PSA density improves prediction of prostate cancer

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Introduction: *Prostate-specific antigen (PSA) and the digital rectal exam (DRE) have moderate sensitivity but low specificity for cancer diagnosis, potentially causing unnecessary treatment complications with prostate biopsy. Transrectal ultrasound (TRUS) to evaluate prostate size and calculate PSA density can improve the specificity of PSA in predicting cancer. We evaluated the sensitivity and specificity of different pre-biopsy tests to detect prostate cancer.*

Materials and methods: *Pre-biopsy data were collected from 521 men referred for biopsy from January-December 2011 and cancer aggressiveness data from 96 men who had radical prostatectomy. Model predictors included total PSA, DRE, the ratio of free to total PSA (PSAf/t), and PSA density. We used logistic regression and ROC curve analyses to compare the accuracy of different models to predict positive biopsy.*

Results: *The area under the curve (AUC) for model A (PSA total, DRE, PSAf/t) was moderate, but significant (AUC = .59, $p < .05$); only PSAf/t was a significant independent predictor of positive biopsy (OR = .002, $p < .05$). In model B (PSAf/t and PSA density; AUC= .66, $p < .05$), PSA density was the only strong predictor (OR = 1067.93, $p < .05$). Both models had comparable sensitivity (74% versus 72%) but model B had greater specificity (44% versus 61%). PSA density was also a significant predictor of different indices of aggressive cancer.*

Conclusions: *PSA density has discriminative predictive power for prostate cancer. It had similar sensitivity, but greater specificity compared to using PSA total, DRE and PSAf/t. These results support the value of using PSA density to improve prediction of prostate cancer and reduce unnecessary biopsies.*

Key Words: prostate-specific antigen, prostate volume, PSA density, aggressive cancer

Introduction

Accurately diagnosing clinically significant prostate cancer at a time when the benefits of treatment outweigh the harm continues to elude clinicians because of the complex nature of prostate cancer. Prostate-specific antigen (PSA) testing and/or digital rectal exams (DRE) remain the standard screening and assessment tools to identify men who are at risk for prostate cancer. They are easy to conduct and inexpensive. However, today, there is substantial controversy over the effectiveness of using total PSA levels or DRE exams to refer men for biopsy to receive a definitive diagnosis. DRE exams often detect prostate cancer in later stages when surgical

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removal is more difficult or fail to identify cancers in areas that are unpalapable. PSA total cut-off levels (e.g. > 4.0 ug/L) are associated with numerous false positives, causing men undue anxiety about the threat of cancer.[1]

Moreover, PSA totals greater than 4.0 ug/L often warrant referral for prostate biopsy that reveals a low-grade cancer (e.g. Gleason score 6) resulting in radical treatment. Unfortunately, many of these cancers would have been slow-growing and never caused any clinical harm to the patient.[2,3] Biopsy and treatment of these indolent cancers can cause more harm than benefit due to psychological stress, incontinence, impotence, bowel dysfunction and pain.[1,4] For men aged 50-70, recent large scale clinical trial evidence suggests that there is little benefit to PSA screening in reducing morbidity and mortality associated with prostate cancer.[5,6] Therefore, finding a diagnostic test that can accurately identify only aggressive tumors that should be treated in early stages remains an urgent priority.

Improvements to prostate cancer screening and assessment include measuring PSA changes over time (PSA velocity),[7,8] the ratio of free to total PSA (PSAf/t),[9] isoforms of the PSA protein, such as proPSA,[10] and the use of transrectal ultrasound (TRUS) to estimate the size of the prostate gland and calculate PSA density (the amount of PSA relative to the size of the gland).[11] Men with PSAf/t less than .24 or .25 have a higher probability of cancer than men with PSAf/t greater than or equal to .25.[9] Integrating information about the size of the prostate gland can be especially beneficial because like cancer, age and benign prostatic hyperplasia increase PSA total levels,12,13[11,12], making prostate biopsy the only way to rule out cancer if only PSA total levels are used for referral. Higher PSA in smaller prostate glands is more indicative of cancer than in a larger gland. These other causes of increased PSA explain, in part, the low specificity associated with predictions of prostate cancer based on PSA total alone.

PSA density, in particular, has shown promise over PSA total and DRE (and PSAf/t in some cases) in improving the specificity of prostate cancer detection while maintaining sufficient sensitivity.[14-22] PSA density also shows a stronger relationship than PSA alone with measures of aggressive cancer, such as extracapsular disease,[16,17] Gleason score greater than or equal to 7,[23] Gleason score upgrading,[24] and biochemical recurrence.[25] One group found that increasing PSA density from less than 0.1 to greater than .19 ng/mL/cc was associated with multiple worsening clinicopathological prognostic features (e.g. organ confined, Gleason score, cancer volume and biochemical recurrence).[11] However, PSA density remains underutilized in prostate cancer assessment compared to PSA total and DRE.

At our center, we collect and track data from all pre-biopsy diagnostic tests as well as data from TRUS on clinical characteristics and prostate size, which is used to calculate PSA density. The purpose of this study was to evaluate the effectiveness of different tests conducted in our health region to identify men who have a higher probability of a positive biopsy and more aggressive cancer. In particular, we were interested in determining any potential benefit of using TRUS and PSA density compared to the standard use of total PSA, PSAf/t and DRE in the diagnosis of prostate cancer.

Materials and methods

Retrospective data were collected from patient charts of 526 men assessed at the prostate assessment center in the hospital from January to December 2011. Referrals were made to the center primarily from urologists and family physicians for prostate exam and TRUS-guided prostate biopsy. Men were assessed by a prostate nurse and a radiologist.

Measures

We collected information on patient demographics, DRE result as performed by radiologist, PSA total (ug/L), the ratio of free to total PSA (PSAf/t), prostate volume (mL), PSA density (ng/mL/cc), and the Gleason score from the pathology report. PSAf/t was calculated automatically when testing PSA total and only generated for men with PSA total between 4 ug/L and 10 ug/L. Prostate dimensions were determined using a TRUS probe and the volume was calculated using the formula for an ellipse (volume ¼ 0.52 X length X weight X height). PSA density was automatically calculated by the machine.

Additional data were collected from the provincial cancer clinic from a subgroup of 96 men who had radical prostatectomy after a diagnosis of cancer. Measures included Gleason score after prostatectomy, gland weight (g), tumor size (mm), proportion of the gland that was tumor, clinical stage, pathological stage, and metastasis. Clinical stage was determined using the AJCC Staging System (2002). Pathological stage was conducted by an experienced pathologist and included extraprostatic extension, seminal vesicle invasion, perineural invasion, venous invasion, and lymphatic invasion. Metastasis at the time of pathology was recorded for both lymph nodes and other areas.

Our primary outcome measure was whether the biopsy result was negative or positive. Secondary outcomes were measures of aggressiveness for those men with radical prostatectomies, including the Gleason score after surgery, proportion of the gland that is tumor, clinical stage, and pathological stage.

TABLE 1. **Frequencies of negative and positive biopsies and Gleason scores for different diagnostic categories**

Category		N	Negative biopsy n (%)	Positive biopsy n (%)
Total sample		521	225 (43%)	296 (57%)
PSA total < 4 µg		52	31 (60%)	21 (40%)
PSA total 4-10 µg		328	148 (45%)	180 (55%)
	PSAf/t < .24	290	122 (42%)	168 (58%)
	PSAf/t > = .24	34	25 (74%)	9 (26%)
PSA total > 10		141	46 (33%)	95 (67%)

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio

Analysis

Comparisons of baseline characteristics for patients with negative and positive biopsies were calculated with chi-square tests or non-parametric tests (e.g. Mann-Whitney U) where appropriate when data were skewed. The primary analyses used univariate and multivariate logistic regression and ROC curve analyses to compare the predictive accuracy of different prostate tests (PSA total, DRE, PSAf/t, PSA density), including combinations of these tests, in predicting a positive biopsy. In particular, we were interested in comparing a model using traditional diagnostic information (PSA total, DRE and PSAf/t) to models incorporating information from PSA density. The area under the curve (AUC) was derived for all models. Sensitivities and specificities for quantitative variables were estimated using ROC curve. Comparisons of ROC curves were made using the DeLong method. Because of the high base rate of cancer in this sample, positive and negative predictive values were not evaluated. Statistical analyses were conducted using SPSS Version 17.0 and Medcalc. This research was approved by the Regina Qu'Appelle Health Region Research Ethics Board.

Results

The total sample included data from 526 men. The data for five men were excluded because their values for PSA total were considered outliers (> 3 standard deviations from the mean) leaving a final sample size of 521.

There were 296 (57%) positive results out of 521 completed biopsies. Of 291 positive biopsies with pathology Gleason score data, 149 (51%) were between Gleason score 0 and 6, 78 (27%) were Gleason score 7 and 64 (22%) were between Gleason score 8 and 10. Table 1 shows the breakdown of individuals with a positive or negative biopsy using the standard PSA total categories of < 4, 4-10 and > 10 ug/L, as well as the ratio of free to total PSA ratio (PSAf/t) categories of < .24 and >= .24. Table 2 shows the descriptive data for quantitative variables and Table 3 for DRE results from patients with

TABLE 2. **Descriptive statistics of clinical assessment for patients with positive and negative biopsies**

	Positive biopsy			Negative biopsy		
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)
Age (years)	296	68.15 (8.97)*	68.50 (13.00)	225	64.31 (7.61)	64.00 (11.00)
PSA total (µg/L)	296	13.39 (7.95)*	7.95 (6.90)	225	7.39 (4.73)	6.40 (4.20)
PSAf/t	177	.13 (.06)*	.12 (.08)	147	.16 (.07)	.15 (.09)
PSA volume (mL)	293	44.79 (20.23)*	39.90 (27.00)	221	59.16 (31.96)	51.40 (42.20)
PSA density	293	.37 (.48)*	.19 (.19)	221	.15 (.12)	.11 (.10)
Gleason score	290	6.74 (.95)	6.00 (1.00)			

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio
*significantly different from those with a negative biopsy (p < .001, Mann-Whitney)

TABLE 3. **Proportion of patients with positive vs. negative biopsies that had normal and abnormal DRE results ($\chi^2(1) = 4.63$, p =.03; Phi = .11)**

		Positive biopsy		Negative biopsy	
		N	%	N	%
DRE					
	Normal	90	38.0%	85	48.6%
	Abnormal	147	62.0%	90	51.4%
	Total	237	100%	175	100%

DRE = digital rectal examination
PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio

positive and negative biopsies. As expected, patients with positive biopsies were older, had a higher PSA total, a lower PSAf/t, a larger prostate volume, higher PSA density (all p < .001, Mann-Whitney U) and were also more likely to have an abnormal DRE exam (n = 412; $\chi^2(1) = 4.63$, p = .03; Phi = .11) than those with negative biopsies.

Univariate analyses

Table 4 shows the AUC of the ROC curve for each univariate variable in predicting a positive biopsy. We only focused on variables that could be used clinically prior to biopsy. PSA total, PSAf/t, PSA density and age were all significant predictors of positive biopsy. A comparison of all the ROC curves revealed that PSA density had significantly larger AUC compared to the other four variables (all p < .05), whereas the AUC for age, DRE, PSA total and PSAf/t were all statistically similar. Therefore, PSA density had the best overall diagnostic performance (AUC = .72, p < .05; Table 4 and Figure 1). The two most optimal PSA density cut off scores in predicting positive biopsy were .14 with sensitivity (73%) and specificity (61%), and .15 with sensitivity (68%) and specificity (66%). To examine the influence of age, we compared the performance of PSA density with a cut off of .15 for three clinically relevant age groups: 50-59, 60-69, and 70+. PSA density had consistently high AUC for all age groups: 50-59 (.62; 95%CI: .51, .74); 60-69 (.72, 95%CI: .66, .79); and 70+ (.78, 95%CI: .71, .85; all p < .05). We also did a supplementary analysis on PSA total because some centers use age-specific total PSA cut offs as an indirect way to account for prostate size growth with age.[26] The AUC for PSA total for each age group was: 50-59 (.54; 95%CI: .41, .66; p > .05); 60-69 (.58; 95%CI: .50, .64; p = .05); and 70+ (.63; 95%CI: .55, .71; p < .05).

Multivariate analyses

We chose to estimate the predictive performance of different combinations of pre-biopsy tests that are used clinically to determine appropriateness of prostate biopsy. Only clinically relevant and statistically significant models are reported in this paper. We chose to compare a standard model (model A) using information from PSA total, PSAf/t, and DRE with a

TABLE 4. **Areas under the curve (AUC) for univariate variables in predicting positive biopsy result**

			95% CI	
Predictor	N	Area (SE)	Lower	Upper
PSAf/t	324	.63* (.03)	.56	.69
PSA density	514	.72* (.02)	.68	.77
PSA total	521	.61* (.03)	.56	.66
DRE	423	.54 (.03)	.49	.60
Age	521	.63* (.02)	.59	.68

PSAf/t = free to total prostate-specific antigen ratio;
PSA = prostate-specific antigen; DRE = digital rectal examination
*significantly different from 0.5, p < .05

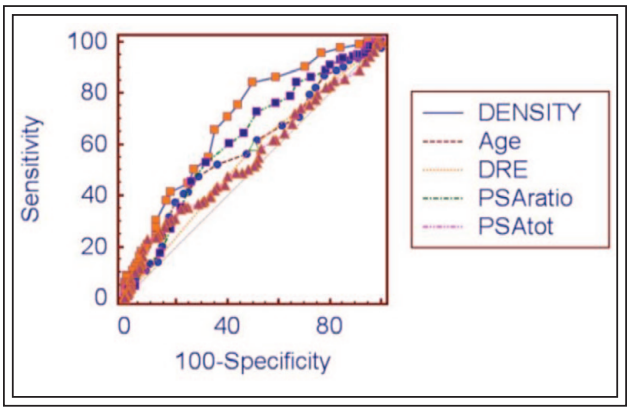

Figure 1. ROC curves for univariate variables predicting positive biopsy.

TABLE 5. **Multivariate logistic regression analysis of factors associated with prostate cancer used in standard model (model A; n = 265)**

		95% CI for odds ratio		
Included	B (SE)	Lower	Odds ratio	Upper
Constant	.49 (.58)	1.63		
PSA total	.12 (.07)	.98	1.13	1.31
PSAf/t	-6.25(2.01)*	.0009	.002	.10
DRE	-.45 (.26)	.95	1.57	2.59

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio; DRE = digital rectal examination
Note: R^2 = .01 (Hosmer & Lemeshow), .06 (Cox & Snell), .08 (Nagelkerke). Model $\chi^2(3) = 15.76$, $p < .01$.
*$p < .05$

modified model (model B) based on information from PSA density. We also included PSAf/t as a predictor in model B because an initial multivariate model using all predictors entered simultaneously revealed that PSAf/t was also a significant predictor of positive biopsy (data not shown).

Overall, model A (standard) was a statistically significant model of positive biopsy for prostate cancer ($\chi^2(3) = 15.76$, $p < .01$; Table 5). PSAf/t (Beta = -6.25, $p < .05$; OR =.002) was a significant predictor of positive biopsy. However, PSA total and DRE were not significant predictors within the model ($p > .05$). Model B (modified) was also a significant model of positive biopsy ($\chi^2(2) = 35.10$, $p < .01$; Table 6). In this model, PSAf/t was a worse predictor than in model A and no longer statistically significant (beta = -3.73, $p > .05$; OR = .02). In contrast, PSA density had a very strong impact on prediction of positive biopsy (beta = 6.97, $p < .05$; OR =1067.93).

Using a direct comparison of the AUC from the two ROC curves, we found that model B was significantly better at discriminating positive and negative biopsy than model A ($z = 2.58$, $p < .05$; Table 7, Figure 2). The models had comparative sensitivity, but model B had higher specificity (61% versus 44%). Therefore, the modified model that only included PSAf/t and PSA density was overall a significantly better model at discriminating positive and negative biopsies than the model with PSA total, PSAf/t and DRE. The performance of model B somewhat varied between three clinical age groups, Table 7. Although the AUC was highest in the 70+ age group, the specificity for this group (43%) was much lower than the 60-69 group (65%). The performance of the individual predictors also changed with each age group, Table 8. The lack of statistical significance for PSAf/t was likely due to the 50-59 age group, where neither variable was a significant predictor of positive biopsy (although the OR for PSA density was still very large). In contrast, both predictors were significant in the 60-69 and 70+ groups.

Cancer aggressiveness

With limited data available on aggressiveness of cancers diagnosed in this sample (n = 96), we primarily used categorical analyses as opposed to logistic regression, which is not as appropriate for sample sizes

TABLE 6. **Multivariate logistic regression analysis of factors associated with diagnosis of prostate cancer used in modified model (model B; overall; n = 321)**

		95% CI for odds ratio		
Included	B (SE)	Lower	Odds ratio	Upper
Constant	-.37	.69		
PSAf/t	-3.73 (1.95)	.00	.02	1.09
PSA density	6.97 (1.73)*	35.99	1067.93	31693.07

PSAf/t = free to total prostate-specific antigen ratio; PSA = prostate-specific antigen
Note: R^2 = .03 (Hosmer & Lemeshow), .10(Cox & Snell), .14 (Nagelkerke). Model $\chi^2(2) = 35.10$, $p < .01$.
*$p < .05$

TABLE 7. **Areas under the curve (AUC) and sensitivity and specificity for model A versus model B in predicting positive biopsy**

Model	N	Area (SE)	95% CI lower	95% CI upper	Sensitivity	Specificity
Model A (PSA total, PSAf/t, DRE)	265	.59* (04)	.53	.66	74%	44%
Model B (PSAf/t, PSA density)						
Overall	321	.66* (.03)	.60	.72	72%	61%
Age 50-59	74	.57 (.07)	.44	.70	41%	73%
Age 60-69	155	.63* (.05)	.54	.72	60%	65%
Age 70+	92	.66* (.07)	.53	.79	89%	43%

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio; DRE = digital rectal exam
*significantly different from 0.5, $p < .05$

under 100. Clinicopathological characteristics of these patients are shown in Table 9.

We examined the relationship between PSA density and cancer aggressiveness using a cut off of .15, which has been used clinically to determine appropriateness of biopsy in some clinics and patients with densities greater than these cut offs have a greater probability of aggressive cancer.[14,15,18,27,28] In the current study, we also found that PSA density of .14-.15 had the best balance of sensitivity and specificity in predicting a positive biopsy. We categorized clinical stage into two groups: stage < pt3 and ≥ pt3. Due to small numbers in each group, we defined "expansion outside the prostate" as a dichotomous variable to include any cancer that had seminal vesicle invasion, perineural invasion, venous invasion, or lymphatic invasion. PSA density (cut off = .15) was significantly associated with two measures of aggressive cancer: clinical stage ($\chi^2(1) = 4.62$, $p = .03$, Phi = .22, Table 10) and cancer with expansion outside of prostate ($\chi^2(1) = 16.43$, $p < .001$, Phi = .41, Table 11). PSAf/t was also significantly associated with expansion outside the prostate ($\chi^2(1) = 8.62$, $p < .05$, Phi = -.33, Table 11). However, the majority of patients had a ratio < .24 (97%) so these results should be interpreted with caution.

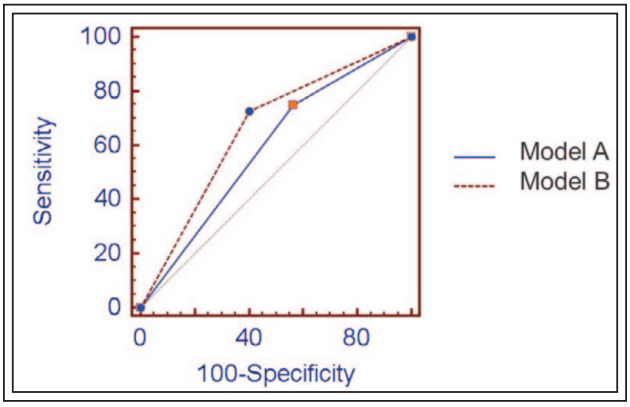

Figure 2. ROC curves for multivariate model A (PSA total, DRE, PSAf/t) and model B (PSA density, PSAf/t) in predicting positive biopsy.

In contrast, PSA total ($\chi^2(2) = 3.95$, $p > .05$) and DRE ($\chi^2(1) = 1.69$, $p > .05$) were not significantly associated with cancer that had expansion outside of the prostate. Similarly, PSA total ($\chi^2(2) = 1.26$, $p > .05$), PSAf/t ($\chi^2(1) = .63$, $p > .05$) and DRE ($\chi^2(1) = 2.01$, $p > .05$) were not associated with clinical stage. No variables were significantly associated with other measures of aggressiveness, such as tumor size, proportion of the gland that is tumor and Gleason score (data not shown).

Discussion

The results of this study support a growing body of evidence supporting the utility of PSA density in predicting which patients are likely to have a positive result upon prostate biopsy, as well as more aggressive cancer. In this study, incorporating information about PSA density with PSAf/t ratio maintained similar sensitivity, but increased specificity in biopsy prediction compared to using information from PSA total, DRE and PSAf/t. Moreover, PSA density was significantly associated with some measures of cancer aggressiveness, such as clinical stage and pathological stage (whereas PSA total and DRE were not). Age was also an important factor as the performance of these models varied with men in different decades. In

TABLE 8. **Multivariate logistic regression analysis of factors associated with diagnosis of prostate cancer using model B separated by age range**

Age range				95% CI for odds ratio		
	N	Included	B (SE)	Lower	Odds ratio	Upper
50-59[#]	74	Constant	-.94		.39	
		PSAf/t	-1.33 (3.68)	.00	.27	356.93
		PSA density	5.82 (3.43)	.41	337.07	280183.31
60-69[##]	155	Constant	.15		1.16	
		PSAf/t	-7.60 (3.30)*	.00	.001	.32
		PSA density	5.95 (2.33)*	3.96	384.01	37215.94
70+[###]	92	Constant	-.51		.60	
		PSAf/t	-3.12 (3.70)*	.00	.40	62.00
		PSA density	12.44 (5.07)*	12.22	251995.63	5.198E9

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio
[#]R^2 = .09 (Hosmer & Lemeshow), .05 (Cox & Snell), .07 (Nagelkerke). Model $\chi^2(2) = 4.08$, p = .13.
[##]R^2 =.04 (Hosmer & Lemeshow), .13 (Cox & Snell), .17(Nagelkerke). Model $\chi^2(2) = 21.48$ p < .01. *p < .05
[###]R^2 =.07 (Hosmer & Lemeshow), .15 (Cox & Snell), .22 (Nagelkerke). Model $\chi^2(2) = 15.27$, p < .01. *p < .05

TABLE 9. **Clinicopathological characteristics in patients with prostate cancer undergoing radical prostatectomy (n = 96)**

	N	Mean (SD)	Median (IQR)
Prostate volume (cc)	96	40.89 (19.26)	37.45 (20.4)
Prostate weight (g)	90	51.42 (20.42)	45.0 (22.25)
Pathology Gleason score (/10)	96	7.02 (.85)	7.0 (.75)
Tumor size (mm)	67	15.96 (7.45)	15.0 (9.0)
Proportion of prostate involved by tumor	92	20.86 (20.47)	15.0 (17.5)
Pathology Gleason score (n = 96)	**N**	**%**	
6	24	25.0%	
7	54	56.3%	
8-10	18	18.7%	
Clinical stage (n = 96)			
pT2a	7	7.3%	
pT2b	3	3.1%	
pT2c	46	47.9%	
pT3	5	5.2%	
pT3a	21	21.9%	
pT3b	12	12.5%	
Pathological stage (n = 96)[#]			
Extraprostatic extension	31	32.0%	
Seminal vesicle invasion	11	11.5%	
Perineural invasion	74	77%	
Venous invasion	2	2.1%	
Lymph invasion	6	6.4%	
Metastasis (n = 96)			
Lymphatic	4	4.2%	

[#]some individuals had more than one site of invasion

TABLE 10. **Association between pre-biopsy factors and cancer stage (> or < stage pt3)**

Grouping	Stage < pt3 N (%)	Stage > = pt3 N (%)	Total N (%)
PSA total			
< 4	2 (67%)	1 (33%)	3 (100%)
4-10	47 (62%)	29 (38%)	76 (100%)
10+	7 (47%)	8 (53%)	15 (100%)
PSA density*			
< .15	22 (76%)	7 (24%)	29 (100%)
>= .15	34 (52%)	31 (48%)	65 (100%)
PSAf/t			
< .24	46 (61%)	29 (39%)	75 (100%)
>= .24	1 (100%)	0	1 (100%)

PSA = prostate-specific antigen
PSAf/t = free to total prostate-specific antigen ratio
*significant chi-square association (p < .05)

particular, men aged 50-59 seem to be the most difficult to predict with these tools, although the sample in this age group was also smaller.

Similar to other studies, we found that PSA density was associated with both positive biopsy[11,16,20] and measures of aggressiveness.[11,15,16,21-25,27-29] Notably, the effect size in our study was quite substantial compared to others. Increased PSA density was associated with a greater than 1000 increase in the odds of a positive biopsy relative to the odds of a negative biopsy. We also confirmed previous results showing that PSA density is better than PSA at predicting either diagnosis and cancer aggressiveness.[14,15,17-20-25] In this study, we found that a cut off of .15 was optimal, whereas other studies have also found 0.2,[22] 0.3[29] or 0.35[30] to be most effective. Variation in cut off levels may be related to whether the models were univariate or multivariate, methods of calculating PSA density or the outcome measured.

Although PSA total was independently associated with positive biopsy in univariate analyses similar to other studies,[12,16,28,31] neither PSA total nor DRE were associated with biopsy result or aggressiveness when combined in the multivariate models. Notably, the AUC of DRE alone was only .54, suggesting an almost equal probability that a man with an abnormal DRE has a positive or negative biopsy. The value of this predictor did not improve when combined with other variables in multivariate analyses. The continued use of the DRE when other available tests with much better discrimination are available should be questioned given the negative consequences of false positives. It has been suggested that age-specific PSA total ranges could be adopted as an indirect method for accounting for prostate size.[26] Although this is a limited sample, we found that PSA total was only a moderate predictor of positive diagnosis in 70+ men. For men under 70, the AUC was only slightly better than .50. Therefore, for the majority of the population assessed, total PSA was not useful. In another study, age-specific PSA cut offs missed 20% to 60% of cancers in men older than 60 years of age.[15] Therefore, although PSA total has some value in predicting prostate cancer in older men, on the whole, it appears to be only relevant within the context of prostate size. Without TRUS estimated prostate size, PSA total loses its ability to discriminate between positive and negative biopsies.

TABLE 11. **Association between pre-biopsy factors and expansion outside prostate**

Grouping	Localized tumor N (%)	Expansion outside prostate N (%)	Total N (%)
PSA total			
< 4	2 (67%)	1 (33%)	3 (100%)
4-10	15 (19%)	63 (81%)	78 (100%)
10+	3 (20%)	12 (80%)	15 (100%)
PSA density*			
< .15	14 (45%)	17 (55%)	31 (100%)
>= .15	6 (9%)	59 (91%)	65 (100%)
PSAf/t*			
< .24	13 (17%)	63 (83%)	76 (100%)
>= .24	2 (100%)	0	2 (100%)

PSA = prostate-specific antigen; PSAf/t = free to total prostate-specific antigen ratio
*significant chi-square association (p < .05)

The role that PSAf/t plays in cancer detection is less clear. Although it was an independent predictor of positive biopsy and when used in conjunction with PSA total and DRE in model A, it was not a good predictor when combined with PSA density in model B. Its performance was most optimal for men aged 60-69; however, the smaller sample sizes in the other age groups make it difficult to compare. Previous research on PSAf/t is mixed,[32] with some recent studies also finding poor discrimination for PSAf/t for organ confined-disease.[16,17] However the sample sizes in these studies were particularly small for this type of analysis. In our center, PSAf/t is only generated for patients with total PSA between 4 ug/L and 10 ug/L so its usefulness is restricted to that population.

Many centers/clinicians do not use TRUS prior to biopsy and/or do not calculate PSA density using TRUS estimates of prostate size. The reasons for this vary, including the cost of TRUS and that urologists are commonly the primary physician performing assessments of prostate health. However, the current results suggest that there is value in using PSA density to avoid unnecessary biopsies that are likely to lead to a negative biopsy result or a positive biopsy of a low risk cancer. A man that is referred for biopsy with a high PSA total value and few or no other indications could be first assessed with TRUS to estimate the size of the prostate and rule out gland size as a reason for high PSA. Following thorough discussion about the risks and benefits of prostate biopsy, some men may choose not to proceed with biopsy at that time. These men could continue to track PSA over time with their family physician or urologist, but avoid a biopsy until more evidence builds that they may have aggressive cancer. This process is currently used for a small proportion of patients at our center that are directly referred for biopsy from family physicians, a process that reduces wait times for assessment because of a small number of urologists in the region. Although there is a cost to using TRUS, the results of this study suggest that potential benefits of reducing unnecessary harm may outweigh the cost associated with performing biopsies on every man with either high total PSA or abnormal DRE in order to catch all possible cancers. Alternatively, information about PSA density determined during biopsy could be used to help the clinician and patient decide whether to stay on active surveillance or proceed with treatment following a positive diagnosis.[18,23,25,27,29]

A limitation of this study was the lack of data on cancer aggressiveness. We were not able to examine different forms of expansion outside the prostate to determine if there were differences in type of expansion. The fact that PSA density was only related to clinical stage and pathological stage could have been a power issue. Alternatively, there may be other biological factors that better explain tumor aggressiveness than factors related to the presence or absence of cancer (e.g. certain biomarkers).[10] The number of positive cores on biopsy is often a good predictor of cancer aggressiveness.[32] However, the purpose of this study was restricted to examining pre-biopsy measures in an effort to avoid unnecessary biopsies. Research of other biomarkers of prostate cancer may reveal what better characterizes aggressive and metastatic prostate cancer.

Conclusion

In conclusion, our study suggests that using TRUS to image the prostate and calculate PSA density adds substantial predictive power to diagnostic testing for prostate cancer. There is clinical value in using TRUS imaging to improve detection rates of aggressive prostate cancer and depending when used, this information may help reduce unnecessary biopsies or refine treatment plans after initial diagnosis. □

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