Prostate Size Does Not Predict High Grade Cancer

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Purpose: Several radical prostatectomy series have linked small prostates with high grade cancer based on the hypothesis that a small prostate results from a low androgen milieu that selects for less hormone dependent, more aggressive tumors. We previously reported that this association resulted from ascertainment bias from the performance characteristics of prostate specific antigen rather than from tumor biology in our radical prostatectomy cohort. In this study we analyzed this association in a more generalized population of men who underwent prostate needle biopsy.

Materials and Methods: The prostate needle biopsy database at our institution was queried for all initial biopsies. Included patient characteristics were age, race, family history of prostate cancer, prostate specific antigen, abnormal digital rectal examination and prostate volume in ml on transrectal ultrasound. Multivariate logistic regression was used to determine the influence of prostate volume on the odds of high grade cancer.

Results: The study population included 1,295 patients during 2000 to 2010, of whom 582 (44.9%) had prostate cancer and 398 (30.7%) had high grade cancer. When all patients were pooled, the OR for high grade cancer was 0.85 (95% CI 0.78–0.92) for each 10 ml increase in prostate volume. When patients were divided by clinical T stage, the corresponding ORs for those with T1c disease was 0.83 (95% CI 0.74–0.93) and for those with T2 or greater disease it was 0.99 (0.98–1.00).

Conclusions: The association between small prostates and high grade cancer exists only in men with clinical T1c (normal digital rectal examination) prostate cancer. It likely resulted from ascertainment bias due to the performance characteristics of prostate specific antigen rather than tumor biology.

Key Words: prostate, organ size, prostate-specific antigen, prostatic neoplasms, prognosis

Abbreviations and Acronyms

DRE = digital rectal examination

PSA = prostate specific antigen

SPND = Stanford Prostate Needle Biopsy Database

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Several groups have reported an association between small prostates and an increased risk of adverse outcomes such as high grade cancer, extraprostatic extension, positive surgical margins and biochemical recurrence in men undergoing radical prostatectomy.[1–3] To explain this observation some investigators advanced the theory that a small prostate acts as a surrogate marker for an androgen depleted milieu that selects for more aggressive, less hormone dependent tumors. To support this reasoning they cited prior studies linking low pretreatment serum testosterone to poor outcomes in men with newly diagnosed metastatic prostate cancer.[4]

In a recently published study of 1,404 patients from the radical prostatectomy database at our institution we reported that the association between small prostates and adverse pathological features, particularly the

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volume and percent of high grade cancer, exists only in patients with clinical T1c prostate cancer.[5] This association was not observed in men undergoing radical prostatectomy for clinical T2 disease. This disparity most likely represented ascertainment bias between the 2 groups due to PSA performance characteristics. If tumor biology drove the size-grade association, one would expect to see it in each group.

A limitation of making inferences from the results of radical prostatectomy series is selection bias. Cohorts that undergo surgery represent a subset of men who have cancer on prostate needle biopsy, who represent a larger subset than those who undergo surgery. To address this limitation of radical prostatectomy series we studied the association of prostate size and high grade cancer in a contemporary group of patients from SPND.

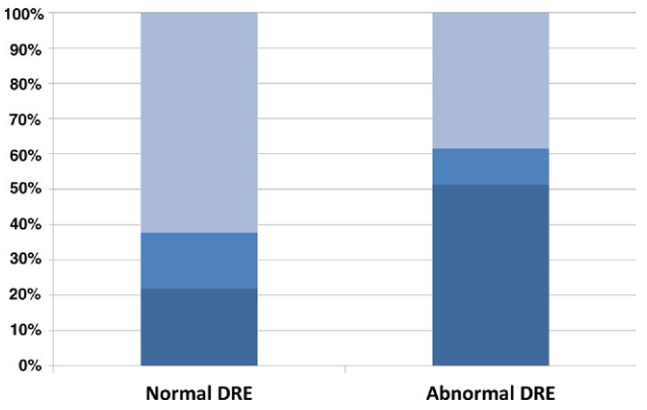
MATERIALS AND METHODS

SPND is an institutional review board approved, prospectively maintained database of all prostate needle biopsies performed at our institution. We reviewed SPND for all extended scheme (12 cores or more) biopsies since database inception. Patients with an existing diagnosis of prostate cancer, eg those on active surveillance, those evaluated for local recurrence after radiotherapy and those undergoing biopsy to confirm a diagnosis made elsewhere, were excluded from analysis. Those with prior negative biopsies were also excluded since the detection of cancer and high grade cancer in this patient group differs significantly from that in men undergoing initial biopsy.

Patient characteristics used in our analysis included age in years, race (white, black, Asian or other), family history of prostate cancer (yes/no), abnormal DRE (yes/no) and prostate volume in ml ascertained by volume (V) estimates based on transrectal ultrasound measurements using the formula, $V = \pi/6 \times \text{length} \times \text{width} \times \text{height}$ in cm. High grade prostate cancer, defined as a positive biopsy with a Gleason score of 7 or higher, was modeled as a dichotomous variable (yes/no).

Table 1. *Demographics of patients with prostate cancer on prostate needle biopsy*

	Normal DRE		Abnormal DRE		p Value
Median age (IQR)	65	(59–71)	67	(62–75)	<0.0001
No. race (%):					0.21
White	257	(75.4)	171	(70.1)	
Asian	42	(12.3)	40	(16.6)	
Black	30	(5.9)	9	(3.7)	
Other	22	(6.5)	21	(8.7)	
No. prostate Ca family history (%):					0.65
Yes	82	(24.1)	54	(22.4)	
No	259	(76.0)	187	(77.6)	
Median ng/ml PSA (IQR)	5.8	(4.5–8.4)	6.9	(4.3–15.0)	0.02
Median ml prostate vol (IQR)	40	(27–53)	34	(26–49)	0.02
No. high grade Ca (%):					<0.0001
Yes	197	(57.8)	201	(83.4)	
No	144	(42.2)	40	(16.6)	



Biopsy result by DRE status. Light blue indicates normal, medium blue low grade cancer and dark blue high grade cancer.

The Wilcoxon rank sum test was used to compare medians between different groups. The chi-square test was used to compare frequencies between different groups. Multivariate logistic regression was done to model the odds of high grade prostate cancer as a function of patient prostate size, PSA, age, race and family history of prostate cancer. Since we did not having missing variables, a complete case analysis was performed. To completely control for the effect of clinical T stage we generated separate models for men with normal (clinical T1c) and abnormal (clinical T2 or higher) DRE. The OR of each predictor is reported with the Wald 95% CI. Statistical analysis was done with SAS® 9.2. Tests for significance were 2-sided with $p \leq 0.05$ considered significant.

RESULTS

Table 1 lists the demographics of our study cohort. A total of 1,435 patients who were never diagnosed with prostate cancer underwent an extended prostate biopsy scheme during 2000 to 2010. We excluded 140 men who underwent a prior negative biopsy, leaving 1,295 as the study population.

The figure shows biopsy results stratified by DRE findings. As expected, the overall positive biopsy rate and the risk of finding high grade cancer were higher in men with abnormal DRE and these observations were statistically significant. Of these men 582 (44.9%) had cancer and 398 (30.7%) had high grade cancer. Of the 582 men with cancer 341 (58.6%) had normal DRE and 241 (41.4%) had abnormal DRE. Although there was a statistically significant difference in median age between the 2 groups, a difference of 2 years likely had no clinical significance. Differences in the distribution of race and family history of prostate cancer between the 2 groups were not statistically significant. Median PSA was lower in men with normal DRE in a statistically significant manner. Conversely median prostate volume was higher in those with normal