


# Prostate volume index and prostatic chronic inflammation have an effect on tumor load at baseline random biopsies in patients with normal DRE and PSA values less than 10 ng/ml: results of 564 consecutive cases

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## Abstract

**Background:** To assess the association of prostate volume index (PVI), defined as the ratio of the central transition zone volume (CTZV) to the peripheral zone volume (PZV), and prostatic chronic inflammation (PCI) as predictors of prostate cancer (PCA) load in patients presenting with normal digital rectal exam (DRE) and prostate-specific antigen (PSA)  $\leq 10$  ng/ml at baseline random biopsies.

**Methods:** Parameters evaluated included age, PSA, total prostate volume (TPV), PSA density (PSAD), PVI and PCI. All patients underwent 14 core transperineal randomized biopsies. We considered small and high PCA load patients with no more than three (limited tumor load) and greater than three (extensive tumor load) positive biopsy cores, respectively. The association of factors with the risk of PCA was evaluated by logistic regression analysis, utilizing different multivariate models.

**Results:** 564 Caucasian patients were included. PCA and PCI were detected in 242 (42.9%) and 129 (22.9%) cases, respectively. On multivariate analysis, PVI and PCI were independent predictors of the risk of detecting limited or extensive tumor load. The risk of detecting extensive tumor load at baseline biopsies was increased by PSAD above the median and third quartile as well as PVI  $\leq 1$  [odds ratio (OR)=1.971] but decreased by PCI (OR=0.185; 95% CI: 0.088–0.388).

**Conclusions:** Higher PVI and the presence of PCI predicted decreased PCA risk in patients presenting with normal DRE, and a PSA  $\leq 10$  ng/ml at baseline random biopsy. In this subset of patients, a PVI  $\leq$  or  $>1$  is able to differentiate patients with PCA or PCI.

**Keywords:** prostate biopsy, prostate cancer, prostate-specific antigen, prostate tumor grade, prostate volume index, prostatic chronic inflammation, tumor volume

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## Introduction

Prostate cancer (PCA) is a worldwide age-related disease associated with elevated prostate-specific-antigen (PSA) levels. Benign prostatic hyperplasia (BPH), prostatitis and other prostatic conditions can also lead to an increased PSA level. Thus, it is considered to be a prostate-specific but not a cancer-specific marker. PSA is a fundamental laboratory examination in the management of PCA, but the entire clinical scenario needs to be considered, including the digital rectal examination (DRE), in the selection of the patients who should undergo prostatic biopsy.<sup>1,2</sup> Actually, the patients presenting with normal DRE and PSA levels between 2 and 10 ng/ml represent a nonhomogeneous category that can include patients with PCA or other benign conditions. For this reason, they need to be carefully studied in order to avoid unnecessary prostate biopsies. In this group, PSA density (PSAD) is shown to have a limited predictive power because of its close dependence on total prostate volume (TPV). In this subset of patients, new markers and multiparametric magnetic resonance imaging (mp-MRI) do not show enough evidence to recommend their use at baseline biopsies and a risk calculator involving different parameters has been suggested in order to provide a definite indication for prostate biopsy.<sup>1,3</sup>

In the literature, many PCA predictive factors have been proposed with the intent of stratifying this subset. Of these, prostate volume (PV), that can mirror the possible presence of benign prostatic enlargement and prostatic chronic inflammation (PCI) seem to have a pivotal role in PCA prediction.<sup>4,5</sup> In this context, our research group previously evaluated the predictive role of prostate volume index (PVI), defined as the ratio of the volume of the central transition zone (CTZV) to the peripheral zone volume (PZV) of the prostate. We showed an inverse association between PVI and PCA risk.<sup>6,7</sup> In particular, we demonstrated that PVI is able to stratify the risk of PCA for biopsy-naïve patients.<sup>8</sup>

On the other hand, the correlation between PCI and PCA is unclear and debated. Our group has previously shown an inverse association between PCI and PCA risk.<sup>9-11</sup> On the contrary, clinical studies have shown that the personal history of prostatitis, as well as symptom duration, were significantly associated with an increased risk of PCA.<sup>12</sup> Further, Gurel and colleagues demonstrated chronic prostatic inflammation being

associated with a 30% increase in the PCA risk.<sup>13</sup> Interestingly, a correlation between PCI and BPH (and thus, with PV) has been proposed.<sup>10,14</sup>

In this study, we aimed to assess the role of both PVI and PCI in the risk of PCA as well as the tumor load in patients presenting with normal DRE and PSA levels  $\leq$  10 ng/ml at baseline random biopsies.

## Materials and methods

### *Study population and inclusion criteria*

The study had Institutional Board Review approval. All patients signed informed consent for data collection and analysis. The records of 1910 White patients were retrospectively evaluated during a period from September 2010 to September 2017. The study evaluated patients who opted to undergo baseline random biopsies with normal DRE and PSA levels less than or equal 10 ng/ml. Indications to perform biopsies were increased PSA levels, abnormal DRE or abnormal imaging of the prostate. Baseline biopsies were systematically taken in different zones of the gland according to a standard pattern including 14 cores. Analysis of adjunctive targeted cores were excluded in order to avoid skewing phenomena. The number of cores sampled was not increased according to the TPV.

### *Evaluation of patients and prostates at baseline biopsies*

Each patient was evaluated for age (years), body mass index (BMI, kg/m<sup>2</sup>), and PSA (ug/l). DRE findings were coded as normal or abnormal. TPV and central transition zone volume (CTZV) were directly measured before biopsy by transrectal ultrasound (TRUS). In both cases, volume was measured by the formula for an ellipsoid and converted into volume (ml). The volume of the peripheral zone of the prostate (PZV) was measured by subtracting CTZV from TPV, and PVI was calculated as the ratio of CTZV to PZV. PSAD was also computed and calculated as the ratio of total PSA to TPV.

### *Evaluation of cores*

Each core was evaluated by our dedicated pathologist, who systematically assessed the following features: (a) length (mm); (b) International Society for Urological Pathology (ISUP) tumor

grade group;<sup>15</sup> (c) number of positive cores (from 0 to 14); (d) percentage of cancer involving each core; (e) prostatic intraepithelial neoplasia (PIN); (f) PCI; (g) glandular atrophy; and (h) atypical small acinar cell proliferation. In the present analysis, the following features were considered: ISUP tumor grade group, number of cores involved by cancer and PCI which has been evaluated. The presence of PCI was defined as type IV, according to the National Institutes of Health classification (NIH).<sup>16</sup>

### Study design

The study was designed to investigate the association of PVI and PCI, among other factors, with the risk of intraprostatic tumor load which was evaluated by the C (NPCs) and stratified by absent (0 NPC), limited (1–3 NPC), and extensive (>3 NPC), tumor load in patients with normal DRE and  $\leq 10$  ng/ml PSA levels.

### Statistical methods

Summary statistics of population and subpopulations were computed. Continuous variables were evaluated as medians with relative interquartile ranges (IQRs). Categorical factors were evaluated as frequencies with relative rates. PSAD, because it is expressed as a nonhomogeneous measure (ratio of PSA levels on prostate volumes), was transformed into natural logs. Differences of factors between groups were assessed by the Kruskal–Wallis test for continuous variables and by Chi-squared test or Fisher's exact test when appropriate for categorical factors. The association of factors with the risk of tumor load was assessed by the multinomial logistic regression model (univariate and multivariate analysis). The software used to run the analysis was IBM-SPSS version 20 (SPSS Inc., IBM Corp., Armonk, NY, USA). All tests were two sided, with a significance level of  $p < 0.05$ .

### Results

We evaluated 564 patients who met the inclusion criteria. Statistics of the different parameters are reported in Table 1. Overall, PCA was detected in 242 (42.9%) cases, of whom 138 (24.5%) had one to three positive cores and 104 (18.4%) had more than three positive cores. Differences among groups were all significant except for BMI and PSA. The medians PVI were 1, 0.82 and 0.84 in patients with negative, limited and extensive

tumor load, respectively. Considering PCA patients, 57% had one to three positive cores (limited) and 43% more than three positive cores (extensive). Patients with more than three positive cores showed higher rates of aggressive tumors (ISUP > 3: 10.6% versus 2.9%) than cases with limited tumor load. Negative cases had higher median values of PVI (1.0) than cases with limited (0.82) or extensive (0.84) tumor load, as well as more likely to have PCI (32.5%) than patients with limited or extensive tumor load (10.1% and 9.6%, respectively). Patients with extensive tumor load showed higher PSAD [0.21 (ng/ml)/ml] than cases with limited tumor load [0.16 (ng/ml)/ml] or negative subjects [0.13 (ng/ml)/ml]. Finally, patients with extensive tumor load were older and had smaller prostates when compared with patients with limited tumor load or negative cases.

Table 2 shows univariate and multivariate models of the factors associated with the risk of detecting limited or extensive tumor load. On univariate analysis, age [odds ratio (OR) = 1.054;  $p < 0.0001$ ], TPV (OR = 0.972;  $p < 0.0001$ ), PSAD (2.126;  $p = 0.001$ ), PVI (0.355;  $p < 0.0001$ ) and PCI (0.233;  $p < 0.0001$ ) were associated with the risk of detecting limited tumor load compared with negative cases; moreover, the association was positive for age and PSAD, but negative for TPV, PVI, and PCI. On multivariate analysis, the independent predictors of the risk of detecting limited tumor load, is shown in model I including, age (OR = 1.072;  $p < 0.0001$ ), PSAD (Table 2) (1.938;  $p = 0.005$ ), PVI (0.355;  $p < 0.0001$ ), and PCI (0.233;  $p < 0.0001$ ), as well as shown in model II, including age (OR = 1.075;  $p < 0.0001$ ), TPV (Table 2) (OR = 0.977;  $p = 0.002$ ), PVI (0.456;  $p = 0.009$ ), and PCI (0.256;  $p < 0.0001$ ). When comparing patients with extensive tumor load with negative cases, all factors were associated with the risk of extensive tumor load on univariate analysis; moreover, the association was positive for age (OR = 1.063;  $p < 0.0001$ ), and PSAD (7.482;  $p < 0.0001$ ), but negative for TPV (OR = 0.932;  $p < 0.0001$ ), PVI (0.287;  $p < 0.0001$ ), and PCI (0.110;  $p < 0.0001$ ). On multivariate analysis, all factors were independent predictors, as shown in model I, including age (OR = 1.077;  $p < 0.0001$ ), PSAD (Table 2) (OR = 7.033;  $p < 0.0001$ ), PVI (0.387;  $p = 0.005$ ) and PCI (0.157;  $p < 0.0001$ ) and in model II independent predictors of risk include age (OR = 1.086;  $p < 0.0001$ ), TPV (0.932;  $p < 0.0001$ ), and PCI (0.232;  $p < 0.0001$ ) but not PVI (0.631;  $p < 0.198$ ). TPV was the only independent predictor of extensive

**Table 1.** Statistics of factors at baseline biopsies in patients with normal digital rectal exam and PSA with 10 ng/ml.

Factors	Population	0 positive cores	1–3 positive cores	>3 positive cores	p value
n (%)	564	322 (57.1)	138 (24.5)	104 (18.4)	
Age, years					<0.0001
Median (IQR)	66 (59–71)	64 (57–69)	67 (62–72)	69 (62–73)	
Body mass index, kg/m <sup>2</sup>					0.57
Median (IQR)	26.1 (24.4–28.1)	26.1 (24.3–28.1)	26.1 (24.5–28.1)	26.4 (24.5–28.7)	
Prostate-specific antigen (PSA), ng/ml					0.404
Median (IQR)	5.9 (4.8–7.4)	6 (4.8–7.5)	5.68 (4.8–6.8)	6 (4.7–7.8)	
Total prostate volume (TPV), ml					<0.0001
Median (IQR)	39.4 (28.3–52.8)	43.9 (32.9–58.6)	35.3 (26.9–46.4)	28.5 (22–39.3)	
Central transition zone volume (CTZV), ml					<0.0001
Median (IQR)	18.2 (12.1–26.2)	22 (15–30.8)	16.5 (10.1–23.5)	12.8 (9–17.9)	
Peripheral zone volume (PZV), ml					<0.0001
Median (IQR)	19.7 (15.4–25.3)	21.2 (16.4–27)	19.2 (15.6–24.1)	12.8 (9–17.9)	
PSA density, (ng/ml)/ml*					<0.0001
Median (IQR)	0.15 (0.11–0.21)	0.13 (0.09–0.18)	0.16 (0.11–0.21)	0.21 (0.15–0.27)	
Prostate volume index**					<0.0001
Median (IQR)	0.92 (0.70–1.23)	1 (0.75–1.3)	0.82 (0.62–1.08)	0.84 (0.61–1.01)	
Prostatic chronic inflammation (PCI), n (%)					<0.0001
Absent	435 (77.1)	217 (67.4)	124 (89.9)	94 (90.49)	
Present	129 (22.9)	105 (32.5)	14 (10.1)	10 (9.6)	
ISUP grade group					
1			104 (75.4)	48 (46.2)	
2			21 (15.2)	32 (30.8)	
3			9 (6.5)	13 (12.5)	
4			4 (2.9)	6 (5.8)	
5			0 (0.0)	5 (4.8)	
Number of positive cores					
Median (IQR)			2 (1–3)	5 (5–7)	
*Ratio of PSA to TPV. **Ratio of CTZV to PZV. IQR, interquartile range; ISUP, International Society of Urological Pathology.					

**Table 2.** Factors associated with the risk of detecting positive cores for cancer at baseline biopsies in 564 cases with normal digital rectal exam and PSA within 10 ng/ml.

Parameters	1–3 positive cores versus none		>3 positive cores versus none		>3 positive cores versus 1–3	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Univariate models						
Age	1.054 (1.027–1.081)	<0.0001	1.063 (1.032–1.054)	<0.0001	1.009 (0.976–1.042)	0.610
TPV	0.972 (0.960–0.984)	<0.0001	0.932 (0.814–0.950)	<0.0001	0.959 (0.940–0.979)	<0.0001
PSAD	2.126 (1.370–3.299)	0.001	7.482 (4.304–13.007)	<0.0001	3.519 (1.948–6.355)	<0.0001
PVI	0.355 (0.213–0.592)	<0.0001	0.287 (0.158–0.522)	<0.0001	0.808 (0.406–1.608)	0.543
PCI	0.233 (0.128–0.425)	<0.0001	0.220 (0.110–0.439)	<0.0001	0.942 (0.401–2.219)	0.891
Multivariate models I						
Age	1.072 (1.042–1.102)	<0.0001	1.077 (1.044–1.111)	<0.0001		
TPV						
PSAD	1.938 (1.225–3.066)	0.005	7.033 (3.860–12.812)	<0.0001		
PVI	0.354 (0.204–0.613)	<0.0001	0.387 (0.198–0.796)	0.005		
PCI	0.234 (0.126–0.437)	<0.0001	0.157 (0.093–0.416)	<0.0001		
Multivariate models II						
Age	1.075 (1.045–1.105)	<0.0001	1.088 (1.054–1.123)	<0.0001		
TPV	0.977 (0.962–0.991)	0.002	0.932 (0.312–0.952)	<0.0001	0.974 (0.950–1.000)	0.047
PSAD					1.931 (0.931–4.002)	0.077
PVI	0.456 (0.252–0.823)	0.009	0.631 (0.313–1.272)	0.198		
PCI	0.256 (0.138–0.477)	<0.0001	0.232 (0.110–0.493)	<0.0001		

CI, confidence interval; OR, odds ratio; PCI, prostatic chronic inflammation; PSAD, prostate-specific-antigen density; PVI, prostate volume index; TPV, total prostate volume.

tumor load compared with limited tumor load and the association was found to be inversely proportional (OR=0.974;  $p=0.047$ ).

Table 3 shows several multivariate models depicting the risk of detecting limited tumor load (one to three positive cores) or extensive tumor load (more than three positive cores). In these models, age, TPV, and PSAD were stratified according to their quartiles, while PVI remained a continuous variable. ORs and 95% confidence intervals (CIs), as well as adjustments are also reported. Limited tumor load

compared with negative cases was independently predicted by age groups, PSAD above the third quartile, PVI, and PCI (model I), as well as by older age groups, TPV above the median, PVI, and PCI (model II); moreover, associations were significant, as indicated by the OR 95% CI. When comparing extensive tumor load with negative cases, the risk of detecting PCA was predicted by age groups above the median, PSAD groups above the median, higher PVI and PCI (model I), as well as by age groups above the median, TPV groups, and PCI but not PVI (model II);

**Table 3.** Association of factors with the risk of prostate cancer with one to three positive cores or more than three positive cores in patients having normal digital rectal exam and PSA values within 10 ng/ml.

Multivariate models	1–3 positive cores (n = 138) versus none (n = 322)		More than 3 positive cores (n = 104) versus none (n = 322)		
Multivariate model I					
Factors	OR (95% CI)	Adjusted OR (95% CI)	OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age					
<60	Reference		Reference		
60–76	2.242 (1.223–4.110)	2.266 (1.239–4.144)	2.014 (0.975–4.162)		
67–71	2.698 (1.412–5.156)	2.789 (1.467–5.300)	3.460 (1.650–7.255)	2.392 (1.288–4.442)	2.292 (1.240–4.234)
>71	4.344 (2.266–8.331)	4.395 (2.291–8.393)	5.023 (2.402–10.506)	3.436 (1.865–6.328)	3.415 (1.857–6.281)
PSAD					
<0.12	Reference		Reference		
0.12–0.15	1.316 (0.690–2.508)		2.630 (1.019–6.839)	2.582 (0.095–6.701)	
0.16–0.21	1.736 (0.933–3.230)		3.404 (1.352–8.568)	3.454 (1.375–8.679)	1.952 (1.016–3.751)
>0.21	2.740 (1.424–5.272)	2.023 (1.219–3.558)	12.898 (5.246–31.714)	12.445 (5.080–30.484)	6.959 (3.792–12.807)
PVI	0.382 (0.220–0.663)	0.355 (0.205–0.613)	0.403 (0.207–0.786)	0.432 (0.226–0.828)	0.419 (0.221–0.794)
PCI	0.231 (0.124–0.431)	0.232 (0.124–0.443)	0.192 (0.091–0.404)	0.194 (0.093–0.408)	0.198 (0.094–0.415)
Multivariate model II					
Factors	OR (95% CI)	Adjusted OR (95% CI)	OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age					
<60	Reference		Reference		
60–76	2.350 (1.275–4.332)	2.213 (1.210–4.048)	2.147 (1.037–4.443)	2.046 (0.994–4.210)	
67–71	2.900 (1.510–5.568)	2.647 (1.396–5.019)	3.706 (1.767–7.773)	3.613 (1.730–7.547)	2.477 (1.339–4.581)
>71	4.707 (2.446–9.058)	4.634 (2.416–9.888)	6.197 (2.949–13.024)	5.560 (2.692–11.482)	3.829 (2.088–7.020)
TPV					
<28.4	Reference		Reference		
28.4–39.4	0.586 (0.318–1.078)		0.322 (0.170–0.609)	0.308 (0.163–0.580)	0.337 (0.181–0.628)
39.5–52.8	0.403 (0.212–0.776)	0.545 (0.316–0.939)	0.211 (0.170–0.609)	0.186 (0.096–0.363)	0.198 (0.181–0.628)
>52.8	0.392 (0.201–0.767)	0.535 (0.302–0.946)	0.046 (0.016–0.132)	0.035 (0.013–0.095)	0.219 (0.014–0.382)
PVI	0.420 (0.238–0.342)	0.406 (0.230–0.718)	0.583 (0.290–1.171)		
PCI	0.248 (0.133–0.462)	0.253 (0.136–0.470)	0.229 (0.109–0.481)	0.218 (0.004–0.457)	0.219 (0.105–0.458)
CI, confidence interval; OR, odds ratio; PCI, prostatic chronic inflammation; PSA, prostate-specific antigen; PSAD, PSA density; PVI, prostate volume index; TPV, total prostate volume.					

**Table 4.** Multivariate models of factors associated with the risk of positive cores for prostate cancer in patients with normal digital rectal exam and PSA values within 10 ng/ml (see also Table 3).

Factors	1–3 positive cores ( <i>n</i> = 138) versus none ( <i>n</i> = 322)		More than 3 positive ( <i>n</i> = 104) cores versus none ( <i>n</i> = 322)
	Model I OR (95% CI)	Model II OR (95% CI)	Model I OR (95% CI)
<b>Age</b>			
<60	Reference	Reference	Reference
60–76	2.273 (1.242–4.161)	2.20 (1.213–4.064)	Reference
67–71	2.671 (1.410–5.029)	2.541 (1.344–4.806)	2.186 (1.185–4.034)
>71	3.971 (2.097–7.521)	4.343 (2.280–8.272)	3.152 (1.729–5.743)
<b>TPV</b>			
<28.4		Reference	
28.4–39.4		Reference	
39.5–52.8		0.529 (0.308–0.909)	
>52.8		0.461 (0.264–0.804)	
<b>PSAD</b>			
<0.12	Reference		Reference
0.12–0.15	Reference		Reference
0.16–0.21	Reference		2.029 (1.059–3.885)
>0.21	2.136 (1.291–3.536)		7.380 (4.034–13.513)
<b>PVI</b>			
>1	Reference	Reference	Reference
≤1	2.229 (1.409–3.525)	1.970 (1.229–3.168)	1.971 (1.150–3.376)
<b>PCI</b>			
Absent	Reference	Reference	Reference
Present	0.216 (0.116–0.403)	0.231 (0.129–0.444)	0.185 (0.088–0.388)

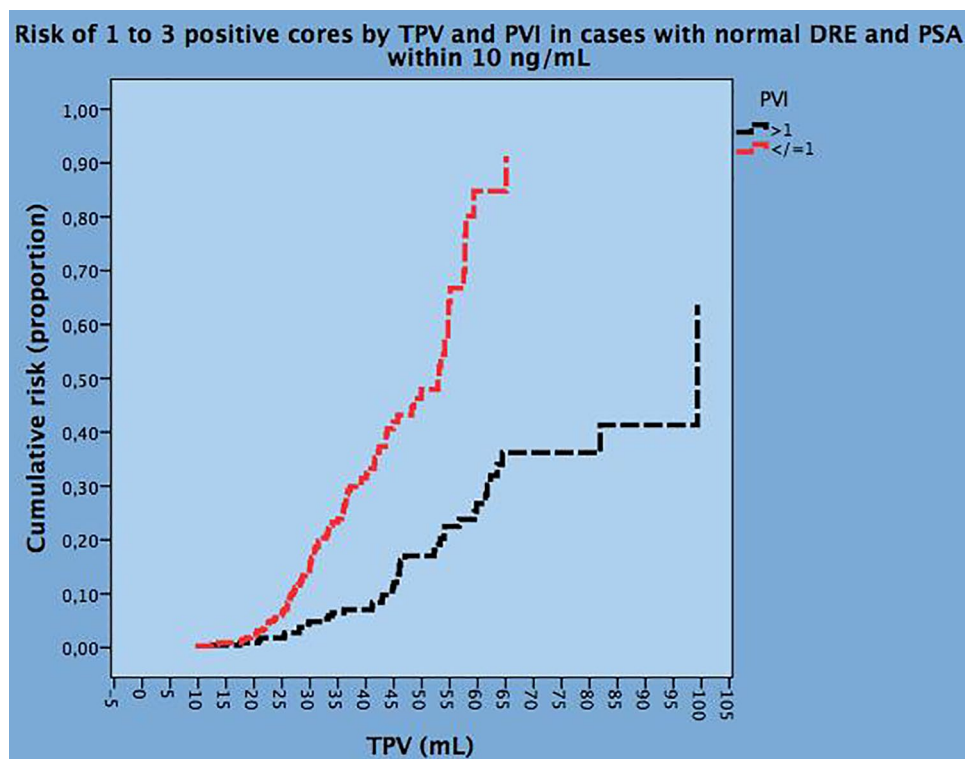
CI, confidence interval; OR, odds ratio; PCI, prostatic chronic inflammation; PSA, prostate-specific-antigen density; PVI, prostate volume index; TPV, total prostate volume.

associations with the risk were significant, as indicated by the 95% CI.

Table 4 shows multivariate stratified models in which PVI has also been dichotomized into PVI > 1 (reference group) and PVI ≤ 1 (risk group), to assess its ability to independently

predict the risk of detecting small or large tumors in patients with normal DRE and PSA values ≤ 10 ng/ml. OR and 95% CI are reported to evaluate the strength of this association between factors and the risk related to tumor load (see also Table 3). As shown in model I, the risk of detecting limited tumor load is stronger for increasing





**Figure 1.** Cumulative risk curves of detecting small cancers (one to three positive cores) by TPV stratified by PVI  $\leq 1$  or  $> 1$ .

As shown, the cumulative risk of increasing TPV increased if PVI  $\leq 1$ .

DRE, digital rectal examination; PSA, prostate-specific antigen; PVI, prostate volume index; TPV, total prostate volume.

age group, PSAD values above the third quartile, and PVI  $\leq 1$  (OR=2.229; 95% CI: 1.409–3.525) but decreased by PCI (OR=0.216; 95% CI: 0.116–0.403); moreover, all factors were significant as indicated by the OR 95% CI. In model II, the risk of detecting limited tumor load was increased by age groups, TPV values above the median and third quartile, PVI  $\leq 1$  (OR=1.970; 95% CI: 1.229–3.168), but decreased by PCI (OR=0.231; 95% CI: 0.129–0.444), with predictive factors all being significant as indicated by 95% CI of OR. In model I, the risk of detecting extensive tumor load at baseline biopsies was increased by increasing age groups, PSAD above the median and third quartile, as well as PVI  $\leq 1$  (OR=1.971; 95% CI: 1.150–3.376) but decreased by PCI (OR=0.185; 95% CI: 0.088–0.388) in multivariate model I.

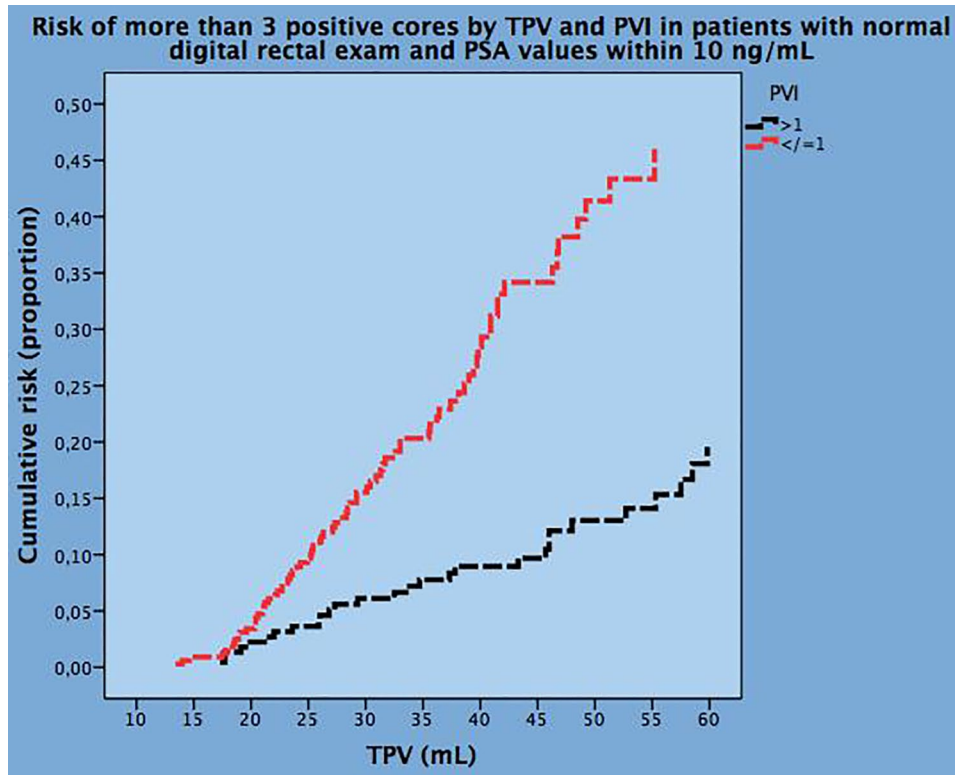
Figure 1 shows the cumulative risk curves of detecting limited tumor load by TPV stratified by PVI  $\leq 1$  or  $> 1$ . As shown, the cumulative risk of increasing TPV increased if PVI was  $\leq 1$ . Figure 2 depicts the cumulative risk curves of detecting extensive tumor load (more than three positive

cores) by TPV stratified by PVI  $\leq 1$  (increased cumulative risk) or  $> 1$  (decreased cumulative risk).

### Discussion

Patients with PSA less than 10 ng/ml and negative DRE represent a nonhomogeneous group because they can have many different benign prostate conditions as well as PCA. In this subset of patients, new markers and mp-MRI do not show enough evidence to recommend their use at baseline biopsies, and a risk calculator that uses different parameters has been suggested in order to provide a definite indication for prostate biopsy.<sup>1,3</sup> In this study, we considered a cohort of 564 patients with those characteristics who underwent an initial systematic prostate biopsy. In our cohort, PCA was present in 42.9% patients, and 57% had limited tumor load and 43% had extensive tumor load. PCI was present in 22.9% patients. PSA did not differentiate between patients with PCA or PCI. Elderly patients presenting with small prostates were likely to have extensive tumor load and more aggressive cancer.





**Figure 2.** Cumulative risk curves of detecting large tumors (more than three positive cores) by TPV, stratified by  $PVI \leq 1$  or  $> 1$ .

PSA, prostate-specific antigen; PVI, prostate volume index; TPV, total prostate volume.

On the contrary, men with large prostates were less likely to have cancer but more likely to have PCI. Increased PVI levels as well as the presence of PCI were independent PCA protective factors. An interesting finding was that a  $PVI \leq 1$  was the best predictor of the presence of limited or extensive tumor load. On the contrary, PSAD predicted the PCA risk only for values above the third quartile; in accordance with existing literature.<sup>17</sup>

PV increases in patients with BPH enlargement that can involve the transitional zone and is a response to specific micro-environmental changes that are related to systemic and local hormonal and non-hormonal aberrations.<sup>18</sup> On the other hand, the peripheral zone responds in a specific way to systemic and local changes to induce PCA.<sup>19</sup> In a smaller variable percent of cases PCA can also occur in the transitional zone and it can present in a different way.<sup>20</sup>

PV has been demonstrated to have an inverse correlation with prostate cancer risk.<sup>4,21–24</sup> Additionally, there may be a higher chance of

accurately sampling a cancer lesion with the biopsy needle in patients with smaller prostates compared to patients with larger prostates with similarly lesions. This phenomenon could also explain lower cancer detection rates in large prostates. However, this hypothesis is debated and has not been confirmed in the literature,<sup>25</sup> therefore in our clinical practice we did not increase the number of biopsy cores according to the PV.

PVI compares the variations of two important prostate regions and its increase reflects the age-related volume changes. Thus, our findings suggest that PVI should not only be considered just a measure, but a dynamic combination of age-related changes of histologically nonhomogeneous volumes of the two main prostate zones.<sup>6,7</sup> Further, we previously demonstrated that  $PVI \leq$  or  $> 1$  was associated with a positive or negative biopsy, respectively, in patients undergoing first random biopsy set.<sup>8</sup> According to these findings, in prostate-biopsy-naïve patients presenting with normal DRE and a  $PSA \leq 10$  ng/ml, a  $PVI \leq 1$  can be associated with a higher probability of having limited or extensive PCA load.

Inversely, a PVI  $> 1$  can be associated with a lower probability of having PCA and a higher probability of having PCI. In light of this evidence, PVI should be a part of the risk calculator used in the management of these patients with negative DRE and PSA  $\leq 10$  ng/ml in order to avoid unnecessary prostate biopsies.

Moreover, PCI retains a controversial role in its influence on the prostatic microenvironment and its effect on PCA. Some evidence suggests it has a pivotal role in PCA induction.<sup>12,13</sup> On the other hand, many findings suggest it has a protective role against PCA.<sup>5,9-11</sup> In the present study, we wanted to test the hypothesis that the presence of PCI could be associated with a decreased tumor load. When comparing patients bearing limited and extensive tumor loads with negative cases, PCI was an independent factor decreasing the risk of extensive tumor load in prostate cancer patients. These results are interesting because they further illustrate the biologic relationships between tumor volume and PCI.

Biological studies demonstrated that immunologic cells that are present in the prostatic microenvironment physiologically, can influence the growth of prostatic cells in a benign or malignant direction through the production of different inflammatory immune mediators in response to different noxious pathogens.<sup>26,27</sup> Furthermore, this can mirror the different expression of CD4-CD8 lymphocyte subtypes in accordance with the different noxious pathogens.<sup>28</sup> Specifically, some interleukins such as IL-17 secreted by T-lymphocytes in PCI, can influence macrophage activation and subsequently, the secretion of transforming-growth-factor-beta (TGF- $\beta$ ) subtypes correlated with BPH induction, in association with systemic and local hormonal changes.<sup>14</sup> These findings are confirmed by the frequent coexistence of PCI and BPH.<sup>29</sup> In the same way, the secretion of other mediators such as TGF- $\alpha$ , vascular endothelial growth factor, and various growth factors can contribute to PCA initiation.<sup>26,30</sup>

In this way, PCI can represent the link between PV and PCA and provides support to our findings. Confirmatory higher-level studies are required in order to assess these theories.

Due to its negative predictive value of PCA risk in patients who underwent an initial baseline random prostate biopsy, it should be considered in the management of these patients.

In the last few years, our research group has been focused on the relationship between PCA, PCI and PVI. According to our findings, PVI and PCI are independent factors able to predict prostate cancer load defined as the number of positive biopsy cores in patients who underwent a baseline prostate biopsy set.<sup>6,7,9-11</sup> Particularly, in the present report, we showed that PVI is able to discriminate between PCA and PCI, and PCI is associated with a low probability of detecting PCA in a cohort of patients with negative DRE and PSA less than 10 ng/ml. To the best of our knowledge, this is the first study that investigates this topic in this category of patients that represent a nonhomogeneous group because they can have many different benign prostate conditions as well as PCA. Importantly, we stratified the tumor load based on the number of positive cores at baseline prostate biopsy. Indeed, we previously demonstrated that extensive tumor load at the time of biopsy is a strong predictor of more aggressive PCA in terms of tumor upgrading and upstaging as well as unilateral or bilateral lymph node metastasis and seminal vesical invasion.<sup>31-34</sup> Also, we previously found that the number of positive cores can predict tumor upgrading in patients under active surveillance.<sup>35</sup> In this context, PVI, with other clinical parameters, including PSA, DRE and age, should be included in the risk calculator used in the management of patients in which the indication to perform a baseline prostate biopsy is unclear as well as in the prediction of tumor load that is closely related to PCA aggressiveness. On the other hand, the presence of PCI during baseline prostate biopsy should be considered in the management of patients with negative DRE, and PSA  $\leq 10$  ng/ml.

Our study has many strengths. First, it represents the results of a single center in which cores were evaluated by a single, dedicated pathologist. Second, all biopsies were baseline and taken in a standard fashion with the standard number of 14 cores which were systematic and representing different coded zones, including the transitional zone of the prostate. Third, the analysis did not consider targeted cores in order to avoid skewing phenomena. Fourth, TPV and CTZVs were measured in standard fashion in each patient by trained urologists, performing transperineal prostate biopsies. Fifth, PCI was investigated in each core in standard fashion.

However, our study also has several limitations. First, because it was retrospective and not

prospective, it has all the limitations related to these kinds of studies. Second, PV evaluations were performed using an ellipsoid (TRUS) method that has been demonstrated to have a non-negligible intra- and interobserver variability.<sup>36</sup> According to this evidence, volume parameters might have issues with statistical inconsistencies. Third, prostate volumes were only evaluated clinically; pathologic specimen measurement was not considered and therefore, measured prostate volumes might not reflect true prostate sizes. Finally, PCI was not graded, and inflammatory cells were not qualitatively assessed for immunologic components.

### Conclusion

In patients presenting with a normal DRE and PSA values less than or equal to 10 ng/ml, PVI and PCI were inversely associated with PCA risk and PCA load. PSA  $\leq$  10 ng/ml may be due to the presence of PCI or PCA. The presence of PVI  $\leq$  1 is associated with the presence of PCA, and PVI  $>$  1 is more likely to be associated with the presence of PCI. PVI should be considered as part of the risk calculator in the management of patients with negative DRE and PSA  $\leq$  10 ng/ml to avoid unnecessary prostate biopsies.

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The authors declare that they have no conflict of interest.

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