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SERIAL PERCENT-FREE PSA IN COMBINATION WITH PSA FOR POPULATION-BASED EARLY DETECTION OF PROSTATE CANCER

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Abstract

PURPOSE—To characterize the diagnostic properties of serial percent-free prostate-specific antigen (PSA) in relation to PSA in a multi-ethnic, multi-racial cohort of healthy men.

MATERIALS AND METHODS—6,982 percent-free PSA and PSA measures were obtained from participants in a 12 year+ Texas screening study comprising 1625 men who never underwent biopsy, 497 who underwent one or more biopsies negative for prostate cancer, and 61 diagnosed with prostate cancer. Area underneath the receiver-operating-characteristic-curve (AUC) for percent-free PSA, and the proportion of patients with fluctuating values across multiple visits were determined according to two thresholds (under 15% versus 25%) were evaluated. The proportion of cancer cases where percent-free PSA indicated a positive test before PSA > 4 ng/mL did and the number of negative biopsies that would have been spared by percent-free PSA testing negative were computed.

RESULTS—Percent-free PSA fluctuated around its threshold of < 25% (< 15%) in 38.3% (78.1%), 42.2% (20.9%), and 11.4% (25.7%) of patients never biopsied, with negative and positive biopsies, respectively. At the same thresholds, percent-free PSA tested positive earlier than PSA in 71.4% (34.2%) of cancer cases, and among men with multiple negative biopsies and a PSA > 4 ng/mL, percent-free PSA would have tested negative in 31.6% (65.8%) instances.

CONCLUSIONS—Percent-free PSA should accompany PSA testing in order to potentially spare unnecessary biopsies or detect cancer earlier. When near the threshold, both tests should be repeated due to commonly observed fluctuation.

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Keywords

percent-free prostate-specific antigen; biopsy; prostate cancer; fluctuation

INTRODUCTION

Prostate cancer causes almost 30,000 deaths annually in the United States, but prostate-specific antigen (PSA) screening programs suffer from too many unnecessary tests and biopsies, inflating costs and increasing patient burden. In 2012, the United States Preventive Services Task Force (USPSTF) recommended against annual serum PSA testing for most men, instead suggesting alternative public health approaches for reducing mortality from the disease.¹ This guidance prompted recommendations for alternative screening strategies, ranging from a single PSA measurement at an early age, selective repeat PSA testing following an abnormal test to identify spurious elevated PSA levels, as well as incorporation of additional markers or subsequent reflex tests.^{2–7}

Percent-free PSA is a biomarker that has shown promise as an adjunct test to PSA for prostate cancer detection. Percent-free PSA has proven to be as or more accurate than PSA for the early detection of prostate cancer, with a threshold of less than 25% as suggestive of cancer that could be used concurrent to PSA testing or selectively for equivocal PSA values between 2 and 10 ng/mL.^{6–10} Confirmation of independent predictive value of percent-free PSA to PSA as well as to established risk factors for prostate cancer, including digital rectal exam (DRE), race, age, family and prior biopsy history, has led to its inclusion in prostate cancer risk prediction tools, including the Prostate Cancer Prevention Trial Risk Calculator.¹¹

An Achilles' heel of cancer biomarkers can be test variability over time. Studies investigating annual PSA measurements have observed a remarkable pattern of reversion of abnormal tests one year to normal test values a year later. In one retrospective analysis of serum PSA levels taken annually over a four-year period among men participating in the Polyp Prevention Trial, among 154 men with an abnormal PSA test > 4 ng/mL, 44% had a normal PSA finding one or more years later, leading the authors to conclude that an isolated elevated PSA level should be subsequently confirmed before proceeding with further diagnostic work-up, sparing unnecessary biopsies.¹² Significant annual PSA fluctuation was confirmed in a larger cohort of 2,578 participants in a San Antonio prostate cancer screening study, with 23% of abnormal PSA tests returning to normal one year later. For comparison, 70% of abnormal DRE tests reverted to normal exams one year later in the same study.¹³

Because the San Antonio Biomarkers Of Risk (SABOR) cohort provides 10+ years of annual follow-up with serum screens and PSA-prompted biopsies, it permits separate analysis of fluctuation depending on the long-term outcome of men on study. The vast majority concerns men in whom biopsy was never clinically indicated, men such as these could be spared relief from the anxiety surrounding a single elevated level. Another group comprises men who had undergone one or more negative biopsies over the long-term, who likely suffer from benign disease. Such men could be spared the morbidity and anxiety of unnecessary procedures. Finally, among those men ultimately diagnosed with cancer on

biopsy, constancy of elevated pre-diagnostic measures permits potential earlier confirmative diagnosis and a moving forward to treatment. Motivated by these aims for the different patient populations, percent-free PSA testing was initiated in the San Antonio cohort in order that its cross-sectional and serial operating characteristics be prospectively evaluated.

MATERIALS AND METHODS

SABOR was initiated in 2000 as a NCI sponsored clinical validation center recruiting San Antonio and South Texas area men without a prior diagnosis of prostate cancer, and now comprises more than 4,000 participants. The study was approved by the Internal Review Board of the UT Health Science Center at San Antonio, and all men provided written informed consent upon entry, whereupon extensive demographic and medical data were documented. From 2000 to 2010, participants were seen annually for PSA and DRE, which was thereafter reduced to biannually in men with lower risk based on their PSA levels. Prostate biopsy was recommended for men with PSA > 2.5 ng/mL or an abnormal DRE during the annual visits up through 2010. Beginning in 2007, percent-free PSA was included in annual testing.

Participants with at least one paired percent-free PSA and PSA value collected at the same clinical visit while the patient was on study (and before biopsy if one was performed) were included in this analysis. These participants were stratified into one of three groups: (1) those who never underwent biopsy, (2) those who had one or more negative biopsies, and (3) those diagnosed with prostate cancer on biopsy. Baseline characteristics of the three groups were compared using chi-square and Kruskal-Wallis tests for categorical and continuous measures, respectively. The coefficient of variation (CV) was calculated as the percent ratio of the standard deviation to the mean.

A variety of thresholds for a biomarker can be used to indicate a positive abnormal test, with the operating characteristics, in particular the trade-off between sensitivity and specificity, strongly linked to the choice. We were concerned with evaluation of the thresholds currently used in practice, and so chose < 25% as an indicator for an abnormal percent-free PSA and > 4 ng/mL for an abnormal PSA test by Eastham et al.⁴ However, since clinical experience with percent-free PSA is much less than that of PSA and we observed high false positive rates with the < 25% threshold, we additionally considered a more conservative threshold of 15% for comparison. We tested whether the degree of fluctuation was greater for percent-free PSA than PSA using McNemar's test for correlated categorical measures. For the group of men with one or more negative biopsies over the course of study, using the last observations of percent-free PSA and PSA, we computed the number of cases for which percent-free PSA would have spared a biopsy by testing negative in the presence of a positive PSA test, as well as the number of instances of cancer that would have been detected by percent-free PSA but not PSA.

RESULTS

Patient demographic and clinical summaries

A total of 6,982 serial percent-free PSA and PSA measures were obtained from 1625 men who never underwent biopsy during the study, 497 men who underwent one or more biopsies that proved negative for cancer, and 61 men subsequently found to have prostate cancer on biopsy. Several characteristics differed among the three participant groups, including age, ethnicity, family history, PSA, percent-free PSA, abnormal DRE, and velocity of PSA (all $p < 0.001$, Table 1). Percent-free PSA was lower among cancer cases, and percent-free PSA decreased more rapidly over time in cancer cases compared to the other groups ($p < 0.001$ and $= 0.01$, respectively). Cancer cases had fewer measurements (or annual visits) as, at the diagnosis of prostate cancer, they were no longer undergoing cohort follow-up.

Among participants with two or more measures, the coefficient of variation (ratio of standard deviation to mean) of percent free PSA was 20.2%, 19.0%, and 9.2% among participants in the never biopsy, negative biopsy and cancer groups, respectively.

Fluctuation of serial percent-free PSA measures

Among the 1210 men with two or more percent-free PSA measures and who were never referred to biopsy during the SABOR study, with a percent-free PSA threshold of $< 25\%$ as a positive test, 38.3% fluctuated below the threshold at least once, 40.1% remained above the threshold, and 21.5% tested abnormal on every visit. Using instead a threshold of $< 15\%$ as a positive test, these percentages became 78.1%, 3.3% and 18.6%, respectively. For comparison, when considering PSA exceeding 4 ng/mL as a positive test, only 7.3% ($n = 88$) of the patients experienced fluctuation (Table 2).

Among 417 men with one or more negative biopsies, the fraction with a percent-free PSA that fluctuated below the threshold of 25% at least once increased to 42.2% (Table 2), but for a percent-free PSA threshold of 15%, remained similar to that for PSA (20.9% versus 21.8%, respectively).

Among the 35 men diagnosed with cancer who also had two or more measures available, the fluctuation of percent-free PSA around thresholds of 25% and 15% were lower (11.4% and 25.7% of participants, respectively) compared to PSA (45.7%, Table 2). In this group of cancer patients, multiple measures of percent-free PSA were consistently below the thresholds of 25% and 15%, suggesting a diagnosis of cancer, in 77.1% and 31.4% of the cases, respectively, compared to only 20.0% of cases with consistent elevation of PSA > 4 ng/mL.

Which detects cancer first, percent-free PSA versus PSA?

Figure 1 shows the annual pre-diagnostic serial percent-free PSA and PSA values in the 35 patients diagnosed with prostate cancer during the cohort follow-up. The figure provides a graphical display of the timing of when the marker converted to 'positive'. Among these 35 patients, and using the threshold 25% for a positive percent-free PSA test, percent-free PSA

detected cancer earlier in 25 (71.4%) cases, PSA detected earlier in 4 (11.4%) of cases, and the two markers tied in the remaining 6 (17.1%) patients. Using instead the threshold 15% for a positive percent-free PSA test, percent-free PSA detected cancer earlier in 12 (34.2%) cases, PSA detected earlier in 9 (25.7%) of cases, and the two markers tied in the remaining 14 (40%) patients.

Would percent-free PSA have prevented a negative biopsy prompted by PSA?

Among the 417 men who had one or more biopsies performed during the study that proved to be negative, we considered their last available pair of percent-free PSA and PSA measures, and evaluated the proportion of biopsies that might be spared if the percent-free PSA test served as a reflex test to PSA. For the 79 men who had a PSA ≥ 4 ng/mL, 25 (31.6%) and 52 (65.8%) would test negative by the percent-free PSA test by exceeding the thresholds 25% and 15%, respectively. These numbers increase to 58 (45.7%) and 110 (86.6%), respectively, among the 127 men with PSA between 2 and 4 ng/mL, and to 142 (67.3%) and 195 (92.4%), respectively among the 211 men with PSA < 2 ng/mL.

Would percent-free PSA have caught a cancer missed by PSA?

Among the 41 cancer cases that had a PSA < 4 ng/mL, 35 (85.4%) had a percent-free PSA $< 25\%$, while 18 (43.9%) had a percent-free PSA $< 15\%$.

DISCUSSION

The status of early detection for prostate cancer is at a major crossroads at this time. In 2012, the USPSTF recommended against PSA testing and subsequently, PSA testing has fallen in the U.S. along with what appears to be a fall in incidence of prostate cancer.^{14–16} Perhaps most telltale is the initiative by the Center for Medicare and Medicaid Services (CMS) to penalize physician reimbursement if a PSA test is obtained.¹⁷ These actions and population trends have been an outgrowth of the dramatic increase in prostate cancer screening, prostate biopsy, and the historical resulting treatment with radiation or surgery for about 90% of cases, regardless of tumor risk.¹⁸

With the pendulum accelerating from its prior position to a position where PSA testing is forbidden, some experts are predicting dire consequences for the aging U.S. population and a return to prostate cancer mortality rates of the 1980's. Should this occur, the oncology community must be prepared to detect this change, acknowledge the error, and then re-adopt early detection in a manner that achieves a mortality reduction while mitigating the challenges of disease overdetected.

We have previously posited that an alternative approach to PSA testing with a single threshold-for-biopsy (e.g., > 4.0 ng/mL) would be to risk-stratify individuals based on PSA and other factors including age, family history, digital rectal examination findings, race, and history of prior biopsy.¹⁹ The goal of this approach would be to not only estimate a man's *prior probability* of cancer but to also his risk of high grade cancer, the tumor most likely to benefit from early detection.²⁰

It must also be acknowledged that using only a PSA-based approach in at-risk men will not maximally reduce prostate cancer morbidity and mortality. For example, even with annual PSA testing in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), using regionally-accepted PSA thresholds, 3.7 per 10,000 screened men died of prostate cancer in PLCO after 13 years of follow-up.²¹ Even in men whose PSA's were collectively < 3.0 at study entry and who underwent annual PSA testing in the PCPT, 304 of 1319 (23.0%) men diagnosed with prostate cancer in the placebo arm died of prostate cancer within 15 years.²² Thus, the successor to the national experiment in PSA testing in which only men with a PSA > 4.0 ng/mL underwent biopsy would be a two-pronged effort: (1) in men with a PSA > 4.0 ng/mL, decision tools would be employed to reduce biopsies among men who would be at a low risk of high-grade cancer, and (2) in men with a PSA ≤ 4.0 ng/mL, strategies would be developed to, with very high specificity, identify men harboring high-grade cancer.

While percent-free PSA have been associated with demographic characteristics, such as age, race/ethnicity, and body mass, most of the previous studies of within-subject variability of free PSA have examined small numbers subjects over short time periods.²³ In 2011 Christensson et al. evaluated 149 men suspected of having prostate cancer with multiple measurements over a two-week period, observing a CV for percent-free PSA of 6.0%, smaller than the 20% observed over the approximately annual intervals in this study, which include the further element of time drift.²⁴ Earlier studies in the late 1990s that investigated intervals up to one month between measurements reported higher CVs ranging from 10 to 15%, and up to 32% among cancer and symptomatic patients.^{25, 26, 27, 28} These studies reported no dependence on patient factors, such as PSA and age, though are underpowered for an endpoint of variability. As previously observed for PSA, unexplainable short- and long-term variability remains a point of consideration as percent-free PSA becomes increasingly used as an adjunct to PSA.

CONCLUSIONS

The observations in this manuscript provide important insight into this comprehensive strategy. First, percent-free PSA as a stand-alone biomarker has a very high false-positive rate and cannot substitute for PSA. Second, percent-free PSA as a reflex marker in the setting of PSA testing has demonstrated quite high levels of performance in this study, with the capability to spare 65.8% of unnecessary biopsies, which compares very well with other candidate reflex biomarkers that incur far greater cost. A fascinating observation, allowed only by the availability of serial PSA and percent-free PSA values, was that in men who ultimately were found to have prostate cancer, percent-free PSA provided the first evidence of suspicion 34.2% of the time, suggesting that in the search for high-grade cancers, percent-free PSA may significantly improve screening sensitivity. Finally, the results have shown that percent-free PSA fluctuates above and below thresholds in the 15% to 25% range, commonly used for referral to biopsy, in a substantial number of patients, particularly among the group of men never diagnosed with prostate cancer. As such, in the presence of a normal PSA test, strong consideration should be given to repeating a percent-free test to ensure that a spurious value is not prompting an unnecessary prostate biopsy.

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ABBREVIATIONS

CV	Coefficient of variation
DRE	Digital rectal exam
PSA	Prostate-specific antigen
SABOR	San Antonio Biomarkers of Risk of Prostate Cancer Study

Figure 1.

Serial PSA (orange) and percent-free PSA (blue) measurements for 35 patients diagnosed with prostate cancer following their last measurement visit; + denotes a positive test with percent-free PSA < 25% and PSA > 4 ng/mL and – a negative test with values outside the test positive values.

Table 1

Participant characteristics.

	No biopsy N = 1625	Negative biopsy N = 497	Prostate cancer N = 61	P-value
Age at entry				< 0.001
Median [Min, Max]	61.7 [45.1, 84.7]	67.9 [45.5, 84.9]	65.5 [53.8, 78.6]	
Race, N participants (%)				0.23
White	1443 (88.8)	445 (89.5)	49 (80.3)	
Black	179 (11)	52 (10.5)	12 (19.7)	
Other	3 (0.2)	0 (0)	0 (0)	
Ethnicity, N participants (%)				< 0.001
Non-Hispanic	1017 (62.6)	361 (72.6)	51 (83.6)	
Hispanic Mexican	570 (35.1)	125 (25.2)	9 (14.8)	
Hispanic Other	38 (2.3)	11 (2.2)	1 (1.6)	
Family History, N participants (%)				< 0.001
No	1325 (81.5)	351 (70.6)	38 (62.3)	
Yes	300 (18.5)	146 (29.4)	23 (37.7)	
Number of PSA and percent-free PSA values, N participants (%)				< 0.001
1	415 (25.5)	80 (16.1)	26 (42.6)	
2	292 (18)	84 (16.9)	13 (21.3)	
3	188 (11.6)	68 (13.7)	13 (21.3)	
4	295 (18.2)	77 (15.5)	3 (4.9)	
5	291 (17.9)	106 (21.3)	6 (9.8)	
6	144 (8.9)	82 (16.5)	0 (0)	
Average PSA ng/ml				< 0.001
Median [Min, Max]	1 [0.1, 10.9]	1.9 [0.1, 11]	3.7 [1.1, 8.8]	
Average percent-free PSA				< 0.001
Median [Min, Max]	26.5 [4.3, 100]	24.9 [4.9, 90]	15.7 [3.6, 37]	
DRE, N (%)				< 0.001
All normal	1476 (92.8)	328 (66.9)	42 (70)	
Ever abnormal	115 (7.2)	162 (33.1)	18 (30)	
Prior biopsy, N (%)				< 0.001
0	1625 (100)	1 (0.2)	36 (59)	
1	0 (0)	335 (67.4)	12 (19.7)	
2	0 (0)	161 (32.4)	13 (21.3)	
Velocity PSA ng/ml				< 0.001 *
Median [Min, Max]	0.004 [-0.7, 0.3]	0.004 [-0.2, 0.9]	0.042 [-0.1, 0.3]	

	No biopsy N = 1625	Negative biopsy N = 497	Prostate cancer N = 61	P-value
Velocity percent-free PSA				0.01 [*]
Median [Min, Max]	0 [-5.7, 4.8]	0.015 [-3.6, 6.4]	-0.045 [-0.4, 0.6]	

^{*} Computed for men with two or more measures: N never biopsy no biopsy: 1210, N negative biopsy: 417, N cancer: 35

Table 2

Characteristics of serial measures for percent-free PSA and PSA for men with two or ore measures.

	No biopsy N = 1210	Negative biopsy N = 417	Prostate cancer N = 35
Percent-free PSA, N (%)			
All greater than or equal to 25%	486 (40.2)	127 (30.5)	4 (11.4)
All less than 25%	260 (21.5)	114 (27.3)	27 (77.1)
Fluctuating with at least one of each	464 (38.3)	176 (42.2)	4 (11.4)
All greater than or equal to 15%	945 (78.1)	302 (72.4)	15 (42.9)
All less than 15%	40 (3.3)	28 (6.7)	11 (31.4)
Fluctuating with at least one of each	225 (18.6)	87 (20.9)	9 (25.7)
PSA, N (%)			
All less than 4 ng/ml	1111 (91.8)	303 (72.7)	12 (34.3)
All greater than or equal to 4 ng/ml	11 (0.9)	23 (5.5)	7 (20.0)
Fluctuation with at least one of each	88 (7.3)	91 (21.8)	16 (45.7)
P-value for comparison of percent fluctuation of percent-free PSA 25% threshold to PSA 4 ng/mL threshold	< 0.001	< 0.001	0.001
P-value for comparison of percent fluctuation of percent-free PSA 15% threshold to PSA 4 ng/mL threshold	< 0.001	< 0.001	0.06