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The relationship between prostate volume and prostate-specific antigen variability: data from the Baltimore Longitudinal Study of Aging and the Johns Hopkins Active Surveillance Program

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Abstract

OBJECTIVE—To clarify the relationship between serial prostate-specific antigen (PSA) variability and prostate volume in both cancer-free participants from the Baltimore Longitudinal Study of Aging (BLSA) and patients with low-risk prostate cancer from the Johns Hopkins Active Surveillance Program (AS).

MATERIALS AND METHODS—In all, 287 men from the BLSA and 131 patients from the AS were included in the analysis, all with at least two PSA measurements and concurrent prostate volume measurements.

PSA variability was calculated in ng/mL per year, and a linear mixed-effects model was used to determine the relative effects of prostate volume, baseline PSA and age on PSA change over time.

RESULTS—In a model with prostate volume, age and baseline PSA, there was no significant relationship between prostate volume and PSA variability (BLSA, $P = 0.57$; AS, $P = 0.49$).

Only baseline PSA showed a significant relationship to PSA yearly variability (PSAYV) ($P < 0.001$). Specifically, a one unit higher baseline PSA (ng/mL) corresponded on average to 0.09 and 0.06 ng/mL per year higher PSAYV in the BLSA and AS populations, respectively.

CONCLUSIONS—The results of the present study suggest that the primary driver of PSA variability is the baseline PSA level, rather than prostate volume.

Clinicians might consider the baseline PSA level to help predict the expected variability in serial PSA measurements.

Keywords

PSA; prostate volume; PSA variability

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CONFLICT OF INTEREST

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INTRODUCTION

After the recent release of highly anticipated data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC), the risk-to-benefit ratio of PSA screening remains controversial [1,2]. Nevertheless, PSA-based screening is widespread, driving an ongoing need to improve both PSA test characteristics and the knowledge of expected normal within-individual variability in serial PSA measurements. Greater understanding of this variability could help to discriminate changes in PSA that should be considered clinically significant from random changes, age-associated changes and changes due to modification of prostate volume. Previous efforts have examined the inter-assay variability of repeated PSA testing on a single sample, with Prestigiacomo and Stamey [3] reporting a coefficient of variation of 4.0%. Other studies have attempted to further characterize the normal biological variability in PSA among men without prostate cancer. These reports suggest that PSA variability is unrelated to age [4,5], but there are conflicting data on its association with the baseline PSA level [4,6,7].

Finally, there are limited published data regarding the effects of prostate volume on PSA variability. In a study to assess whether prostate volume changes would confound the use of PSA velocity in clinical practice, Loeb *et al.* [8] reported that prostate volume changes were not significantly related to PSA changes. However, the study did not directly address the effect of baseline prostate volume on serial PSA variability.

The objective of the current study was to further examine the relationship between prostate volume and PSA variability. Our hypothesis was that larger baseline prostate volume would be associated with increased PSA variability in men without known prostate cancer and in those with suspected small-volume disease.

PATIENTS AND METHODS

The overall study population consisted of 1816 male participants in the BLSA and 744 patients with prostate cancer enrolled in the AS program.

The BLSA is a prospective cohort study initiated in 1958 by the National Institute of Aging in Bethesda, Maryland, as previously described [9]. At the time of analysis, 1816 men had enrolled in the BLSA, with 617 active, primarily residing in the Baltimore/Washington DC metropolitan area. The mean age at the initial visit age was 50.4 ± 15.3 years. All subjects provided written informed consent and the study protocols were approved by the institutional review board.

Approximately every 2 years, each BLSA subject undergoes a comprehensive medical evaluation. Beginning in September 1991, this has included prostate cancer screening with PSA level and DRE. PSA measurements for subject visits before 1991 were obtained retrospectively using frozen serum samples, and the mean time between PSA measurements was 2.2 ± 0.3 years. Beginning in February 1993 until 2002, pelvic MRI was also performed as part of the BLSA urological examination for men without prostate cancer. Prostate volume was calculated from T2 axial images using a semi-automated image analysis system,

as previously described [10]. A standard monoclonal immunoradiometric assay (Hybritech® Tandem-R Beckman Coulter, Inc., Fullerton, CA, USA) was used for all PSA measurements, and TRUS-guided prostate biopsy was recommended for a PSA level >4.0 ng/mL or suspicious DRE.

From this population, we identified 287 patients with no history of prostate cancer, at least one MRI-determined prostate volume measurement, and at least two serial PSA measurements separated by no more than 3 years for the current analysis. Their mean age was 58.9 ± 12.0 years, mean baseline prostate volume was 32.1 ± 18.4 mL, and mean baseline PSA value was 1.51 ± 1.64 ng/mL (Table 1). Of these men, 226 were Caucasian, 41 were African American, and 20 were from other ethnic backgrounds.

The AS program was initiated in 1995 by Carter *et al.* [11] for patients with low-risk prostate cancer. Inclusion criteria for this program include: T1c prostate cancer; Gleason score ≤ 6 ; two positive biopsy cores with $\leq 50\%$ core involvement with cancer; and a PSA density <0.15 ng/mL/mL. To date, 744 patients have enrolled in the AS program, with 385 currently active. All patients provided written informed consent and the study protocols were approved by the institutional review board.

After enrolment, each AS participant undergoes semi-annual total and free PSA measurement with DRE, and an annual surveillance prostate biopsy. Prostate volume was determined by the standard ellipsoid formula ($\text{width} \times \text{height} \times \text{length} \times \pi/6$), and a standard monoclonal immunoradiometric assay was used for all PSA measurements. Disease progression was defined by prostate needle biopsy (Gleason score ≥ 7 , any Gleason pattern 4 or 5, more than two cores involved with cancer or more than 50% involvement of any core with cancer). Patients with progression on biopsy were recommended to undergo definitive therapy with radiation therapy or surgery.

For the current analysis, we identified 131 participants from this program with semi-annual PSA measurements and annual TRUS-determined prostate volume measurements without evidence of biopsy progression during follow-up. Their mean age was 67.7 ± 4.6 years, mean baseline prostate volume was 58.7 ± 27.7 mL, and mean baseline PSA value was 5.4 ± 3.7 ng/mL (Table 1). The racial distribution was 119 Caucasian, eight African American, and four other.

In the current statistical analysis, 607 MRI-determined and 445 TRUS-determined unique prostate volume measurements were available from 287 eligible BLSA and 131 eligible AS patients, respectively. All volume measurements were concurrent with a PSA measurement. For each unique volume measurement and its associated PSA measurement, the nearest previous PSA measurement (within 0.7–1.3 years for AS patients; within 3 years for BLSA patients) was used to calculate PSAYV according to the formula $\text{PSAYV} = (\text{PSA}_t - \text{PSA}_{t-1})/(\text{years})$. Thus, PSAYV was used as a metric for the estimated yearly variation in serial PSA levels of the included participants. Patients with multiple prostate volume measurements were included in multiple PSAYV calculations, all of which were used in the analysis.

Distributions of absolute PSAYV and (absolute PSAYV)/baseline PSA by prostate volume and baseline PSA were calculated. A linear mixed-effects model fit by maximum likelihood was used to examine the relationship of prostate volume, baseline PSA and age with absolute PSAYV in both the BLSA and AS populations.

RESULTS

With regard to the relationship among prostate volume, PSAYV and PSAYV/PSA_t, within the BLSA group (Tables 2 and 3), median PSAYV tended to be higher when moving from lower to higher volume quartiles (0–20 mL, 0.062 ng/mL per year; 20–30 mL, 0.077 ng/mL per year; 30–40 mL, 0.100 ng/mL per year; 40 mL, 0.223 ng/mL per year) ($P < 0.001$), while median PSAYV/PSA was relatively constant across quartiles (0–20 mL, 10.56/year; 20–30 mL, 10.00/year; 30–40 mL, 10.24/year; 40 mL, 10.43/year) ($P = 0.11$). Similarly, within the AS group (Tables 4 and 5), median PSAYV tended to be higher when moving from lower to higher volume quartiles (0–40 mL, 0.342 ng/mL per year; 40–55 mL, 0.569 ng/mL per year; 55–75 mL, 0.591 ng/mL per year; 75 mL, 0.994 ng/mL per year) ($P = 0.51$), while median PSAYV/PSA was relatively constant across quartiles (0–40 mL, 18.61/year; 40–55 mL, 17.57/year; 55–75 mL, 12.78/year; 75 mL, 16.04/year) ($P = 0.08$). PSAYV and PSAYV/PSA_t were both greater in the AS group.

With regard to the relationship between baseline PSA and PSAYV, within the BLSA group (Table 6), median PSAYV tended to be higher with higher baseline PSA (0–1 ng/mL, 0.05 ng/mL per year; 1–2.5 ng/mL, 0.17 ng/mL per year; 2.5–4 ng/mL, 0.381 ng/mL per year; 4–10 ng/mL, 0.6 ng/mL per year; >10 ng/mL, 1.452 ng/mL per year) ($P < 1.0 \times 10^{11}$). Within the AS group (Table 6), the median PSAYV also tended to be higher with higher baseline PSA (0–1 ng/mL, 0.155 ng/mL per year; 1–2.5 ng/mL, 0.305 ng/mL per year; 2.5–4 ng/mL, 0.502 ng/mL per year; 4–10 ng/mL, 0.797 ng/mL per year; >10 ng/mL, 1.773 ng/mL per year) ($P = 0.83$).

The results of the mixed-effects model adjusting for volume, age, and baseline PSA are shown in Table 7. Although volume had a statistically significant relationship with PSAYV in both the BLSA and AS populations controlling only for age (slope: BLSA = 0.003, AS = 0.005; P values < 0.001), volume was no longer statistically significant after additional adjustment for the baseline PSA level (slope: BLSA = -0.0002, AS = 0.0075; P value: BLSA = 0.57, AS = 0.49). When adjusting for age, volume, and baseline PSA, the only significant driver of PSAYV was baseline PSA (slope: BLSA = 0.09, AS = 0.06; P value: BLSA < 0.001, AS < 0.001).

DISCUSSION

The utility of PSA screening is currently under debate. With a positive predictive value near 33% [12], two-thirds of men undergo unnecessary prostate biopsies, potentially leading to discomfort, anxiety and significant additional health care cost. An improved understanding of the expected normal variability between serial PSA tests could allow for improved physician decision-making regarding the need for biopsy. The goal of the present study was therefore to examine the relationship between PSA variability and patient age, PSA level and

prostate volume to determine whether higher values of these variables are associated with higher levels of normal PSA variability and thus a greater threshold for the decision to proceed with prostate biopsy.

Among healthy men in the BLSA and patients with low-risk prostate cancer in the AS program, we found that absolute PSA variability was positively associated with prostate volume, even after controlling for age. However, this relationship was no longer statistically significant when baseline PSA was added to the model. We also found no significant association between absolute PSA variability and age, but a significant positive association between PSA variability and baseline PSA. These findings concur with the prior study by Loeb *et al.* [8], who found that prostate volume changes were not independently associated with longitudinal changes in PSA after controlling for age, and with Nixon *et al.* [6], who showed greater PSA variability with higher baseline PSA levels. Overall, these combined findings suggest that the primary driver of PSAYV is the baseline PSA level.

It is important to clarify that the PSAYV calculation differs from and should not be confused with PSA velocity (PSAV) as described by Carter *et al.* [9]. PSAYV is simply a mathematical estimate of the absolute yearly change in PSA (ng/mL per year) between two measurements that can be separated by more than 1 year. PSAYV is not meant to represent the rate of change of PSA over time, which, as described by Carter *et al.* [9], optimally requires three consecutive PSA measurements over a 2-year period [13].

It is noteworthy that absolute PSAYV and PSAYV/baseline PSA were higher in the AS group than in the BLSA group, demonstrating greater fluctuations in PSA for patients with low-risk prostate cancer in AS despite no evidence of biopsy progression in these individuals.

The present study has several limitations. The first is that both PSA measurements and pelvic MRI were performed at $\approx$ 2-year intervals in the BLSA. Accordingly, yearly or more frequent determinations were not available from which to examine short-term PSA variability. In addition, prostate volume was determined via MRI in the BLSA and with TRUS in the AS population. Although TRUS volume estimations are most commonly used in daily clinical practice, MRI-determined volume measurements can be more accurate [14]. Additionally, only a select subset of BLSA patients underwent pelvic MRI from which to determine prostate volume, which could have limited the power to detect a relationship between prostate size and PSA variability. Finally, although we restricted the AS study population to individuals with no evidence of progression on follow-up biopsy, the presence of prostate cancer could have confounded the relationship between PSA variability and age, prostate volume, and the baseline PSA level.

In conclusion, despite a significant association between prostate volume and absolute PSA variability when only controlling for age, the relationship was no longer significant after adjustment for baseline PSA level. Indeed, the results of the present study suggest that the primary driver of PSA variability is the baseline PSA level, which could aid clinicians when examining a PSA history to assess the need for prostate biopsy.

Abbreviations:

AS	Johns Hopkins Active Surveillance Program
BSA	Baltimore Longitudinal Study of Aging
PSAV	PSA velocity
PSAYV	PSA yearly variability

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What's known on the subject? and What does the study add?

Previous studies have attempted to characterize the normal biological variability in PSA among men without prostate cancer. These reports suggest that PSA variability is unrelated to age, but there are conflicting data on its association with the baseline PSA level. There are limited published data regarding the effects of prostate volume on PSA variability. A prior study assessing whether prostate volume changes would confound the use of PSA velocity in clinical practice reported that prostate volume changes were not significantly related to PSA changes. This study did not directly address the effect of baseline prostate volume on serial PSA variability.

The objective of the current study was to further examine the relationship between prostate volume and PSA variability. Our hypothesis was that larger baseline prostate volume would be associated with increased PSA variability in men without known prostate cancer and in those with suspected small-volume disease. The results of the study suggest that baseline PSA, not prostate volume, is the primary driver of PSA variability in these populations.

TABLE 1

Study population age, prostate volume, baseline PSA, and prostate volume measurement intervals (AS and BLSA)

	BLSA		AS	
	Median (range)	Mean $\pm$ SD	Median (range)	Mean $\pm$ SD
Age at prostate volume measurement, years	61.0 (29.9–79.8)	58.9 $\pm$ 12.0	68.1 (55.1–79.8)	67.7 $\pm$ 4.6
Prostate volume, mL	29.0 (8.7–237.3)	32.1 $\pm$ 18.4	55.0 (8.0–184.0)	58.7 $\pm$ 27.7
Baseline PSA, ng/mL	1.0 (0.05–12.08)	1.51 $\pm$ 1.64	4.4 (0.3–22.0)	5.4 $\pm$ 3.7
Time interval for PSAV calculation, years	2.0 (1.3–3.0)	2.2 $\pm$ 0.3	1.0 (0.7–1.3)	1.2 $\pm$ 0.7

TABLE 2

BLSA population: mean PSAYV by prostate volume quartile

Prostate volume, mL (quartiles)	Mean PSAYV (percentiles)				
	10%	25%	50%	75%	90%
0–20	0.009	0.043	0.062	0.148	0.254
20–30	–	0.042	0.077	0.162	0.290
30–40	0.011	0.043	0.100	0.238	0.459
40–500	0.046	0.100	0.223	0.451	0.936

TABLE 3

BLSA population: mean PSAYV/baseline PSA by prostate volume quartile

Prostate volume, mL (quartiles)	Mean PSAYV/PSA1 (percentiles)				
	10%	25%	50%	75%	90%
0–20	1.18	6.07	10.56	19.35	30.01
20–30	–	4.62	10.00	15.87	25.00
30–40	0.91	4.38	10.24	17.96	29.83
40–500	2.54	6.25	10.43	17.23	22.05

TABLE 4

AS population: mean PSAYV by prostate volume quartile

Prostate volume, mL (quartiles)	Mean PSAYV (percentiles)				
	10%	25%	50%	75%	90%
0–40	–	0.100	0.342	0.745	1.745
40–55	0.098	0.267	0.569	1.117	1.902
55–75	0.178	0.291	0.591	1.423	2.467
75–500	0.192	0.502	0.994	2.251	3.473

TABLE 5

AS population: mean PSAYV/baseline PSA by prostate volume quartile

Prostate volume, mL (quartiles)	Mean PSAYV/PSA1 (percentiles)				
	10%	25%	50%	75%	90%
0–40	–	8.342	18.606	38.008	55.583
40–55	2.935	10.675	17.569	26.758	45.212
55–75	2.601	6.143	12.777	23.622	43.200
75–500	3.268	7.271	16.044	26.858	44.900

TABLE 6

Mean PSAYV by baseline PSA range for the BLSA and AS populations

Baseline PSA range, ng/mL	Mean PSAYV (percentiles)				
	10%	25%	50%	75%	90%
BLSA population					
0–1	–	0.022	0.050	0.100	0.176
1–2.5	0.037	0.081	0.170	0.289	0.450
2.5–4	0.061	0.170	0.381	0.600	0.997
4–10	0.086	0.300	0.600	1.043	1.662
10–500	0.926	1.166	1.452	2.044	2.279
AS population					
0–1	–	0.087	0.155	0.361	0.678
1–2.5	0.089	0.182	0.305	0.626	1.842
2.5–4	0.058	0.197	0.502	0.856	1.777
4–10	0.184	0.371	0.797	1.423	2.353
10–500	0.401	0.932	1.773	3.306	4.902

TABLE 7

Linear mixed-effects model to predict PSAYV in the BLSA and AS populations, adjusting for age, baseline PSA and prostate volume

	Coefficient	Standard error	P value
BLSA population			
Intercept	0.0110	0.0310	0.722
Volume	(0.0002)	0.0004	0.573
Age	0.0003	0.0006	0.599
Baseline PSA	0.0915	0.0046	–
AS population			
Intercept	0.1400	0.3093	0.651
Volume	0.0075	0.0011	0.491
Age	0.0014	0.0047	0.766
Baseline PSA	0.0609	0.0075	–