

## Editorial and EAU Guideline

**The PSA Era is not Over for Prostate Cancer**

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Accepted 20 July 2005

Available online 15 August 2005

**Keywords:** Prostate cancer; Screening; PSA; Detection; Threshold**1. Prostate cancer trends and screening**

In the United States (US), prostate cancer (CaP) accounts for the largest percentage of new cancer cases (33%) and is the second leading cause of cancer death (10%) in men. In 2005, there will be an estimated 232,090 new cases and 30,350 deaths from prostate cancer in our country [1]. Based upon cases diagnosed between 1992 and 1999, it is estimated that approximately 86% of these cases are local or regional at diagnosis. The incidence of distant stage disease began to decrease at a dramatic rate of 17.9% per year in 1991 in whites, and has been decreasing in other races as well. This represents a large difference in terms of treatment outcomes, considering that the 5-year survival rate is nearly 100% for local or regional disease, and only 33.5% for distant stage disease [1]. Furthermore, according to the US Surveillance, Epidemiology and End Results (SEER) program, the overall 5-year relative survival rate for CaP was 75% from 1983 to 1985, and 99% from 1995 to 2000 – the greatest improvement for any tumor [2]. It is likely that screening is at least in part responsible for the trend toward decreasing prostate cancer-specific mortality in the US. Similar results occurred when PSA testing was made freely available in Tyrol, Austria [3]. The prostate cancer mortality declined at a significantly faster rate in Tyrol than in the remainder of Austria, where screening was then not as widely used.

Despite these favorable trends, screening has continued to be the subject of heated controversy. In the

placebo group of the Prostate Cancer Prevention Trial (PCPT), prostate cancer was detected in 15.2% of men with PSA levels less than 4 ng/ml and a benign-feeling prostate gland followed for 7 years [4]. Although this is not surprising in light of autopsy data showing that more than one-third of men over age 50 have histologic evidence of prostate cancer [5], critics have used this result to support the notion that PSA screening leads to the unnecessary diagnosis and treatment of cancer that may never have become clinically apparent during the patient's lifetime. Yet it is clear that the great majority of autopsy cancers remain undetected despite serial screening, since the life-time clinical cancer detection rate is approximately 17% in the US, where screening is probably more prevalent than anywhere in the world.

Those who argue that insignificant prostate cancer is overdiagnosed fail to acknowledge that it is impossible to identify with certainty cancers that do not have the capacity to cause suffering or death during the patient's life span. With respect to prostate cancer, many experts believe that the word "latent" is a misnomer when applied to prostate cancer (David Bostwick, M.D., Personal Communication). The natural history of prostate cancer is to progress, and it is impossible to determine whether or when progression will occur during the lifetime of any given individual. Even prostate cancer found at low PSA levels can be highly aggressive [4].

**2. PSA and tumor volume**

In 2004, Stamey et al. analyzed the correlation between PSA and various pathological tumor features observed at his institution over the past 20 years [6].

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They concluded that PSA is now merely a marker for benign prostatic hyperplasia (the correlation coefficient with prostate volume was less than 0.25 throughout the entire study period) and that the “PSA era is over for prostate cancer.”

In the PCPT, as the PSA level increased in the ranges  $\leq 0.5$ , 0.6 to 1.0, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/ml, the cancer detection rate steadily increased (6.6%, 10.1%, 17.0%, 23.9%, and 26.9%, respectively). Contrary to Stamey’s assertion that PSA is no longer a marker for prostate cancer, this contemporary study demonstrated a very striking linear relationship between the PSA level and the prostate cancer detection rate with sextant biopsies.

Stamey’s analysis was based upon the finding that from 1983 to 1998 (the earliest study period), PSA correlated well with the volume of the index cancer ( $r^2 = 0.659$ ,  $p < 0.0005$ ). In the most recent study interval (1999 to 2003), using a different PSA assay, they found that the correlation, while still statistically significant ( $p < 0.045$ ), had decreased to 0.148.

Fig. 1 shows a pathology diagram of what the typical prostate cancer looked like in the pre-PSA era as compared with today. A decade ago, it was not uncommon to find a large (but likely incurable) index tumor, such as that in the upper right column of Fig. 1. If the index tumor is quite large, we would expect that the serum PSA level would correlate strongly with it, and, therefore, it is not surprising that PSA had a very robust correlation with the size of the index tumor a decade ago. On the other end of the spectrum, a single prostate cancer cell would leak very little PSA into the serum, so PSA would not be a good marker in this situation either. Fortunately, it is the intermediate range that we

are concerned with. Because tumor volume has decreased significantly across the range of clinical stages (T1–T3) [7], it is to be expected that the correlation coefficient would decrease over time. Furthermore, although PSA had a stronger correlation with the volume of the index tumor in the past era, it was not necessarily a marker for curable cancer at that time, and what use is a marker for cancer if the cancer is detected in an incurable stage?

In the bottom row of Fig. 1 are two prostate diagrams that are more representative of tumor pathology in 2005. In this example, both prostate glands contain an index tumor measuring  $2 \text{ mm}^3$ , yet clearly these two cases are not the same. Considering only the volume of the index tumor is not taking into account the multifocal nature of CaP. Alternative measurements, such as the total tumor volume or the percent of carcinoma in the radical prostatectomy specimen, may have more prognostic value in the modern era [8].

We recently reported on the correlation of PSA with prostate size and cancer volume in 2044 patients treated with radical prostatectomy [9]. Fig. 2 shows the results of this analysis. In the smallest prostate glands ( $< 40 \text{ cc}$ ), PSA correlated with cancer volume but not with prostate size. In the medium-sized prostate glands (40 to 55 cc), PSA also correlated only with cancer volume. In both cases, the correlation between PSA and cancer volume was stronger with cancer volumes greater than 3 cc. Finally, in men with a prostate gland larger than 55 cc, PSA correlated only with prostate size when the cancer volume was smaller than 3 cc; whereas, it correlated with both prostate size and cancer volume when the tumor volume was larger than 3 cc. Thus, in only 11% of the 2044 patients did

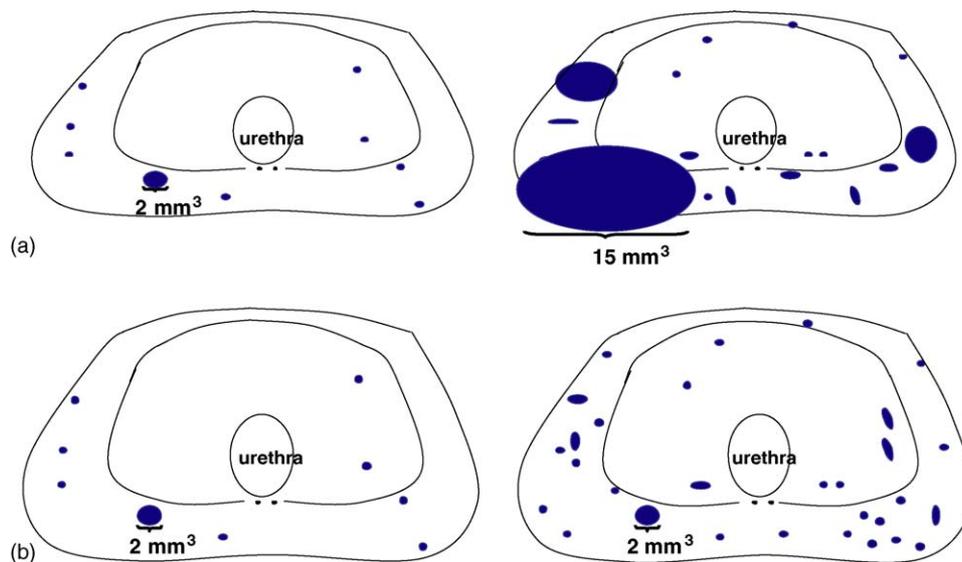


Fig. 1. Typical pathology diagrams of prostates with cancers in (a) 1991, compared with (b) 2005.

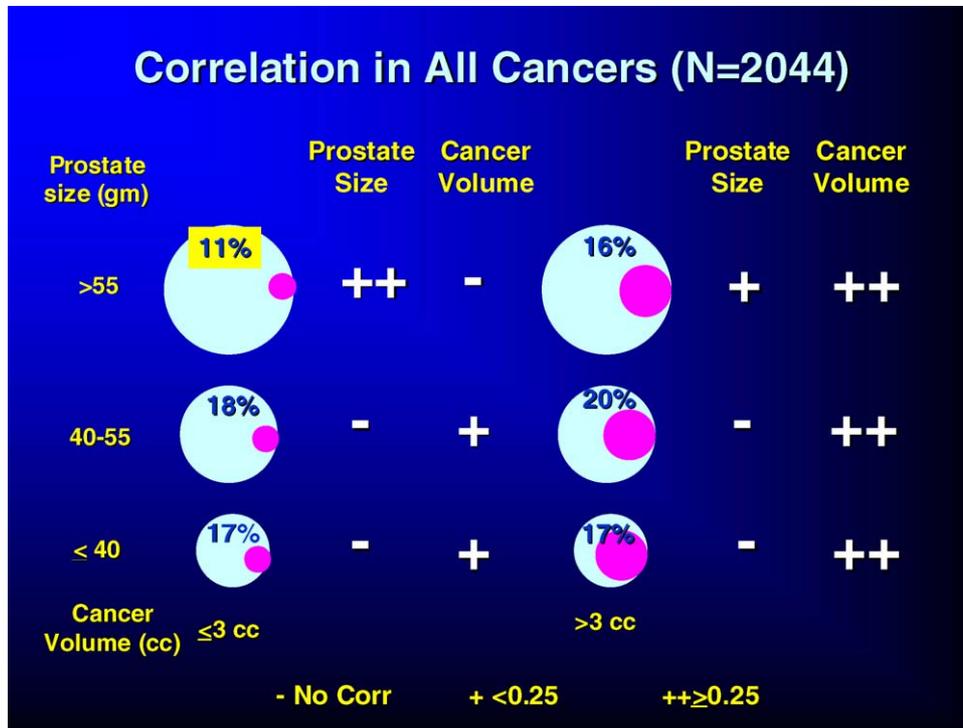


Fig. 2. Correlation of serum PSA with prostate size and cancer volume in 2044 patients with clinically localized prostate cancer treated with radical prostatectomy. The left column shows the correlations for small tumors ( $\leq 3$  cc), and the right column shows the correlation for larger tumors ( $> 3$  cc). “-” indicates no significant correlation; “+” indicates  $R$  (Spearman)  $< 0.25$ ; “++” indicates  $R$  (Spearman)  $\geq 0.25$ .

PSA correlate exclusively with prostate volume. Even for these individuals, however, PSA is far from useless. It merely requires that prostate volume be factored into the equation, such as through the calculation of PSA density. In our analysis, PSA density significantly correlated with prostate cancer volume, regardless of the size of the prostate gland. Thus, our studies suggest that in evaluating a man with a PSA level in the diagnostic gray zone (2 ng/ml to 10 ng/ml) and a prostate gland larger than 55 cc, the PSA density should be calculated, and a biopsy should be performed if the PSA density is 0.1 ng/ml/cc or higher [10]. This should avoid performing a biopsy in a man whose PSA is elevated solely because of BPH. In the future, other PSA isoforms, such as B-PSA and pro-PSA may provide further discrimination [11,12].

PSA velocity measurements are also helpful, as clinically significant prostate cancer is more likely to be found in men with a rapidly rising PSA. Recent studies suggest that for men with a total PSA higher than 4 ng/ml, a PSA velocity of 0.75 ng/ml/year is an indication for biopsy. However, in men whose total PSA level is lower than 4 ng/ml, a lower PSA velocity cutoff should be used, in the range of 0.1 to 0.5 ng/ml/year [13,14]. More clinical research is needed to evaluate PSA velocity cutoffs for men with low PSA levels.

### 3. PSA and outcomes

Undoubtedly, the prediction of adverse pathologic features (such as a large tumor volume) is valuable both for surgical planning and to give men considering definitive therapy a realistic expectation of their hope for cure. Nevertheless, pathological tumor features are considered an intermediate outcome; whereas, biochemical progression and cancer-specific survival represent more definitive, clinically relevant endpoints [15]. PSA has not lost its ability to predict these outcomes over the past 2 decades. Our research group and others have data confirming that this is not the case.

Kikuchi et al. examined a series of 1302 radical prostatectomies performed for clinical stage T1c to T3 CaP, and found a weak overall correlation between PSA and tumor volume. Nonetheless, PSA was found to be an independent predictor of cancer progression on multivariate analysis, whereas tumor volume was not [7].

Mitchell et al. reported on 1330 radical prostatectomies performed at Columbia University from 1988 to 2003, to determine whether PSA has lost its power to predict biochemical failure over the past 15 years [16]. Their study re-confirmed that the triad of preoperative PSA, stage and grade continues to be the best predictor of biochemical outcomes in the current era, and that the

ability of PSA itself to predict biochemical progression has not decreased when controlling for these confounding variables.

Moreover, our group published a study demonstrating that preoperative PSA velocity predicts the risk of cancer-specific death following radical prostatectomy [17]. Of course, only by continuing to measure serial PSA levels can we accurately calculate the PSA velocity. Certainly the ability to identify men with potentially lethal prostate cancer is more important than the ability to predict the volume of the index tumor.

Media headlines suggesting that “PSA is useless” or that “PSA is no longer a marker for prostate cancer” have potentially dangerous consequences. Such media misinterpretation and the resultant confusion has undoubtedly caused numerous men to stop having their PSA measured to their possible considerable detriment.

#### 4. The quality of a screening test

Before discarding PSA or DRE as screening tools, it is important to consider the factors that make a screening test useful. It must be easy to apply in clinical practice, which the PSA test and DRE certainly are. It must detect disease at an earlier stage, but not “overdiagnose” a substantial proportion of cancers that may never have caused clinical manifestations during the patient’s lifetime. The estimates of prostate cancer “overdiagnosis” (30% to 50%) have been exaggerated in the literature [18]. This may be due in part by the fact that much of the data have been derived from older men, in whom overdiagnosis is a greater concern because of their limited life expectancy. In younger men, who are most likely to benefit from early diagnosis and treatment, the criteria for calling overdiagnosis are much less frequently met (~15%) [19]. Even then, it is impossible to say with certainty that any prostate cancer diagnosed in a young man has been overdiagnosed.

To determine whether PSA- and DRE- based screening results in the detection of too many “harmless” cancers, we recently examined the features of all cancers detected for the duration our screening study (Loeb et al., in press). We found that only 93 of 1410 (6.6%) would be considered unimportant based upon the definition of Ohori et al. [20] (less than or equal to 0.5 cm<sup>3</sup>, confined to the prostate, no primary or secondary Gleason pattern 4 or 5), and even fewer (6 of 1410, 0.4%) meet the criteria for insignificant by Epstein et al. [21] (less than 0.2 cm<sup>3</sup>, confined to the prostate, Gleason sum less than 7). In addition, to determine whether the morphology of screen-detected

cancer has changed over time, we divided the study period into three distinct time intervals. Fewer than 10% of tumors met either criterion at any time during the 12 year study interval.

However, we must also consider the other extreme: screening will not improve outcomes if the cancers detected are either already incurable or if the available treatment options are ineffective. With prostate cancer this is not the case. The Scandinavian Prostate Cancer Group Study recently reported on 347 men with early, albeit not screen-detected, prostate cancer randomized to radical prostatectomy, compared to 348 men randomized to watchful waiting [22]. The risk of overall mortality, cancer-specific mortality, distant metastasis, and local progression were all significantly reduced in the radical prostatectomy group at 10 years follow-up. Thus, for those patients and physicians considering surgical management for prostate cancer, this randomized data provides strong evidence screening could help reduce prostate cancer mortality rates by providing a consistent means to detect cancers at a sufficiently early stage. Once prostate cancer has progressed to an advanced stage, however, there are fewer treatment alternatives for the patient.

#### 5. Conclusion

PSA has recently been criticized as “useless” for prostate cancer detection. On the contrary, we believe that PSA continues to be the best biomarker available for early prostate cancer detection. Although PSA does indeed correlate less with the volume of the index tumor than in the bygone era of large palpable advanced cancers, PSA continues to predict even more important outcomes following definitive therapy. Furthermore, there are several variations of PSA testing, such as PSA density, PSA velocity, and the free-to-total or complexed-to-total PSA ratio, that could not be calculated if screening programs were to abandon the PSA measurement altogether. It is likely that in the future new biomarkers will be discovered with an even greater ability to differentiate aggressive disease, but until such a time, the PSA era is not over for prostate cancer.

Based on the currently available data, we believe that PSA screening should begin at age 40 when the PSA level should be well below 1 ng/ml and PSA testing should be repeated annually. Biopsy should be considered if the PSA is rising and does not return to baseline levels with antibiotic therapy or repeat measurements. PSA should be used intelligently, incorporating PSA derivatives such as PSA velocity, PSA

density, percentage of free or percentage of complexed PSA, and, perhaps in the future, B-PSA and pro-PSA, in addition to the total PSA value. Biopsy should be recommended if the PSA velocity exceeds 0.2 to 0.5 ng/ml/year in men with a total PSA level less than 2.5 ng/ml/year (more data is needed to determine optimal PSA velocity cutoffs, and perhaps a percentage change in the range of 20% per year will prove useful), or if the PSA velocity is greater than 0.75 ng/ml/year and the total PSA is above 4 ng/ml. Biopsy also should be considered if the total PSA is higher than 2.5 ng/ml

and the PSA density is greater than 0.1 ng/ml/year or if the percentage of free PSA is less than 10%. These measures should help identify life-threatening prostate cancers at a stage when they can be cured.

## Acknowledgements

Dr. Catalona's research is supported in part by Beckman Coulter Incorporated, a manufacturer of PSA tests.

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