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Blood prostate-specific antigen by volume of benign, Gleason pattern 3 and 4 prostate tissue

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Declaration of interests

- Andrew Vickers: Opko, Arctic Partners, Steba, Insightec
- Matthew Cooperberg: Abbvie, Janssen, Astellas, Bayer, Astra Zeneca, Myriad, Genomic Health, Merck
- Peter Carroll: Nutcracker Therapeutics, Insightec, Francis Medical, Progenics
- Brian Helfand: Ambry Genetics, Exact Sciences, GoPath, Blue Earth Diagnostics
- Scott Eggener: Insightec, Profound Medical, Janssen, Francis Medical

The remaining authors have no conflicts of interest to declare.

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Abstract

Objective—To evaluate how blood levels of prostate-specific antigen (PSA) relate to prostate volume of benign tissue, Gleason pattern 3 (GP3) and Gleason pattern 4 (GP4) cancer.

Methods—The cohort included 2,209 consecutive men undergoing radical prostatectomy at two academic institutions with pT2N0, Grade Group 1-4 prostate cancer and an undetectable postoperative PSA. Volume of benign, GP3, and GP4 were estimated. The primary analysis evaluated the association between PSA and volume of each type of tissue using multivariable linear regression. R^2, a measure of explained variation, was calculated using a multivariable model.

Results—Estimated contribution to PSA was 0.04/0.06 ng/ml/cc for benign, 0.08/0.14 ng/ml/cc for GP3, and 0.62/0.80 ng/ml/cc for GP4 for the two independent cohorts, respectively. GP4 was associated with 6 to 8-fold more PSA per cc compared to GP3 and 15-fold higher compared to benign tissue. We did not observe a difference between PSA per cc for GP3 vs. benign tissue (p=0.2). R^2 decreased only slightly when removing age (0.006/0.018), volume of benign tissue (0.051/0.054) or GP3 (0.014/0.023) from the model. When GP4 was removed, R^2 decreased 0.051/0.310. PSA density (PSA divided by prostate volume) was associated with volume of GP4 but not GP3, after adjustment for benign volume.

Conclusion—Gleason pattern 4 cancer contributes considerably more to PSA and PSA density per unit volume compared to GP3 and benign tissue. Contributions from GP3 and benign are similar. Further research should examine the utility of determining clinical management recommendations by absolute volume of GP4 rather than the ratio of GP3 to GP4.

Keywords

Prostate Cancer; Prostate-Specific Antigen (PSA); Gleason Score; Grade Group

Background

Gleason grade is a major determinant of prostate cancer management and the single most important predictor of prostate cancer outcomes.[1] Gleason grading, a histologic assessment of prostate cancer, is a unique classification system based on the relative proportion of pattern 3 (low-grade), 4 (intermediate grade) and 5 (high-grade). The two most common patterns are added together to construct the final Gleason score, ranging from 6 to 10. A newer grouping system aims to simplify prostate cancer grading by using Grade Groups 1 to 5.[2] Although Gleason grading has evolved since its inception in 1965, the use of ratios has been constant.[3] Anatomic and biological considerations suggest absolute rather than relative tumor volume drives prostate cancer outcomes. Since oncologic aggressiveness depends specifically on the volume of pattern 4 and 5, it may be a better surrogate of prostate cancer risk than the current system.[4,5]

Prostate-specific antigen (PSA) is a key component of prostate cancer screening, risk assessment, and active surveillance. There are many potential etiologies for an elevated, continuously rising, or fluctuating PSA, and clinical decisions are routinely influenced by both absolute PSA level and relative increases.

For prostate cancer screening, as PSA levels rise, the likelihood of prostate cancer and specifically higher-grade cancer concordantly increases. PSA density, calculated as the PSA divided by prostate volume, is also strongly correlated to the presence of cancer. Yet, there is a paucity of data evaluating the relative level of PSA (and PSA density) attributable to varying amounts of different histologic features within an individual prostate: benign tissue, low-grade prostate cancer, high-grade prostate cancer. The primary aim of our study was to evaluate how the relative volume of benign, Gleason pattern 3 (GP3), and Gleason pattern 4 (GP4) prostate tissue contribute to PSA level.

Subjects and Methods

After institutional review board approval, we collected data on consecutive men undergoing radical prostatectomy (RP) at the University of Chicago and University of California, San Francisco (UCSF) for pT2N0 (organ-confined) prostate cancer with exclusively GP3 or GP4 disease (i.e. Grade Group <5). To rule out the contribution of PSA production originating elsewhere from unresected local cancer or metastases, we included only men with an undetectable postoperative PSA. As the aim of our study is to evaluate the contributions of GP3 and GP4 to PSA, we excluded men with GP5. For each man, estimated volume (cc) of benign, GP3, and GP4 were extracted from the prostatectomy specimen. PSA density (ng/ml/cc) was calculated as PSA (ng/ml) divided by prostate volume (cc).

Histopathological methods

RP specimens were reviewed by genitourinary pathologists at each institution. According to the 2014 International Society of Urological Pathology (ISUP), prostate weight, modified Gleason grading, tumor percentages and GP4 percentages were recorded.[6,7] The volume of tumor and proportion of GP4 were assessed by visual estimation in the prostate sections, with volume of GP3 and GP4 then calculated.[8]

Statistical methods

The primary analysis estimating the association between PSA and volume of each type of prostate tissue – benign, GP3, GP4 – was conducted by a multivariable linear regression, with adjustment for age. Heterogeneity in estimates between cohorts was assessed by Cochran's Q. We then added non-linear terms for all predictors using restricted cubic splines with knots at the tertiles. We assessed the change in R^2, as a measure of explained variation, when each predictor and associated non-linear terms were removed from the model. We separately assessed R^2 for volume of GP4 alone, for total prostate volume plus Grade Group, and for Grade Group alone. In two separate models, we evaluated the association between PSA density and either GP3 or GP4, including non-linear terms and adjusting for benign volume. Finally, as an exploratory analysis, we tested the interaction between age and the volume of each type of tissue as well as all pairwise interactions between types of tissue.

These models included all predictors plus the interaction term. All analyses were conducted using Stata 16 (Stata Corp., College Station, TX).

Results

A total of 2,209 radical prostatectomy specimens were assessed (Chicago = 872 and UCSF = 1,337). Age, preoperative PSA and Grade Group were similar between institutions (Supplementary Table 1). Median estimated volume of cancer (4.8 vs 1.6 cc), GP3 (3.3 vs 1.1 cc), and GP4 (0.6 vs 0.2 cc) were approximately 3 times greater in the University of Chicago cohort. The volume of GP4 was correlated with Grade Group, with a mean of 0.9, 3.6, and 5.6 cc in Grade Groups 2, 3 and 4, respectively. However, as shown in Figure 1, there was considerable overlap. For instance, in the 64 patients with 4–6 cc of GP4, the proportion in Grade Group 2, 3 and 4 were approximately 20%, 40% and 40%.

The estimated contribution of each prostate histologic subtype (per cc) to PSA was similar between cohorts: 0.04/0.06 ng/ml/cc for benign, 0.08/0.14 ng/ml/cc for GP3, and 0.62/0.80 ng/ml/cc for GP4 in the University of Chicago and UCSF cohorts, respectively (Table 1). The estimated contributions of benign and GP3 (per cc) were similar, suggesting an equivalent increasing volume of GP3 or benign (or combination) impact PSA similarly. However, within each cohort, the estimated contribution (per cc) of GP4 was approximately 6 to 8-fold higher compared to GP3 and 15-fold higher compared to benign. We did not observe a difference between PSA per cc of GP3 vs. benign tissue (p=0.2).

The univariate association between estimated volume of different prostate tissue types and PSA showed a much steeper slope for GP4 than for GP3 or benign tissue (Figure 2a; Table 1). At low estimated volumes of benign tissue (<15 cc), there is an apparent inverse relationship with PSA levels, likely due to a relatively small number of prostates with a very high tumor volume, as reflected in the wide confidence intervals. For instance, in the 129 men with benign volume <15 cc, mean volumes of GP3 and GP4 were 2.6 and 6.5 cc, considerably higher than the overall mean (Supplementary Table 1). Repeating the main analyses excluding men with low benign volume did not materially change the overall findings (supplementary Table 2). We repeated the main analyses using the endpoint of PSA density. After adjusting for benign volume, PSA density was strongly associated with volume of GP4 (p<0.0001), while no relationship was found with volume of GP3 (p=0.3; Figure 2b).

In a multivariable model, GP4 was the dominant predictor of PSA (Table 2). Although the amount of variation (R^2) in PSA explained by the predictors was lower in the UCSF cohort, the relative differences between individual predictors were similar in both cohorts. While removing age, volume of benign tissue, or volume of GP3 from the multivariable model reduced explained variation only fractionally (e.g., from 0.387 to 0.364 in the University of Chicago cohort), the models lost much of their predictiveness when volume of GP4 was removed (e.g., R^2 0.387 to 0.077).

Importantly, volume of GP4 as a sole predictor explained far more variation in PSA than Grade Group, with an R^2 approximately three-fold higher. It was also equal or superior to a

model including Grade Group plus total prostate volume. These results were not sensitive to the exclusion of patients with low benign volume or high PSA (supplementary Table 3).

We found interactions between age and benign volume, age and GP3, and between GP3 and GP4. However, on sensitivity analyses, excluding patients with low benign volume or high PSA, only the interaction between GP3 and GP4 remained significant (p=0.001). The interaction has a negative sign, meaning the difference in PSA level for a 1 cc difference in GP4 is less for higher volumes of GP3 than for lower volumes, and, comparably, a 1 cc difference in GP3 is associated with a smaller difference in PSA where GP4 volume is higher.

Discussion

Based on volumetric analysis of radical prostatectomy specimens, PSA per unit volume appears similar for benign tissue and GP3, and substantially higher for GP4. The absolute volume of GP4 was clearly the strongest predictor of an elevated PSA level, outperforming the contemporary grading system. Similarly, GP4, but not GP3, predicted PSA density.

There is a dearth of literature evaluating absolute levels of GP3 versus GP4 since most research and classification systems use the ratio of GP3 to GP4. There are studies, dating back 25 years, showing the proportion of cancer with GP4 (+/− GP5) as a primary driver of recurrence following local treatment, although absolute amounts were not evaluated.[5,9] In the 1990s, Stamey et al.[9] suggested the proportion of GP4 and GP5 was a powerful predictor of disease recurrence following prostatectomy, more so than Gleason score itself. In a contemporary series of nearly 10,000 men undergoing radical prostatectomy, Sauter et al.[5] showed the ratio of GP3 to GP4 strongly stratified risk of disease recurrence among patients within the same Grade Group. For instance, 5-year risk of recurrence in men with Grade Group 2 varied between 10 - 35% depending on the percent of cancer with GP4 (ranging between 5% - 49%). Analogously, we show when PSA is used as a biomarker prior to surgery, it is far more impacted by the absolute amount of GP4 compared to the Grade Group or other factors. However, volume of GP4 in the radical prostatectomy specimen may not independently predict disease recurrence,[10] perhaps due to a ceiling effect, as the concordance index of a base model (including Grade Group, PSA and pathologic stage) is very high at 0.86.

The current grading approach can result in counterintuitive scenarios.[11] For instance, a biopsy core with 2 mm of GP4 and 1 mm of GP3 is defined as Grade Group 3, whereas a core with 4 mm of GP4 and 5 mm of GP3 - a higher volume of the aggressive phenotype as well as more cancer overall – would paradoxically be defined as a ‘lower’ Grade Group 2. Similarly, a core with 1 mm of GP4 and no GP3 has less aggressive disease and less cancer overall than either of the first two cases and yet is assigned to the higher-risk Grade Group 4.

Nevertheless, in the current Grade Group system, the determination of Grade Group 2, 3 or 4 depends on the relative volume (ratio) of GP3 and GP4. Management guidelines use Grade Group to recommend when a metastatic evaluation is appropriate, whether active surveillance is an option, or if radiation therapy requires concomitant androgen deprivation.

The system remains a powerful predictor of progression while on active surveillance, disease recurrence after primary treatment, and likelihood of metastases or death.[2,12-14] Our findings are consistent in that we found a strong correlation between Grade Group and volume of GP4 (Figure 1). However, there was also considerable overlap with amount of GP4 between Grade Groups. Therefore, we suggest further research to determine whether future prostate cancer grading modifications are based on the amount of GP4 rather than dichotomizing based on the ratio of GP3 to GP4.

Considerable amounts of data suggest GP3 (Grade Group 1) without the presence of higher grade components is incapable of metastasizing to regional lymph nodes or more distant sites.[14,15] Accordingly, a growing number of groups have questioned whether it should even be called cancer.[16-19] Despite the histological features distinguishing GP3 from benign (e.g., loss of basal cell layer), the architectural destruction does not appear to lead to a difference in either metastatic potential or contribution per cc to PSA.

Despite these indolent clinical features, GP3-related PSA elevations frequently lead to unnecessary biopsies or treatment. The ideal screening biomarker would identify GP4 (and GP5) but not be impacted by GP3, benign tissue, or inflammation. Newer biomarkers (e.g. prostate health index, 4Kscore, Select MDx) outperform PSA by reducing the number of men requiring a biopsy, lowering the likelihood of a Grade Group 1 diagnosis, while identifying a similar proportion of men with Grade Group ≥ 2.

It is unclear why different types and amounts of prostate cancer result in proportionally different contributions to PSA. However, numerous studies and tissue-based genomic biomarkers highlight differences in DNA replication, cell cycle regulation, mRNA expression, metabolomic profile, and genomic instability (amplifications, deletions, point mutations) between GP3 and GP4.[20-22] These alterations within GP4 putatively lead to increased intracellular production of PSA, increased ‘leakiness’ into the blood, or both. Downregulation of adhesion molecules and loss of cell polarity are hypothesized as potential causes of increased PSA efflux from the glandular lumen into the prostatic stroma and bloodstream, leading to higher levels of PSA.[23,24] This disruption of the normal glandular architecture is the hallmark of GP4 and logically explains the direct and stark correlation of volume of GP4 with increasing PSA.[24,25]

To optimally estimate proportional tissue-based contributions to PSA, we included only men with organ-confined GP3 or GP4 prostate cancer with an undetectable postoperative PSA. We did not include the highest-grade cancer (GP5) since it is usually associated with metastatic disease and often so poorly differentiated it doesn’t produce a meaningful amount of PSA.[26] We were also not able to quantify the amount prostate inflammation and its relative contribution to PSA. There were significant differences between the two cohorts, most notably in the estimated volumes of total cancer, GP3, and GP4, reflecting either patient selection, methods of local pathologic processing and volume estimations, or both. Nevertheless, the relative increase in PSA associated with every additional unit volume (cc) for the different types of prostatic tissue were quite similar between cohorts.

Grade drives management in prostate cancer and further research is required to determine how best to use the GP4 volume in prognostication and clinical decisions. In particular, the amount of GP4 on biopsy should be estimated. This is naturally essential for further research and could arguably be used in clinical practice given that it it is more strongly predictive of adverse pathology at prostatectomy compared to the percentage of GP4.[4] This is particularly the case in clinical "toss ups" such as the decision to treat GG2 disease.

The intent of screening, timely diagnosis, and select treatment of men with early-stage prostate cancer is to identify men with cancers that might eventually cause symptoms or metastasize. Since GP3 and benign disease have a similar effect on PSA and PSA density, coupled with lack of metastatic potential, screening should focus exclusively on detection of higher-grade cancers (GP4 or GP5).

Whether in the setting of primary screening or active surveillance of early stage prostate cancer, PSA fluctuation is common. Based on our data, stable PSA levels or slow PSA rises are more likely to be associated with benign tissue or GP3, while more steadily or dramatically rising (and confirmed) changes may warrant further investigation with secondary biomarkers, imaging, or biopsy. Our data explains why preoperative PSA is a major factor in predicting long-term outcomes following surgery, while its prognostic capability is dramatically tempered once the prostate is removed and histopathological features such as Gleason score are factored into a model.[14,27,28] Lastly, we suspect most physicians who offer prostate cancer screening ostensibly believe GP3 leads to considerably higher PSA levels compared to benign tissue, a notion that does not appear to be accurate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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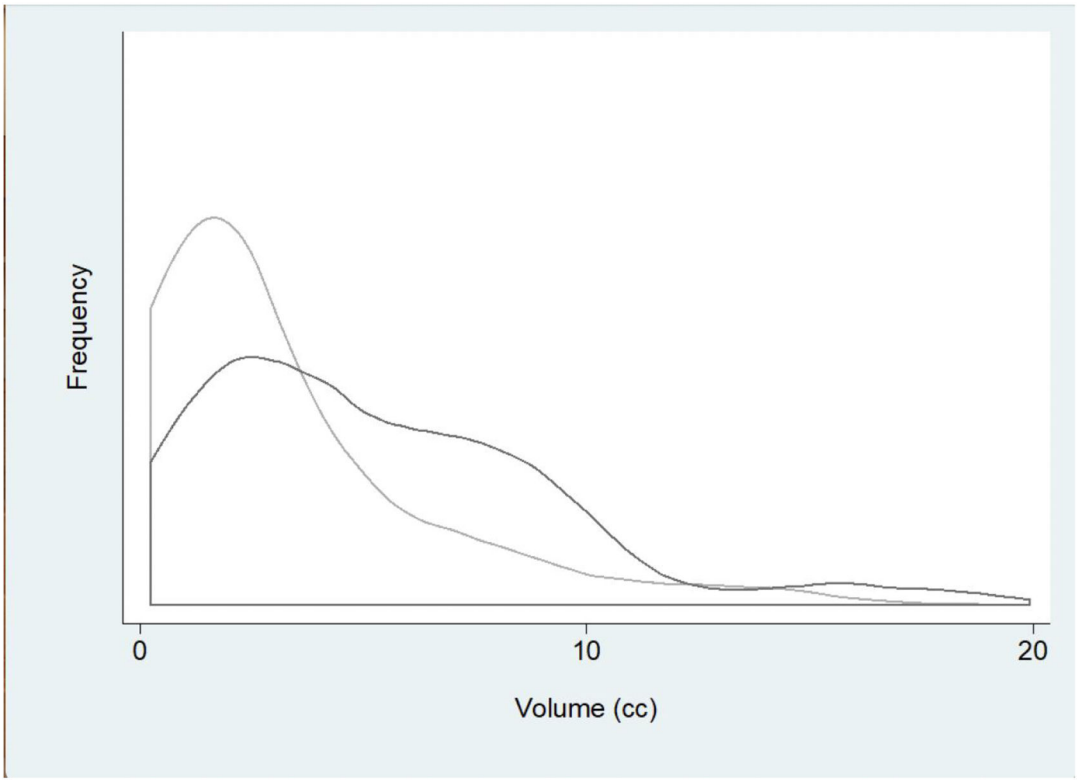

Figure 1.
Distribution of Gleason pattern 4 (GP4) volume for Grade Group 2 (light grey), Grade Group 3 (intermediate grey) and Grade Group 4 (dark grey).

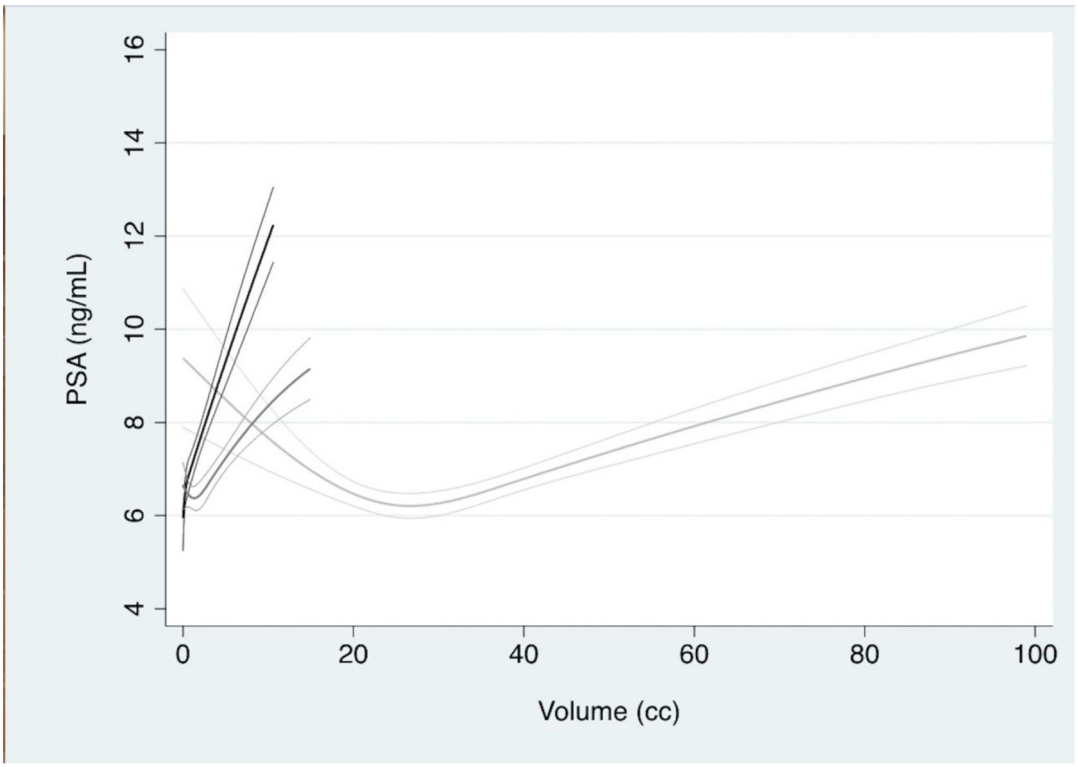

Figure 2a.

Association between PSA and volume of different types of prostate tissue. Dark: Gleason pattern 4 (steepest line, far left). Intermediate: Gleason pattern 3 (moderately steep line on left). Light: Benign tissue (U-shaped relationship). Thin lines are 95% C.I.

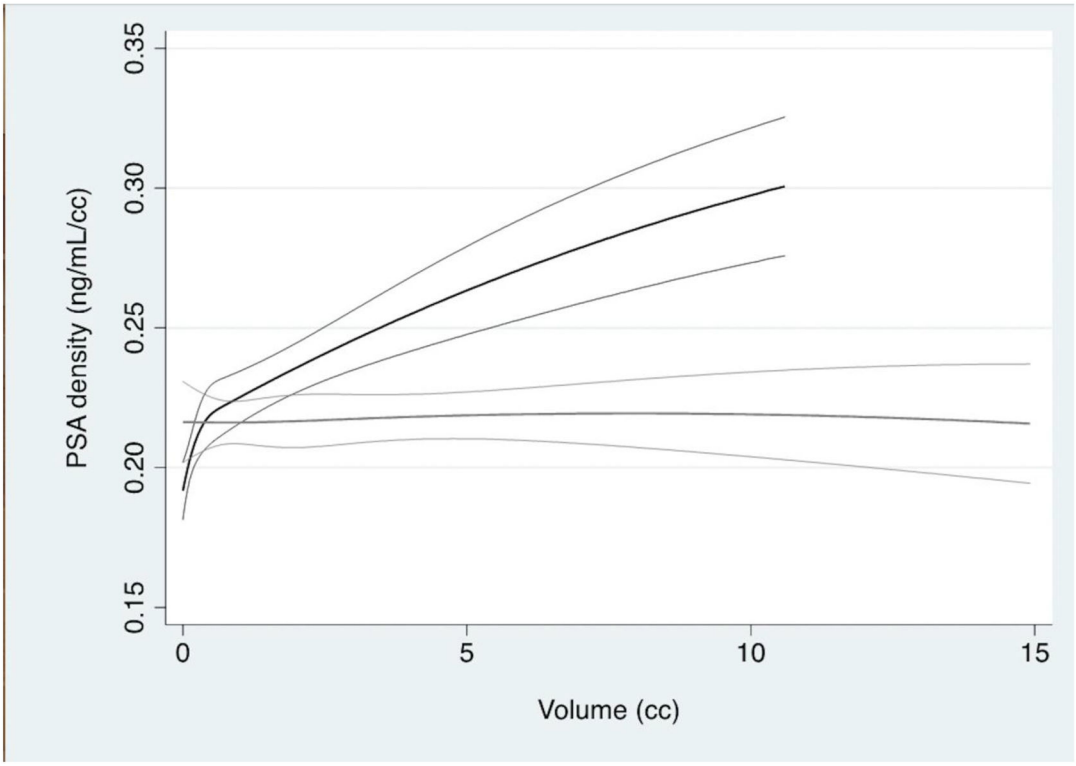

Figure 2b.

Association between PSA density and volume of different types of prostate cancer tissue for a patient with 30 cc of benign tissue. Dark: Gleason pattern 4. Intermediate: Gleason pattern 3. Thin lines are 95% C.I.

Table 1.

Multivariable model for PSA

The β denotes the increase in PSA associated with a one unit increase in age or volume of different types of prostate tissue. The heterogeneity p-value tests the null hypothesis that the estimates are similar between cohorts.

Predictor	University of Chicago (n=872)			UCSF (n=1337)			Heterogeneity
	β	95% C.I.	P-value	β	95% C.I.	P-value	P-value
Age (year)	0.00	−0.03, 0.03	0.9	0.02	−0.02, 0.06	0.3	0.4
Volume (cc) benign	0.04	0.03, 0.05	<0.0001	0.06	0.04, 0.07	<0.0001	0.067
Volume (cc) pattern 3	0.08	0.03, 0.13	0.001	0.14	0.07, 0.21	<0.0001	0.15
Volume (cc) pattern 4	0.62	0.56, 0.68	<0.0001	0.80	0.60, 1.00	<0.0001	0.089

Table 2.

Explained variation for different combinations of predictors

The full model consists of age, volume in cc of benign, pattern 3 and pattern 4, plus non-linear terms for all predictors

	Chicago (n=872)	UCSF (N=1376)
Full model	0.387	0.147
Removing each predictor		
Age	0.381	0.137
Volume of benign tissue	0.336	0.098
Volume of pattern 3	0.364	0.136
Volume of pattern 4	0.077	0.084
Alternative models		
Volume of pattern 4 alone	0.296	0.077
Total prostate volume plus grade group	0.223	0.077
Grade group alone	0.122	0.026