23-0.87
Lung	93	140.195	0.66**	0.54-0.81
Prostate	497	407.809	1.22**	1.11-1.33
Bone	6	3.153	1.90	0.70-4.15
Leukemias	46	44.140	1.04	0.76-1.39
Lymphomas	63	67.882	0.93	0.71-1.19
Brain and CNS	49	51.144	0.96	0.71-1.27

Possibly due to more participation in PSA screening and higher income area

Source: Colorado Central Cancer Registry, Colorado Department of Public Health and Environment

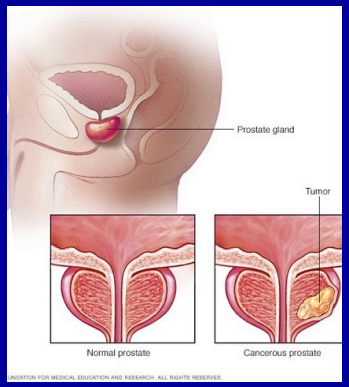
More prostate cancers diagnosed than expected in Boulder

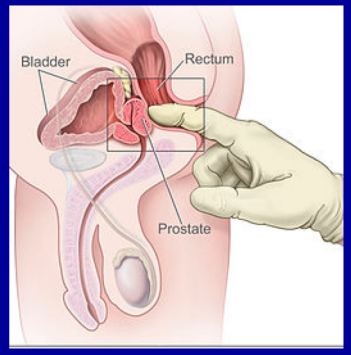
Table 12 - "Boulder City - Periphery" Regional Statistical Area RSA 103) 1990-2014, Ratios of Observed to Expected Counts of Prostate Cancers by Race/Ethnicity and by Age

Race/ Ethnicity	Cancers Diagnosed	Cancers Expected	Diagnosed/ Expected Ratio	95% C.I. for Ratio
White Non-Hispanic	482	392.662	1.23**	1.12-1.34
Hispanic	13	5.366	2.42**	1.29-4.14
Black	0	5.032	0.00	NC
Other	2	4.749	0.42	NC
Age				
0-44	0	2.016	0.00	NC
45-54	38	40.768	0.93	0.66-1.28
55-64	148	141.074	1.05	0.89-1.23
65-74	193	151.450	1.27**	1.10-1.47
75+	118	72.501	1.63**	1.35-1.95
Total	497	407.809	1.22**	1.11-1.33

- Possibly due to more use of PSA screening which is often seen in higher income areas

Where is the prostate?





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Topics to cover

- Risk factors for prostate cancer
- Prostate specific antigen (PSA)
- U.S. Preventive Task Force recommendations on screening
- Present and Future Screening
  - Multiparametric MRI
  - Biomarkers
- Risk stratification to guide treatment

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RISK FACTORS

Prostate cancer risk factors

- Male gender
- Older age
- Ethnicity
  - African Americans 1.6 x more likely to have disease
  - African Americans 2.2 x more likely to die of disease
- Family History of Prostate cancer
  - Father w prostate ca 2x more likely
  - Brother w prostate ca 4x more likely
  - Father and brother w prostate ca 8x more likely

Genetic risk factors

- Recent data
- 16 DNA repair genes may be associated with prostate ca
  - *BRCA2* (5%–9%), *ATM* (2%), *CHEK2* (2%–4%), *BRCA1* (1%), *FH* (1%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.
- The overall prevalence of DNA repair gene mutations
  - 11.8% metastatic prostate cancer is
  - 6% localized high-risk prostate cancer
  - 2% low-to-intermediate-risk prostate cancer

Albright F et al, Prostate 2015;75:390-398; Bratt O, et al., J Natl Cancer Inst 2016;108; Jansson J Clin Oncol 2018:JCO2017766907; Pritchard CC,et al, N Engl J Med 2016;375:443-453; Abida W; JCO Precis Oncol 2017;2017.

Genetic risk factors

- *BRCA1* and *BRCA2* mutations
  - Associated with hereditary breast and/or ovarian cancer
  - *BRCA2* mutations associated with 2 - 6x increase in risk for prostate cancer
  - Recommend *BRCA1/2* mutations start prostate cancer screening at age 45.

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PROSTATE SPECIFIC ANTIGEN (PSA)

PSA: The Past

- In 1994, the PSA blood test approved by FDA for screening and early detection of prostate cancer.
- Age-adjusted death rates from prostate cancer dropped 52% from 1989 to 2015 due to early detection and treatment.
- Normal PSA value is <4ng/ml
  - but higher values accepted at older ages.

PSA not a cancer-specific marker

- PSA can be higher
  - Large prostates (Benign Prostate Hyperplasia)
  - Infections (prostatitis, urinary tract infections)
  - Recent ejaculation
  - Trauma
  - Recent catheterization
  - Recent biking
  - Prostate cancer

PSA not a cancer-specific marker

- Only 25% of men with PSA 4 - 10 ng/mL have a subsequent positive biopsy.
  - Catalona et al, JAMA 1998;279:1542-1547.
- If an abnormally high PSA is observed, then repeat the test
  - PSA measured by different commercial assays are not necessarily interchangeable
  - 25% of men with initial PSA levels between 4 and 10 ng/mL had normal PSA values upon repeat testing.
  - Lavallee LT, et al, Mayo Clin Proc 2016;91:17-22.
- Still, men with low PSA values have a significant risk of prostate cancer
  - Some prostate cancers don't make PSA.

The Value in PSA cutoff at 4.0

- 15% of men with a PSA level of 4.0 ng/mL or less and a normal DRE had prostate cancer.
  - Thompson IM, et al, N Engl J Med 2004;350:2239-2246.
- 30% to 35% of men with PSA 4 to 10 ng/mL range will be found to have cancer.
- PSA levels >10 ng/mL have >67% likelihood of prostate cancer.
  - Catalona et al. N Engl J Med 1991;324:1156-1161.

Early detection →Overtreatment

- unnecessary side effects from unnecessary treatments
- Some prostate cancers do not threaten life expectancy or quality of life
- Anxiety
- Increased health care expenditures

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RESPONSE TO OVERTREATMENT:

U.S. PREVENTIVE TASK FORCE RECOMMENDATIONS

USPTF 2008 and 2012 recommendations

- Recommended against PSA testing for men >=75yrs in 2008
- ALL men in 2012

- USPTF is a panel of 16 experts
  - 16 volunteer members in fields of family medicine, general internal medicine, nurses, obstetrician-gynecologists, occupational medicine physicians, and pediatricians.
  - PANEL DID NOT INCLUDE UROLOGISTS OR CANCER SPECIALISTS

Outcome of USPTF recs

- The incidence of prostate cancer has declined
  - Not exactly a desired outcome.
  - What we don't look for, we don't find.

Outcome of USPTF recs

- MORE DEATHS FROM PROSTATE CANCER
  - Prostate cancer deaths are predicted to increase in 2018 for the first time in 2 decades from an estimated 26,730 in 2017 to 29,430 in 2018.
    - Siegel et al, Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
  - Death from prostate cancer which had been in decline for 2 decades, has stabilized since 2012.
    - Negoita S et al. Cancer 2018.

Outcome of USPTF recs

- MORE CASES OF METASTATIC PROSTATE CANCER
  - Prostate cancer found outside the prostate and in the lymph nodes, bladder, bones, and other organs.
  - Increase seen 2010 to 2014 and MORE RAPIDLY since 2012.

USPTF 2008 and 2012 recommendations

- RISE IN BOTH FUTURE INCIDENCE AND NUMBER OF NEW CASES BY 2025.
- Kelly SP, et al. Eur Urol Focus 2017

2017 USPTF revised recommendations

- For men >=70yrs
  - USPTF continues to recommend against PSA testing.

American Urological Association (AUA) guidelines

- **Guideline Statement: Age 40-54 Years**
- – Screening as a *routine* is not recommended, unless risk factors
- – Why?
  - The evidence for benefit is marginal
  - The evidence for harm is high
- – Doesn't apply to high risk populations.

AUA guidelines

- **Guideline Statement: Age 55-69 Years**
- **Shared Decision Making** and proceeding based on a patient's values and preferences.

- This is population with greatest benefit
- Weigh the benefit of preventing 1 prostate cancer death per 1000 screened over a decade vs the harms of screening and treatment.

AUA guidelines

- **Guideline Statement: Age 70 Years and Above**

- Recommend against *routine* PSA-based screening in men age 70+ years, **or** in any patient with less than a 10-15yr life expectancy

- Some men over age 70yrs who are in excellent health may benefit from prostate cancer screening

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CURRENT AND FUTURE OF SCREENING

SMARTER DECISION MAKING

- NEED INDIVIDUALIZED AND INFORMED DECISION MAKING

SMARTER DECISION MAKING

- Maximize detection of early prostate cancer in patient with life expectancy of >10-15yrs.
- Accurately characterize the biology of the tumor.
- Risk stratification of the cancer
  - Minimize immediate treatment (over-treatment) of indolent cancers.
  - Proceed with treatment of intermediate and high risk prostate cancer.

Standard initial evaluation

- Digital rectal exam + PSA
- PSA and DRE should be done on men >50y.
- A DRE should be done in all men with an abnormal PSA.
- PPV of a suspicious DRE + elevated PSA level for prostate cancer is 48.6% vs 22.4% for men elevated PSA and a normal DRE.
  - Gosselaar et al,European urology 2008;54:581-588.

Abnormal DRE, normal PSA

- Some prostate cancers do not make PSA.
- Positive predicative value of an abnormal DRE in men with normal PSA only 4%– 21%.
- BUT an abnormal DRE shoud be evaluated!!
  - Standard approach= biopsy if abnormal DREs
    - But standard biopsy has risks of pain, infection and may miss the lesion.
  - New school = recommend MRI to further characterize the prostate.

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PROSTATE MRI

Novel MRI techniques

- Multiparametric(mp) MRI of the prostate
  - Anatomic evaluation
  - Diffusion weighted imaging
  - Dynamic contrast enhanced MRI
- Needs to be with and without contrast
- Helps
  - determine who needs a prostate biopsy
  - characterize suspicious lesions felt on DRE
  - Follow men with elevated PSAs but prior normal TRUS (Did we miss a lesion on the random biopsy?)
  - Perform targeted biopsy of a suspicious lesion

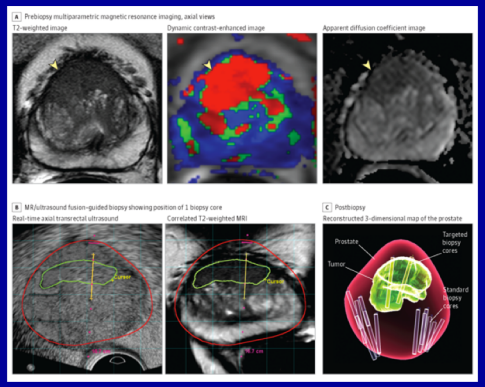
mpMRI PI-RADS score

Prostate Imaging – Reporting and Data System version 2

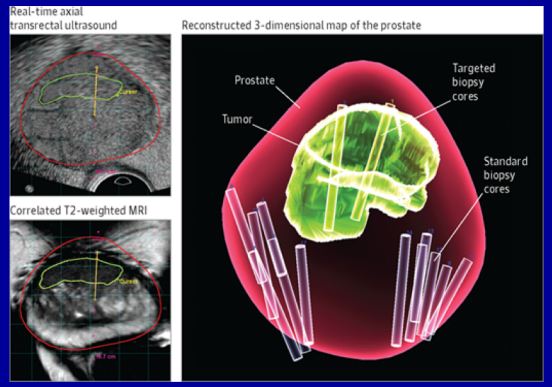
PI-RADS classification	Definition	Total T2 + DWI + DCE score	Total T2 + DWI + DCE + MRS score
I	Most probably benign	3 - 4	4 - 5
II	Probably benign	5 - 6	6 - 8
III	Indeterminate	7 - 9	9 - 12
IV	Probably malignant	10 - 12	13 – 15
V	Most probably malignant	13 - 15	17 - 20

PI-RAD IV and V should have targeted biopsy

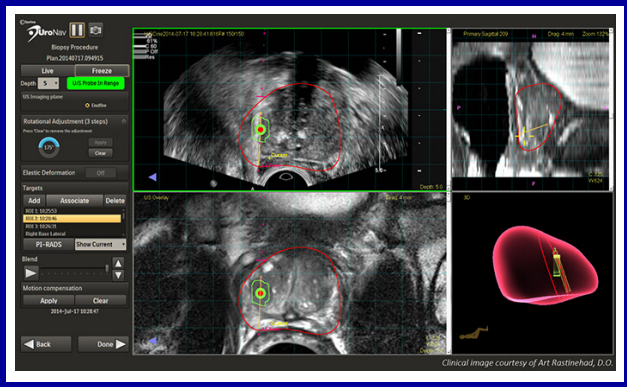
MRI-TRUS fusion target biopsy



TRUS MRI fusion biopsy



TRUS MRI fusion biopsy



Evidence for Prostate MRI

- Prospective study 223 biopsy naïve men
- All had standard TRUS biopsy and MRIs
  - If MRI PIRAD 3-5, then also guided biopsy.
- TRUS bx
  - 126/142 cancer cases (88.7%), including 47 cases classified as low risk.
- MRI-guided biopsies
  - identified 16 additional cases of intermediate/high-risk prostate cancer
  - reclassification of 13 cases from low risk to intermediate/high risk.
- Pokorny et al,. Eur Urol 2014;66:22-29.

Evidence for Prostate MRI

- NOT doing a biopsy on PI-RADS 1 and 2 lesions
  - Reduced biopsy rate by 36%
  - Reduce the identification of low-risk prostate cancer by 87%
  - Increase finding intermediate/high-risk tumors by 18%
  - But miss 6.7% of cancers.
  - Pokorny et al,. Eur Urol 2014;66:22-29

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BIOMARKERS

Biomarkers

- A substance or process that indicates the presence of cancer.
  - a molecule secreted by a tumor.
  - a specific response of the body to the presence of cancer.
- Useful if PSA 3-10ng/ml
- However, some cancers will not be detected using biomarkers.

Prostate cancer biomarkers

- Give a probability of finding cancer before proceeding with biopsy.
- Decrease unnecessary biopsies.
- Increase the specificity of cancer detection, without missing a substantial number of higher-grade (Gleason ≥7) cancers.

Novel Biomarkers

- Tests for those who have not had a biopsy
  - Percent free PSA (%f PSA)
  - Prostate Health Index (PHI)
  - 4Kscore®
- Tests for those who have had a biopsy and deciding on further biopsy or treatment
  - Percent free PSA (%f PSA)
  - PHI
  - 4Kscore®
  - PCA3
  - ConfirmMDx for negative biopsy
  - OncotypeDX for positive biopsy

Biomarkers

- At this time, no one biomarker can be recommended over another due to lack of head-to-head clinical trials.

%free PSA

Percentage of free PSA	Probability of prostate cancer
0 –10%	56%
10% –15%	28%
15% –20%	20%
20% –25%	16%

Journal of the American Medical Association, May 20, 1998.

- 25% fPSA cutoff detected 95% of prostate cancers while avoiding 20% of unnecessary prostate biopsies.

Partin et al, Prostate Cancer Prostatic Dis 1998;1:197-203.

Prostate Health Index

- Blood test - Combines tPSA, fPSA, and proPSA
- FDA approved 2012 for PSA 4 - 10 ng/mL
- Use resulted in decrease in biopsies
- Correlated with cancer grade
- Area under the curve (AUC) of 0.72 for discrimination of high-grade (Gleason ≥7) cancer from low- grade cancer or negative biopsy.
  - Catalona WJ, et al, J Urol 2011;185:1650- 1655.
- Optimal cutoff score of 24
- 36% of biopsies avoided
- Approximately 2.5% of high-grade cancers missed.
  - de la Calle C, et al, J Urol 2015;194:65-72.

PCA3

- a noncoding, prostate tissue-specific RNA
- overexpressed in prostate cancer (66x)
- Post DRE urine
- Score independent of prostate volume, age, BPH and prostatitis
- Negative predictive value (NPV) of 90%
  - a sensitivity of 78%, specificity of 57%, Positive predictive value of 34%.
    - Gittelman et al,The Journal of urology 2013;190:64-69.
- The risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%.
  - Thus, PCA3 not recommended for patients without prior negative biopsy

Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32:4066-4072.

4Kscore

- Algorithm patient's age, digital rectal exam, and previous biopsy status
- Panel of 4 known markers
  - total PSA
  - free PSA
  - intact PSA
  - hK2
- Gives percent likelihood of finding high-grade (Gleason ≥7) cancer on biopsy
- Biopsies can be avoided, high grade cancer detected, but 5-10% cancers are missed in reported trials.

ConfirmMDx

- Tissue-based, multiplex epigenetic assay
- Improve the stratification of men with prior negative biopsy being considered for repeat prostate biopsy.
- Hypermethylation of the promoter regions of *GSTP1, APC,* and *RASSF1* is assessed in core biopsy tissue samples.
- Not FDA approved.
- Biopsy samples < 30mo of age

ConfirmMDx

- In two clinical trials
  - The NPV was 90% (95% CI, 87%–93%).
    - Stewart et al, J Urol 2013;189:1110- 1116.
  - The NPV was 88% (95% CI, 85%–91%)
    - Partin et al, J Urol 2014;192:1081-1087.

SelectMDx

- Gene expression assay
- post-DRE urine
- Measures *DLX1* and *HOXC6* expression against *KLK3* as internal reference.
- *DLX1* and *HOXC6* have been associated with prostate cancer aggressiveness.
- Improves the identification of men with clinically significant prostate cancer prior to biopsy, thereby reducing the number of unnecessary biopsies.

Select MDX

- Prospective multicenter trials
- AUC of 0.76
- Sensitivity of 91%
- Specificity of 36%
- NPV of 94%, and a PPV of 27% for the prediction of Gleason score ≥7 prostate cancer.
- When combined with PSA levels, PSAD, DRE results, previous negative prostate biopsies, age, and family history in a multimodal model, the overall AUC was 0.90 in the training set and 0.86 (95% CI, 0.80–0.92) in the validation set.
  - Van Neste L, et al, Eur Urol 2016;70:740-748.

Additional biomarkers

- OncotypeDX
  - Evaluate positive biopsies for more aggressive high risk cancer.
- Prolaris
  - Evaluate positive biopsies for more aggressive high risk cancer.
- ProMark
  - may be utilized for low or very low risk patients post biopsy that may be candidates for active surveillance or definitive therapy.

Risk stratification guides management

	AUA Risk Category	NCCN Risk Category
Very Low	—	PSA ≤ 10 ng/mL, Gleason score ≤ 6, clinical stageT1c, < 3 positive biopsy cores, ≤ 50% in each core, and PSA density < 0.15 ng/mL/g
Low	PSA ≤ 10 ng/mL, Gleason score ≤ 6, and clinical stageT1c or T2a	PSA < 10 ng/mL, Gleason score ≤ 6, and clinical stageT1-T2a
Intermediate	PSA > 10-20ng/mL or Gleason score 7, or clinical stage T2b	PSA 10-20 ng/mL, Gleason score 7, or clinical stageT2b-T2c
High	PSA > 20ng/mL or Gleason score 8-10, or clinical stage ≥T2c	PSA > 20ng/mL or Gleason score 8-10, or clinical stage T3a
Very High	—	Clinical stage T3b-T4

Take home messages

- Get your PSA checked.
- Ask your health care provider to do a rectal exam.
- Request the use of novel techniques for diagnosis of prostate cancer.
- Technology and science are allowing individualized characterization of risks and tumor biology so you take control of your health care decisions.