Prostate Specific Antigen Isoforms and Human Glandular Kallikrein 2—Which Offers the Best Screening Performance in a Predominantly Black Population?

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Purpose: Free prostate specific antigen, complexed PSA and human glandular kallikrein 2 have independently been tested against the gold standard of total PSA for prostate cancer screening in largely white populations. With the incidence of prostate cancer much higher in black men, we sought to evaluate these markers simultaneously in a predominantly black population.

Materials and Methods: A total of 138 men, of whom 108 were black, underwent ultrasound guided biopsy of the prostate for tPSA levels greater than 2.5 ng/ml or an abnormal digital rectal examination. Sera were drawn before biopsy and analyzed for tPSA, fPSA, cPSA and hK2 concentrations using standard methods (hK2 assay is for research use only, not for use in diagnostic procedures). The areas under the receiver operator characteristic curves were determined for each marker as well as biomarker combinations. Additionally, each parameter's specificity, positive and negative predictive values, and theoretical screening efficiency were assessed at or above the 95% sensitivity level.

Results: A total of 43 (31.1%) men had prostate cancer by biopsy. While the AUC for %fPSA was statistically the highest (0.822, $p < 0.001$), cPSA offered the highest specificity (31.6%) and positive predictive power (31.7%) of any of the tested biomarkers at comparable sensitivity (greater than 95%). The calculated efficiency of cPSA (51.4%) was also higher than the other markers. Nearly 20% of biopsies would be avoided using cPSA vs standard tPSA screening methods.

Conclusions: Comparing the major PSA isoforms and hK2, cPSA alone appears to offer superior diagnostic discrimination for cancer detection in a predominantly black population.

Key Words: prostate-specific antigen, prostatic neoplasms, African Americans, mass screening

In 2005 an expected 232,090 new cases of prostate cancer will be diagnosed in the United States, and 30,350 men will die due to their disease. Black males have a 54% higher incidence of prostate cancer than white males, but a disproportionate 140% higher mortality rate.[1] Catalona et al,[2] showed that screening in a high risk population such as this detects clinically relevant tumors with a greater chance of being organ confined. Whether this translates to decreased mortality in the future remains to be seen.

To date mass screening efforts have been based on tPSA concentrations and DRE. However, other serum markers have shown some promise in improving screening specificity, such that fewer men may undergo invasive testing without sacrificing cancer detection. The tPSA subfractions, fPSA and cPSA, and hK2 have been evaluated in white men for this purpose, but not independently verified in the particularly at risk black population. Therefore, we examined the screening performance of alternatives to tPSA, namely the isoforms fPSA and cPSA and hK2, and calculated combinations of these markers in a population largely comprised of black males.

MATERIALS AND METHODS

From September 1998 to April 2002 all men appearing for a free prostate cancer screening at the Louisiana State University Health Sciences Center in New Orleans, Louisiana, were prospectively enrolled in this institutional review board approved study. Screening consisted of a serum blood draw followed by a DRE performed by a board certified urologist. All sera were immediately aliquoted and frozen at −80C. For the initial screening, tPSA levels were determined by the Beckman Coulter's Access® immunoanalyzer technique. Those men having tPSA levels greater than 2.5 ng/ml or an abnormal DRE were invited to have a transrectal ultrasound guided biopsy of the prostate. Only the patients who had received biopsy were included in this study. For these patients, serum concentrations of tPSA and cPSA

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TABLE 1. *Median values in cancer versus noncancer groups for all biomarkers*

	Biopsy Result		
	Neg 95	Pos 43	p Value
tPSA, (ng/ml)	4.2	5.0	0.012
cPSA, (ng/ml)	2.86	3.82	0.0003
%fPSA	16.40	8.90	<0.0001
hK2, (ng/ml)	0.053	0.067	0.006
hK2/fPSA	0.072	0.138	<0.0001
hK2*cPSA	0.135	0.364	<0.0001
hK2*cPSA/fPSA	0.224	0.602	<0.0001

were determined by Bayer Immuno1™ methods, while tPSA, fPSA and hK2 levels were measured by Beckman Coulter's Access® immunoanalyzer. For calculation of the %fPSA, the Beckman Coulter tPSA was used; otherwise, Bayer tPSA values were used. However, there was good agreement between the 2 tPSA tests (data not shown).

The individual values of tPSA, cPSA, and hK2 as well as the calculated ratios of %fPSA, hK2/fPSA, hK2*cPSA, and hK2*cPSA/fPSA, were compared between cancer and noncancer groups and between black and white groups using SAS JMP statistical software. The Wilcoxon 1-way test, assuming a chi-square approximation, compared sample medians. Statistical significance was assumed at p values less than 0.05. For each biomarker parameter, ROC and AUC were generated using Analyze-It v1.5 software. From these curves, threshold values for each parameter were chosen sufficient to yield 95% sensitivity or better. The corresponding specificity, positive and negative predictive values were then calculated. Additionally, the screening efficiency of each test was determined using the formula (true positives plus true negatives) divided by the number of patients screened (ie the percentage of patients correctly classified by the screening test). This efficiency indirectly depends on the prevalence of the disease in question; we conservatively assumed a 25% cancer rate in this population with mildly increased tPSA values, based on previously published observations.

RESULTS

A total of 138 men who met the criteria for biopsy were identified through the Louisiana State University Health Sciences Center free prostate screening program from September 1998 to April 2002. Of these men 108 self-reported race as black, 24 as white, 5 as Hispanic and 1 patient claimed "other" as race. A total of 43 of the 138 men were histologically confirmed to have cancer, for a cancer detection rate of 31.2%.

Average age of men in the cancer group was not significantly different from the noncancer group (61.1 vs 59.2 years, p = 0.21). Table 1 displays median values of the biomarkers for the cancer and noncancer groups. For all parameters tested, there was a statistically significant difference between the 2 groups. Comparing black men without cancer to white men without cancer, only the ratio of hK2: fPSA showed a significant difference (p = 0.033), otherwise, there were no differences (data not shown). However, no differences were found with any biomarker between the races in those diagnosed with cancer (data not shown).

ROC curves for each of the biomarkers were plotted. Table 2 relates the AUCs for each parameter generated from the ROC curves. %fPSA had the highest AUC at 0.822, but this was not significantly different than the AUCs for the ratios hK2*cPSA/fPSA (0.795) or hK2*cPSA (0.708).

Table 2 also displays the screening performance of each biomarker when an appropriate cutoff was chosen to yield 95% sensitivity or higher. Traditional cutoff values for tPSA (4.0 ng/ml) and for %fPSA (25%) are shown as well. While %fPSA had the greatest sensitivity, it also had the least specificity (8.4%). The highest specificity and positive predictive value as a screening test belonged to cPSA (31.6% and 31.7%, respectively), while still maintaining an excellent negative predictive value (95.3%). The inclusive measure of screening efficiency suggested that only cPSA offered an efficiency greater than 50% while keeping sensitivity high.

Irrespective of DRE results, 119 of our 138 patients would have had biopsy performed using a tPSA threshold of 2.5 ng/ml, with only 1 cancer being missed. With cPSA, only 112 biopsies were indicated (saving 19% of unnecessary biopsies), with 2 confirmed cancers being missed, but 1 additional case being discovered compared to tPSA. Using a %fPSA cutoff of 25% would not have missed any cancers, but 131 biopsies would have been performed (5% fewer biopsies). Of the other biomarkers tested, only the combined values of hK2*cPSA and hK2*cPSA/fPSA offered savings of unnecessary biopsies (16% and 18%, respectively). A total of 19 men had prostatic biopsy performed solely due to the presence of an abnormal DRE, with tPSA less than 2.5 ng/ml. Only 1 was found to have cancer, and this patient would have had a biopsy using a cPSA threshold of 2.3 ng/ml. Therefore, if only serum markers were considered and not the DRE, 6% fewer biopsies would result with cPSA vs tPSA, with either method missing 1 of 43 tumors. %fPSA would have detected all cases of cancer, but would have required 10% more biopsies.

TABLE 2. *Results of biomarker screening performance for the entire patient population*

	tPSA	tPSA	%fPSA	cPSA	hK2	hK2/fPSA	hK2*cPSA	hK2*cPSA/fPSA
AUC	0.634	0.634	0.822	0.694	0.646	0.679	0.708	0.795
Cutoff	2.5	4.0	25	2.3	0.024	0.03	0.06	0.1
Sensitivity (%)	97.7	72.1	100	95.3	97.7	95.3	95.3	95.3
Specificity (%)	18.9	46.3	8.4	31.6	20.7	16.8	21.1	24.2
PPV (%)	28.7	30.9	26.7	31.7	28.9	27.7	28.7	29.5
NPV (%)	96.1	83.3	100	95.3	96.3	91.6	93.1	94.0
Efficiency (%)	43.5	54.3	37	51.4	44.2	41.3	44.2	46.4