SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 65: Sept.-Oct. 2010

Contents

Your comments and requests for information on a specific topic are welcome at ecweber@nwlink.com

This month's issue plus a compilation of past articles is available online at www.seattleprostateinst.com/pcacommentary.htm

PSA SCREENING: Swedish Goteborg Trial Supports Benefit of PSA Screening.

The Goteborg PSA screening trial (later merged into the larger European Randomized Study of Screening for Prostate Cancer) was reported by Hugosson et al. in Lancet Oncology, August 2010. The study tabulated prostate cancer-specific mortality in 10,000 men "invited" to be screened every 2 years compared with an equal number of men followed as a control group. The threshold for further study initially was a PSA of 3.4 ng/ml in 1994, lowered to 2.9 in 1999, and finally set at 2.5 in 2005. Men whose PSA was above the threshold mark underwent a DRE, a trans-rectal ultrasound, and a sextant prostate biopsy. Men eligible for study were between 50 and 64 years old (median 56 years); median follow-up was 14 years (F/U 9 years, ERSPC; 11.5 years, PLCO). The study is ongoing and the published data represents the first planned analysis.

Among those invited to screening 76% had at least one PSA. PSA testing in the control group was very low during the first five years, whereas over time 24% of men in this group ultimately had a PSA test. This represents a considerably lower rate of "contamination" than in the US Prostate, Lung, Colon, and Ovary (PLCO) screening trial where 40% in the control group were tested in year one and 52% by year six.

In keeping with results of the PLCO and ERSPC trials, cancer was diagnosed substantially more frequently in men who were screened compared to those in the "control" groups, 12.7% vs. 8.2% respectively in the Goteborg study. Other main findings were:

1. The rate of prostate cancer-specific death rate was 0.50% in the screened cohort compared to 0.90% in the control group - a reduction of almost half over 14 years.
2. Low-risk and moderate-risk cancer was found in 27.7% and 34.7%, respectively, in controls, and in 56.4% and 32.4% in the screened cohort. High-risk cancer was diagnosed in 17.5%, control; 7.3%, screened. Advanced disease (metastases or PSA >100 ng/ml) was found in 12.1% in the control group vs. 2.4%, screened.
3. "Half of the attendees who died from prostate cancer were diagnosed at their first screening visit and many of these men were 60 years of age or older at study entry." (Hugosson)

Based on data from this analysis, 234 men would need to be screened and 15 cancers diagnosed to prevent a death from prostate cancer in one man.

The PLCO and ERSPC (and its Goteborg subset) PSA screening trials have demonstrated what critics have termed "overdiagnosis" of prostate cancer and have raised concern that "overtreatment" most times follows directly thereafter. However, in the Goteborg study a total of 44% of men drawn from both cohorts chose active surveillance (40% among screened men and 30% among controls), and 28% of these men have undergone no treatment at the time of this analysis!

In an accompanying editorial in the same issue of Lancet Oncology, David Neal, Cambridge University, conjectured that the superior results in the Goteborg study compared to the PLCO and ERSPC trials might be explained by the younger median age in the Swedish study (56 years vs. 60) and that "younger men are likely to benefit more from early diagnosis than older men" (Neal); its lesser contamination; its longer follow-up; and the trial's setting "in a national context of a low baseline rate of PSA testing." (Neal) In the initial screening in the Goteborg study only 56% were low-risk, whereas in the more heavily screening US population more than 75% of men present with low-risk disease. However, in the second or additional rounds of screening in the ERSPC, there was a trend toward diagnosis of a higher proportion of low-risk cancers, at a rate similar to the more frequently screened US population.

In the NCI Cancer Bulletin, July 13, 2010, Eric Klein, Cleveland Clinic, commented that in the context of the currently heavily screened US population "it makes sense to build on the results of this trial to further refine our screening efforts to identify men at risk for potentially lethal cancers." He suggested "a baseline PSA in men in their 40s and [monitoring] subsequent PSA velocity..." to identify men whose cancers require treatment. To these measures might be added the PCA3 urine test.

BOTT0M LINE: "The weight of the [Goteborg] data clearly shows a benefit to screening." (Klein)

DIAGNOSTICS: The PCa3 Urine Test: An Update

Where did we leave off? In the Jan/Feb, 2010, PCa Commentary we concluded that PCA3 urine test was superior to the standard PSA test for indicating the need for an initial biopsy and useful in detecting cancer after an initial negative prostate biopsy. A PCA3 value of >35 is the threshold for concern. For values above this level the test has a 52-58% sensitivity and a 74-80% specificity for finding cancer on biopsy. A value >100 suggests a 69% likelihood of

underlying cancer. Another conclusion: based on current data increasing PCA3 values above 35 are insufficiently robust to allow confident distinctions about tumor grade and aggressiveness and cancer volume.
What have we learned since then?

The performance of the PCA3 test is under active research, especially in Europe. Here are some of the relevant new findings from the literature:

At the recent AUA meeting, David Crawford (University of Colorado)commented regarding results from multi-practice community-urologist based clinical trial of the PCA3 test: "...these results will help to develop a new paradigm for the detection of early prostate cancer". The PCA3 test was performed in 1994 men prior to biopsy and surgery. The men studied had a PSA above 2.5 mg/ml and/or an abnormal DRE.

Their conclusion: the PCA3 test "is more specific than PSA for prostate cancer detection." The sensitivity and specificity of the urine test was 49% and 78%, respectively, compared to the performance of the PSA, 87% and 21%, respectively. "Using a cut-off value of 35, PCA3 had an odds ratio of 3.4 for predicting prostate cancer, which is very high compared to an odds ratio of only 1.7 for PSA." In their study prostate cancer was diagnosed in 42% of men; 11% had only high-grade intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP); and in 47% the biopsy results were benign. At variance from other reported studies, the Crawford data did show a relationship between increasing PCA3 scores and higher Gleason scores and greater cancer volume. In their study the mean PCA3 value for men with cancer was 50 vs. 25 ($p<0.0001$) for those without the disease. (Abstract 2105, AUA Annual Meeting, April 2010)

The new twist is that further study of the test is showing that the presence of high-grade intraepithelial neoplasia contributes to total test score and can affect interpretation. Two studies address this point.

1. The PCA3 test ideally should allow differentiating men with prostate cancer from those with HGPIN, a condition in which the PCA3 gene is also abnormally over-expressed. A study by Morote et al., "Behavior of the PCA3 gene in the urine of men with high-grade intraepithelial neoplasia" (World J Urol 2010 Jul) compared the test in men known to have *only* HGPIN (based on two prostate biopsies negative for cancer), men with prostate cancer, and a group with BPH. The mean PCA3 score was 15.6 in BPH, 20.1 in HGPIN, and 90 in men with cancer. BPH was clearly distinguished from cancer. However, the distinction between isolated HGPIN and cancer was less clear. Conclusion: [Because HGPIN can elevate the PCA3 score] "The efficacy of the PCA3 score to rule out PCa in men with HGPIN is lower than in men with BPH."

2. An additional study that included information about HGPIN came from a Italian study, Galasso et al., Arch Ital Urol Androl, 2010 Mar, which found that among 105 men with PCA3 scores above 35, men with negative biopsies (25.7%) had a mean score of 54.9; those with HGPIN/ASAP, 79.6; and those with cancer, 141.6. Although the PCA3 values in this study are high compared to the Crawford data, they again demonstrate that HGPIN/ASAP will elevate the PCA3 score compared to the values for men with no cancer.

The PCA3 test usefully offers a high negative predictive value (NPV) for the presence of cancer - in one study >85%. The high NPV of a low PSA3 test has utility in avoiding unproductive biopsies. The PCA3 score is independent of total prostate volume and PSA (Schilling et al. Uro Int. 2010 Apr).

Schilling et al. in another article (BJUI. 2009, Vol. 105) discusses five indications for the use of the test in clinical practice. One example is particularly pertinent here and describes a 72 year old man with obstructive symptoms, a 70 gram prostate, and a PSA of 7 ng/ml. Based on his PCA3 score of 9, he would be expected to have a negative biopsy. A 21-core biopsy was indeed negative.

The *inability* of the PSA3 test to predict the tumor aggressiveness, clinical and pathological stage, cancer volume, and RP Gleason score was confirmed in a study of 351 men (Hessels et al. Prostate. 2010 Jan).

Finally, the Web calculator: "Risk of Biopsy-Detectable Prostate Cancer" based on data from the Prostate Cancer Prevention Trial - http://deb.uthscsa.edu/URORiskCalc/ - has added the option of including PCA3 test results with their basic seven parameters affording greater accuracy in the risk calculation.

BOTTOM LINE: Further research is refining the interpretation of the PCA3 urine test.

BONE METASTASES: "Prostate Specific Antigen at the Initial Diagnosis of Metastases to Bone in Patients After Radical Prostatectomy," Loeb, Walsh, et al., J Urol, July 2010.

There are abundant data indicating that a positive bone scan is rare at *initial* diagnosis of prostate cancer at PSA values of <10 ng/ml. The 2010 NCCN practice guidelines recommend a bone scan in men with T1 and T2 cancer *and* PSA >20 ng/ml, or Gleason score ≥8. (Reviewed under "Bone Metastases," PCa Commentary May/June, 2010.) Little information, however, is available regarding the PSA values in men at the time of *conversion* to a positive bone scan after primary surgery.

The Loeb analysis reports the PSA values at conversion to a positive bone scan in 193 men post prostatectomy who were followed expectantly until the PSA passed the threshold of >0.2 ng/ml. During follow-up PSA measurements and DREs were performed at 3 month intervals in the first year, then at 6 months in year 2, and yearly thereafter, or as needed for evaluation of bone pain or a PSA doubling time of <3 months.

The key findings:

1. "Metastases to bone occurred at a mean of 6 years after radical prostatectomy."
2. Bone scan conversion occurred at a prostate specific antigen of <10 ng/ml in 25.9% of men. In 50.8% of men conversion occurred in the PSA range of 10-100 ng/ml; and in 23% at PSA >100.
3. A lower PSA value at diagnosis *combined* with high-grade disease at RP was "significantly associated with lower PSA at ultimate metastases."
4. The median PSA at conversion was 31.9 ng/ml, but the range was quite wide, 0.2 - 2901.9 ng/ml, with 6 men converting at PSA values of <1 ng/ ml.

This report parallels the seminal report by Pound, Partin, and Eisenberg (JAMA 1999) which followed the same protocol and found that evidence of metastatic disease occurred in 34% of men at a mean of 8 years post surgery.

The authors felt the need to explain their avoidance of the now commonly used early adjuvant testosterone suppression. They found support for delayed intervention in the 2007 JCO report by Loblaw et al. which concluded: [in] "progressive PCa immediate versus symptom-onset institution of ADT results in a moderated decrease (17%) in relative risk (RR) for PCa-specific mortality, a moderate increase (15%) in RR for non-PCa-specific mortality, and no overall survival advantage."

Loeb argues that a delayed intervention schema avoids unwelcome side effects associated with an earlier use of androgen deprivation "provided that men are followed carefully so that metastasis to bone is detected before the development of symptoms."

BOTTOM LINE: "Because metastases may occur in men with low PSA [i.e in 25.9% with PSA <10 ng/ml], men with biochemical progression managed expectantly need regular bone scans, even if the PSA is low, to detect metastases before symptoms" (Loeb).

PSA SCREENING: Saw Palmetto and PSA

Do you know? ... Or would you guess? Does a daily dose of 320 mg of "Permixon," a standard dose of the herb saw palmetto - halve the PSA value as do finasteride and dutasteride? If you guessed "Yes," - the intuitive answer - you would be wrong.

The herbal name of this phytotherapeutic agent is serenoa repens and one respected formulation is marketed under the brand name "Permixon," although many varieties are available and their bioactivity and ingredients may vary considerably.

Caveat: A naturopath friend of mine has seen higher doses and different herbal blends lower the PSA. The following data refers to Permixon

Saw palmetto is a 5alpha-reductase inhibitor, as are finasteride and dutasteride, both of which reduce PSA levels by 50%. So ... wouldn't you expect the herb to have a similar effect on the PSA? This is a significant issue since many men are using saw palmetto to address urinary obstructive symptoms and the effect of the herb on the interpretation of a PSA value affects clinical decision making.

What data do research studies contribute to understanding the biological effects of saw palmetto?

1. A comparison of Permixon with finasteride showed that both decreased (i.e. improved reported function) the International Prostate Symptom Score by ~38% and improved peak urinary flow rate by 25% - 30%. However, whereas finasteride reduced prostate volume (-18%) and serum PSA levels (-41%), "Permixon" improved symptoms with *little effect* on prostate volume (-6%) and *no change* on PSA levels. (Carraro et al. Prostate. 1996 Oct)

2. Saw palmetto reduces intraprostatic dihydrotestosterone as measured on prostate biopsy tissue, but less so than finasteride: 5.01 ng/g to 1.05 ng/g for finasteride; 6.49 ng/g to 4.40 ng/g (32% reduction) for saw palmetto. (Marks et al. Urology. 2001 May)

3. Both saw palmetto and finasteride inhibited 5alpha-reductase Type II in an *in vitro* study. (Pais Adv Ther. 2010 Jul)
4. One randomized study of the herbal product and placebo in 44 men with symptomatic BPH found a non-significant improvement in clinical parameters for saw palmetto group. However, a possible clue as to the mechanism of action for the herb emerged from the study: "Prostate epithelial contraction was noted, especially in the transitional zone [p<0.01], where the percent of epithelium decreased from 17.8% at baseline to 10.7% after 6 months for the saw palmetto herbal blend," with atrophic glands increasing from 25.2% to 40.9%. (Marks, Partin, Epstein et al. J Urol. 2000 May)

Not all studies report a benefit of saw palmetto. In a large systematic review "serenoa repens was found not more effective than placebo for treatment of urinary systems consistent with BPH. (Tacklind et al. Cochrane Database Syst Rev. 2009 Apr)

And here is the clincher. The Prostate Research Group at the University of Edinburgh, School of Molecular and Clinical Medicine (Habib et al.Int J Cancer. 2005 Mar) found: "Serenoa repens (Permixon) inhibits the 5alpha-reductase activity of human prostate cancer cell lines *without interfering* with PSA expression." Their study found that the herb functioned as a dual 5alpha-reductase isoenzyme inhibitor [similar to dutasteride] but "*failed to interfere* with androgen receptor-mediated transcriptional activation of PSA..." The authors concluded: "Our results demonstrate that despite serenoa repens' effective inhibition of 5alpha-reductase activity in the prostate it did not suppress PSA secretion." This represents a very unique deviation from the customary relationship between 5alpha-reductase inhibitors and PSA secretion.

BOTTOM LINE: Saw palmetto, in the commercial formulation, "Permixon", does not reduce PSA values.