PROSTATE CANCER

CHAPTER 2

Screening

Abbreviations and Acronyms

5-ARIs	= 5-Alpha Reductase Inhibitors
ACS	= American Cancer Society
AUA	= American Urological Association
BPH	= Benign Prostatic Hyperplasia
CUA	= Canadian Urological Association
DRE	= Digital Rectal Examination
EAU	= European Association Of Urology
ERSPC	= The European Randomised Study Of Screening For Prostate Cancer
FH	= Family History
FM	= Family Member
mL	= Milliliter
NCCN	= National Comprehensive Cancer Network
ng	= Nanogram
ng/mL	=Nanogram per milliliter
PCa	= Prostate Cancer
PCPT	= Prostate Cancer Prevention Trial
PLCO	= The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	= Positive Predictive Value
PSA	= Prostate-Specific Antigen
Pt	= Patient
TUR	= Transurethral Resection
TZ	=Transition Zone
USPSTF	=U.S. Preventive Services Task Force
UTI	= Urinary Tract Infection
Vs.	= Versus

There has been continuing debate regarding the role of PSA testing in the screening and diagnosis of prostate cancer[1]. In fact, different authors and institutes have quite different and even opposing viewpoints on this issue. The results of ERSPC (The European Randomised study of Screening for Prostate Cancer) and PLCO (The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) studies further added to this controversy. Even world media portrayed prostate cancer screening in a negative light after that[2]. PLCO and ERSPC trials concluded that the decline in mortality rates are quite small compared with the large number of men diagnosed and treated for prostate cancer[3].Then, USPSTF (United States Preventive Services Task Force) mentions that PSA based screening results in small or no reduction in prostate cancer–specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary[4].

On the other hand, the significant reduction in advanced disease and mortality from prostate cancer in several countries including U.S, U.K, France and Austria which had PSA testing policies for the early detection of prostate cancer[5] and shortcomings of above mentioned trials made most professional associations to stand by their guidelines on PSA screening.

To get a glimpse of this debate we have summarized the main results and weakness of PLCO and ERSPC studies, the actual long term results of PSA testing policies, attitudes of different professional bodies and guidelines regarding PSA screening and reactions of AUA (American Urological Association) and CUA (Canadian Urological Association) to remarks of USPSTF in the following figures and tables. Figure 1 illustrates the main points and weaknesses of PLCO and ERSPC trials. Figure 2 shows the actual long-term outcomes of PSA testing policies for the early detection of prostate cancer. Figure 3 compares attitudes of different professional bodies and guidelines regarding PSA screening and finally figure 4 shows the divergence

between viewpoints of most scientific bodies & USPSTF.

Figure 1- The main points and weaknesses of PLCO and ERSPC trials[3, 5-8]

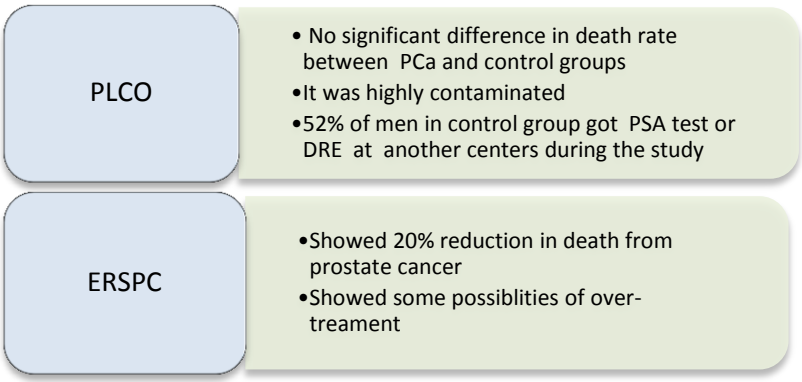


Figure 2- The actual long-term outcomes of PSA testing policies for the early detection of prostate cancer[7-15]

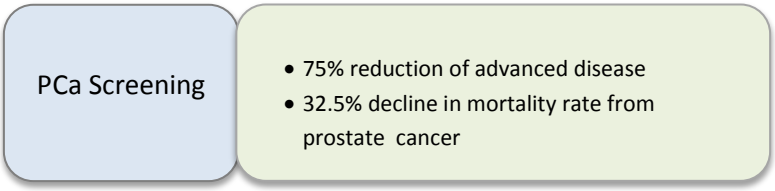


Figure 3- Attitudes of different professional bodies and guidelines regarding PSA screening in a well-informed man who is older than 40-50 years of age and has a life expectancy of more than 10 years have been summarized in the following figure[4-7, 9, 16]

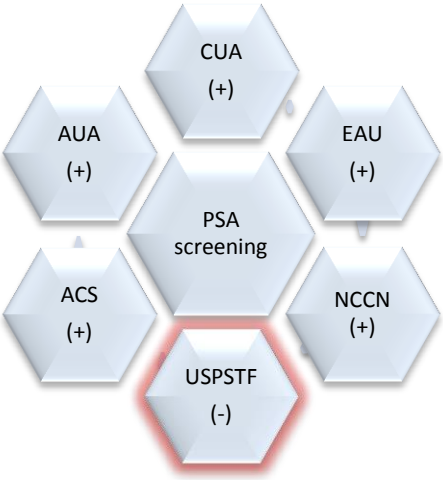


Figure4-Divergence between viewpoints of most scientific bodies & USPSTF[9]

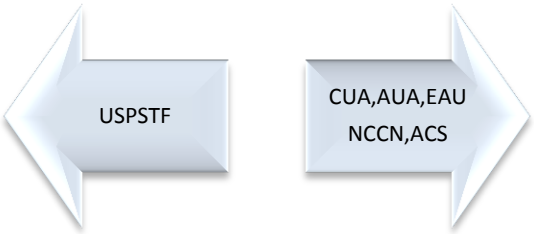


Table 1- Reaction of AUA to USPSTF recommendation

LINTHICUM, MD, October 7, 2011–

«The American Urological Association (AUA) applauds the U.S. Preventive Services Task Force for its interest in reviewing the use of the prostate-specific antigen (PSA) test. ***However, we are concerned that the Task Force's recommendations will ultimately do more harm than good to the many men at risk for prostate cancer*** *both here in the United States and around the world. The AUA's current clinical recommendations support the use of the PSA test, and it is our feeling that, when interpreted appropriately, the PSA test provides important information in the diagnosis, pre-treatment staging or risk assessment and monitoring of prostate cancer patients.*

Not all prostate cancers require active treatment and not all prostate cancers are life threatening. The decision to proceed to active treatment is one that men should discuss in detail with their urologists to determine whether active treatment is necessary, or whether surveillance may be an option for their prostate cancer.»

Table 2- Reaction of CUA to USPSTF recommendation

MONTREAL, Nov. 21, 2011 /CNW Telbec/ -« The Canadian Urological Association (CUA) position on prostate-specific antigen (PSA) as a screening test for prostate cancer differs from the recent position of the US Preventive Services Task Force (USPSTF). The USPSTF concluded that PSA-based screening minimally reduces prostate cancer-specific deaths and is associated with harms related to evaluation and treatments, some of which may be unnecessary. This position differs from the CUA position published in June 2011.2 The CUA stands by its guideline on PSA screening for prostate cancer:

Some men with low-risk prostate cancer can be managed without treatment, avoiding side effects unless and until disease progression suggests that treatment is necessary. ***This strategy of active surveillance for low- risk prostate cancer, now widely practiced in Canada, reduces the problem of over-treatment - the main concern expressed by the USPSTF».***

The recommended age of baseline PSA test has also been a matter of debate by different guidelines (table-3).

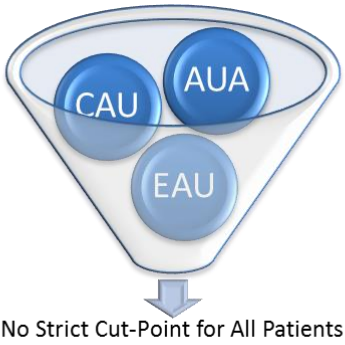
Table 3- Professional bodies recommendations on age of baseline PSA test[4-7,16]

AUA, EAU, NCCN	40 years of age
CUA	50 years of age • 40 years of age in high risk patients (African-American, FH of PCa) • May be beneficial beween 40-50
ACS	50 years of age • 45 in high risk patients • 40 years of age in patients with several first fegree relatives with prostate cancer

PSA Threshold

Exact PSA cut-off for recommending prostate biopsies is another controversial debate in prostate cancer screening. We have noticed different PSA cut-offs during past years. However, most professional guidelines do not recommend a strict cut point anymore (Figure 5).

Figure 5- The current attitudes of guidelines regarding PSA cut-off[5-7]



Some of important considerations regarding PSA screening have been summarized in the table-4.

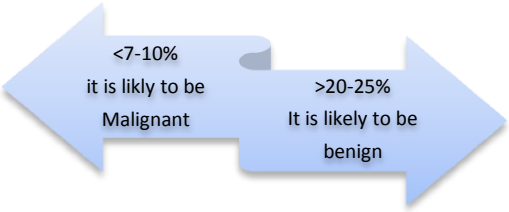
Table 4- Decision making, Intervals and termination of PCa screening [1, 5, 6, 17-19]

- Patients should be aware of availability of PSA test, so they can make an informed decision about the need for routine screening. In fact, the decision to undergo early PSA testing should be a shared decision between the patient and his physician.
- DRE & PSA are the first line modalities in prostate cancer screening. However, contemporary screening involves more than just them.
- Annual screening has been the standard, however, the two screening studies that demonstrated screening was beneficial, screened men every 2-4 years.
- Strong consideration should be given to discontinuing PSA screening for men over 75 years of age.
- If a man who is older than 75 years has an abnormal finding on DRE or if his PSA level is significantly high, then a prostate biopsy is needed and, indeed, treatment for that prostate cancer may be needed.

Parameters in Prostate Biopsy Recommendations

Elevated PSA level and abnormal digital rectal examination are the most common reasons for prostate biopsy. Having said that, we would like to note that current guidelines indicate the recommendation for prostate biopsy should be based on a couple of factors instead of a strict PSA cut-off value. Most of these factors should be interpreted together. These parameters have been discussed in the table-5.

Table 5- Important factors in prostate cancer screening [6, 7,9,17, 20-27]

Parameter	Remarks
DRE	Significant findings Hard nodule Induration Asymetry (Contraversial)
PSA	• The physician should decide based on just more than one PSA measurement • Each patient should be sent to just one laboratory • Data show that there may be 20-25% difference between different laboratories reports
Free/Total PSA	Percentage of free/total PSA adds modest clinical value in the 4-10 ng/mL total PSA range, when it is at extreme ranges[7] (figure 6) Figure 6- Clinical judgement about percentage of free PSA 

Age

- Though different age specific PSA cut-offs have been discussed in past several years, the current guidelines state that there is no single justifiable cut point regardless of age (figure- 7)
- Some evidence suggest that the use of age adjusted PSA increases the risk of missing higher grade cancers in older men and may over detect smaller volume, low grade tumors in younger one

  To have a glimpse of age specific PSA, median PSA values for each group have been summarized in the figure-8

Figure 7- Current guidelines point of view regarding age-specific PSA cut –point

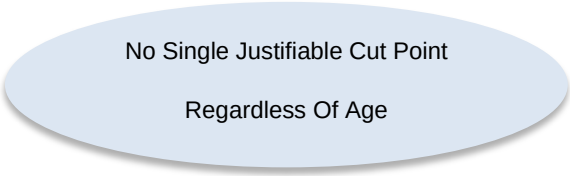
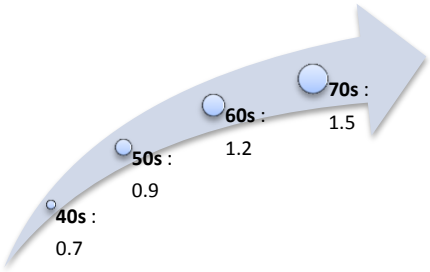


Figure 8- Median age specific PSA values



PSA velocity

- PSA velocity may improve the sensitivity of PSA screening
- To calculate PSA velocity, at least three PSA determinations must be used over a time period of 18 Months
- To get a better results, different PSA velocities are being used based on patients' total PSA values and patients' ages
- PSA velocity alone should not be the whole basis for performing prostate biopsies

Figure 10- Significant PSA velocity (ng/mL) based on total PSA (ng/mL) value

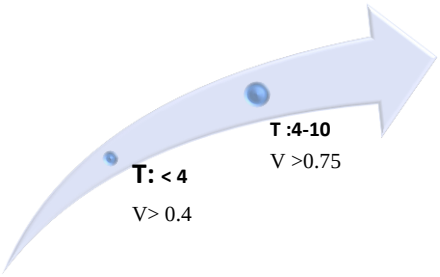
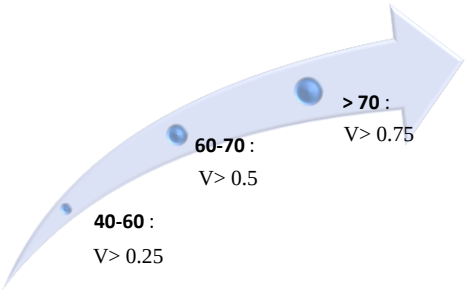
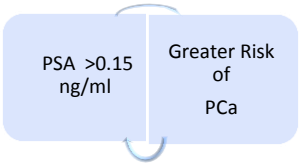


Figure 11- Significant PSA velocity (ng/mL) based on patient's age in years



PSA density	PSA density (Total PSA /Prostate volume) may improve the specificity in detecting prostate cancer when total PSA is in the range of 4-10 ng/mL (figure-9) Figure 9- Commonly used PSA density cut-off to increase specificity of PSA screening 
PSA density of TZ	A cut-off value of 0.35- 0.37 ng/mL/cc for PSA-TZ has been defined with good sensitivity and a specificity in predicting prostate cancer in men with total PSA of 2.5-10 ng/mL
Ethnicity	Increased risk in African-Americans
Prior biopsy	It will be discussed in nomograms section
Co-morbidity	Should be taken into account to avoid unnecessary treatments

PCA3

Urine PCA3-score may play a more significant role in PCa screening, but the current literature to support its use for routine screening is limited[6, 32]. PCA3 is only expressed in human prostate tissue and it is highly expressed in prostate cancer. A summary of current data in this regard has been shown in the table-7.

Table 7–PCA3 assay highlights[5, 9, 34]

- Assays have been developed to measure PCA-3 mRNA in the first 20-30 mL of urine, obtained after a thorough digital rectal examination of the entire prostate.
- Its level is expressed as a ratio to PSA-mRNA
- Increasing PCA3-score (> 35) has been used for predicting repeat biopsy outcome by some authors.

Nomograms and Risk Calculators

As mentioned previously, recent guidelines believe that there is no single justifiable PSA cut-point, regardless of age, to recommend prostate biopsy[6]. In other words, the relationship between PSA and PCa incidence is continuous[6]. So, current guidelines indicate that recommendation for prostate biopsy should be based on a couple of factors instead of a strict PSA cut-off.

Nomograms and Risk Calculators (RC) may help a clinician by combining multiple clinical and paraclinical parameters, such as DRE, PSA, PSA velocity , PSA isoforms, age, race, family history of PCa and genetic data to determine one's risk of PCa[6]. In fact, these tools will aid physicians and patients in determining the need for prostate biopsy[20]. Different Risk Calculators (RCs) are being used by different institutes at the moment. Researches are being done to improve the accuracy of these Risk Calculators in different institutes. Also, it seems some calibrations in some of these calculators may be needed to adjust better in other areas of the world like eastern Asian countries[28]. Sunnybrook, PCPT and ERSPC and some other prostate cancer risk calculators are available online. Some parts of current literature in this regard have been summarized in table-6.

Table 6- Prostate Cancer Risk Calculators highlights[29-31]

- No specific level of risk is recommended for prostate biopsy and this decision should be an individual choice based upon a physician-patient relationship.
- If it is presumed that a PPV of 25% would be a reasonable threshold for a prostate biopsy recommendation.
- A 65-year-old man might have a 25% risk of positive biopsy with different PSA levels like 2.27 ng/mL, 1.66 ng/mL, 0.57 ng/mL based on other risk factors like family history of prostate cancer, abnormal DRE or other risk factors that are included in the Risk Calculators.
- A negative previous biopsy decreases the risk of positive biopsies in further interventions. But, this should be interpreted besides other factors. For example, the calculated risk of one patient with previous negative biopsies might be lower than 25% and does not want the repeat biopsy. On the other hand, the calculated risk of another patient may be more than 25% and need repeat biopsy.
- PCPT and ERSPC calculators where examined in a Canadian cohort study. ERSPC-RC had better calibration and avoided more biopsies in the lower risk range (0–30%). However, this study concluded that calibration would need to be improved to allow routine use of the ERSPC-RC in Canadian practice.
- The Sunnybrook nomogram-based prostate cancer risk calculator performed better than the Prostate Cancer Prevention Trial (PCPT) - based risk calculator , but neither one added clinical benefit for risk thresholds of less than 30%.

Effect of Some Common Scenarios on PSA Level

PSA level is affected in a number of physiologic and pathologic situations. It is also affected by certain drugs. So, in order to predict prostate cancer risk, we should be aware of them. Some of the most important circumstances in this regard have been summarized in the table-8.

Table8- Conditions associated with increase or decrease of PSA levels[6, 9]

May increase PSA level	May decrease PSA level
BPH	Radical prostatectomy
Prostatitis	Prostate Radiotherapy
Prostate cancer	Surgical Castration
Prostate biopsies	Medical Castration
Urethral instrumentation	5-a-RIs (Procar , Propecia)
Cystoscopy	Statins
TUR	Obesity
UTI	
Vigorous DRE *	
Recent ejaculation * *	
exercise Prolong	

*Although DRE can lead to slight increases in serum PSA, the resultant change in PSA falls within the error of the assay and rarely causes false-positive tests[9]

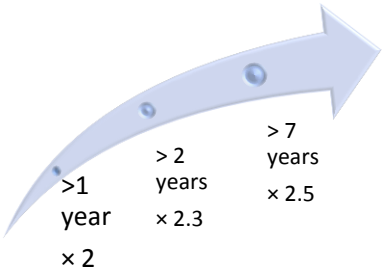
* *A repeat PSA after 48 hours of sexual abstinence may be helpful for interpreting serum PSA levels that are minimally elevated[9]

Both type of 5-alpha reductase inhibitors (5aRIs) including type 2 isoenzyme inhibitors (finasteride) and dual type 1 and 2 isoenzyme inhibitors (dutasteride) reduce the PSA by about 50% by 6 months and this effect is actually non dose-dependent (6,7).

In fact, even the finasteride 1 mg (trade name Propecia) used for male pattern hair loss also results in the same decline in serum PSA levels as the 5-mg dosage[9]. To have a better idea of real prostate cancer risk, different researchers and authors have proposed some kind of calibration for

measured PSA level, based on the duration of drug consumption. This issue has been summarized in the figure-13.

Figure 13.-PSA value calculation in patient who is using finasteride[9]



Another concern could be about PSA level in patients with chronic renal failure. However, fortunately, renal functioning has little effect on serum PSA levels. Even hemodialysis and peritoneal dialysis do not affect the total serum PSA levels, but they may affect the free PSA levels[6, 35].

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