Small Prostate Size and High Grade Disease—Biology or Artifact?

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Abbreviations and Acronyms

DRE = digital rectal examination

PSA = prostate specific antigen

PSAD = PSA density

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Purpose: Prior radical prostatectomy series have shown an inverse association between prostate size and high grade cancer. It has been suggested that smaller size prostates arise in a low androgen environment, enabling development of more aggressive cancer. We propose that this observation is the result of ascertainment bias driven by prostate specific antigen performance.

Materials and Methods: We identified 1,404 patients from the Stanford Radical Prostatectomy Database with clinical stage T1c (723) and T2 (681) disease who underwent surgery between 1988 and 2002, and underwent detailed morphometric mapping by a single pathologist. Multivariate linear regression was performed to assess for the effects of age, prostate weight and prostate specific antigen on total and high grade (Gleason grade 4/5) cancer volume and percentage of high grade disease.

Results: In patients who underwent biopsy due to abnormal prostate specific antigen (stage T1c), prostate weight was negatively associated ($p = 0.0002$) with total cancer volume, volume of high grade disease and percentage of high grade disease. For patients who underwent biopsy based on abnormal digital rectal examination (stage T2) these associations were not observed.

Conclusions: Improved prostate specific antigen performance for high grade disease results in ascertainment bias in patients with T1c disease. Thus, the association between prostate size and high grade disease may be a consequence of grade dependent performance of prostate specific antigen rather than true tumor biology.

Key Words: prostatic neoplasms, prostate-specific antigen, pathology

Prior radical prostatectomy series have demonstrated an association between small prostate size and adverse pathological features such as the presence of high grade disease, extracapsular extension and positive surgical margins, as well as a higher rate of serologic relapse.[1–3] Low pretreatment serum testosterone levels are associated with worse survival in patients with newly diagnosed, metastatic prostate cancer.[4] It has been proposed that smaller prostate size is a surrogate for an androgen deprived environment and that even a localized prostate cancer arising in such an environment might be more aggressive. Hypothetically cancer that arises in such a setting would be less androgen dependent. Is this association between prostate size and cancer grade the result of cancer biology or a consequence of the method in which patients are selected for these studies?

Many patients in radical prostatectomy series are diagnosed due to an increased PSA. These patients are a select group in which ascertainment bias due to PSA test performance characteristics may have a role. A sec-

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ondary analysis of the Prostate Cancer Prevention Trial studied the performance characteristics of PSA by generating receiver operator characteristic curves.[5] In this analysis the area under the curve for the receiver operator characteristic curves for PSA was greatest for the detection of Gleason score 8, followed by Gleason score 7 and lowest for Gleason score 6 cancer. Thus, PSA performs best for high grade disease. In addition, there is a well established link between PSA and prostate size for cancer detection.[6] PSAD attempts to control for size, and a higher PSAD is more indicative of cancer. In addition, in patients with prostate cancer higher PSADs are associated with higher grade disease.[7]

Radical prostatectomy series consist of a highly selected population of patients referred for biopsy for an abnormal PSA and/or an abnormal DRE. The distribution of these clinical indicators in surgical series might produce an ascertainment bias. Ascertainment bias is a type of selection bias in which nonrandom sampling, in this scenario, referral for biopsy due to increased PSA, produces a distorted population that results in an erroneous correlation with a selected end point such as findings on surgical pathology. We believe that the grade dependent performance of PSA may result in ascertainment bias, explaining the association between small prostate size and aggressive cancer. We used detailed pathological data obtained from morphometric mapping of radical prostatectomy specimens in patients who underwent biopsy due to increased PSA or abnormal DRE to determine whether the size-grade association is a consequence of the performance characteristics of PSA or whether it represents true cancer biology.

MATERIALS AND METHODS

We used the Stanford Radical Prostatectomy Database and identified a subset of 1,403 patients with clinical stage T1c (724) or T2 (679) disease who underwent surgery between 1988 and 2002, and had histopathological evaluation by John McNeal, MD. Creation and maintenance of this database were approved by the Stanford University institutional review board. Each surgical specimen was weighed and underwent detailed morphometric mapping at 3 mm intervals as previously described.[8] Pertinent to this study we collected precise data on total cancer volume, volume of high grade cancer (Gleason 4 or 5) and percentage of high grade cancer (volume of Gleason 4 or 5/total cancer volume).

Statistical analysis was performed using JMP 5.0.1.2 software. Comparison of the 2 patient populations (stage T1c and stage T2) was performed using the Mann-Whitney U and Student's t test. Logarithmic transformation was performed for nonnormally distributed variables. Univariate analysis and multivariate linear regression were performed using the continuous variables of interest patient age, PSA and prostate weight, and expressed as β coefficients with 95% confidence intervals and p values. The effect of each variable from the regression was presented as a β coefficient to express the magnitude and direction of the effect in a standardized manner of the variable of interest on the primary end point. Primary continuous variable end points were total cancer volume, volume of high grade disease and percentage of high grade disease.

Table 1. *Patient characteristics*

	Stage T1c Median (IQR)	Stage T2 Median (IQR)	p Value
Age	63.0 (58.2–68.2)	64.7 (59.4–68.7)	0.10
PSA (ng/ml)	8.5 (6.2–13.7)	8.4 (5.1–14.9)	0.04
Prostate wt (gm)	48.0 (40.0–63.7)	44.0 (36.0–56.0)	<0.0001
Total Ca vol (cc)	2.3 (1.0–4.4)	3.0 (1.5–5.9)	<0.0001
Vol Gleason 4 or 5 Ca (cc)	0.4 (0.05–1.4)	0.7 (0.1–2.4)	0.0004
% Gleason 4 or 5 Ca (%)	20 (2–60)	20 (5–60)	0.09

RESULTS

Descriptive statistics comparing patients with T1c and those with T2 disease are shown in table 1. Although PSA was statistically significantly different between the 2 groups, this small difference is unlikely to be clinically relevant. Prostate weight was significantly higher in the T1c group ($p < 0.0001$). Total cancer volume and volume of Gleason 4 or 5 cancer were significantly higher in the T2 group ($p = 0.0001$ and 0.0004, respectively). There was no difference between percentage of Gleason 4 or 5 cancer between the T1c and T2 groups, with both groups containing 20% high grade cancer ($p = 0.09$).

Univariate analyses for each variable (age, log PSA and log prostate weight), and the effect on total, high grade and percentage high grade cancer volume in patients with T1c and T2 disease, are shown in table 2. As expected for patients with T1c disease, higher PSAs were significantly associated with higher total, high grade and percentage of high grade cancer volumes. Lower prostate weight was significantly associated with higher total cancer volume and percentage of Gleason 4 or 5 cancer, but not absolute Gleason 4 or 5 cancer volume. For patients with stage T2 disease PSA was also significantly associated with all pathological end points in a positive fashion. Prostate weight was significantly associated with higher total and absolute Gleason 4 or 5 cancer volume, but not percentage of Gleason 4 or 5 cancer volume.

Multivariate analysis was performed to determine the effects of age, PSA and prostate weight on total, high grade and percentage high grade cancer volume for patients with T1c and T2 disease (table 3). In patients with clinical stage T1c disease PSA continued to be significantly associated with total, high grade and percentage of high grade cancer volume in