Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol

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PEPE P, ARAGONA F. Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol. *Can J Urol* 2013;20(1):6620-6624.

Introduction: *To evaluate Prostate Cancer Prevention Trial (PCPT) risk calculator versus prostate cancer gene 3 (PCA3) score versus case-finding protocol accuracy in prostate cancer diagnosis in patients with prostate-specific antigen (PSA) below 10 ng/mL submitted to repeat saturation biopsy (SPBx).*

Materials and methods: *From December 2010 to December 2011, 100 patients (median 66 years) underwent a SPBx (median 30 cores); the indications for repeat biopsy were those of a case-finding protocol: PSA values between 4.1 ng/mL-10 ng/mL or 2.6 ng/mL-4 ng/mL with F/T PSA ≤ 25% and ≤ 20%, respectively. All patients had negative digital rectal examination (DRE) and median PSA was 7.9 ng/mL. The performance of PCPT risk calculator (alone, combined with PSA free/total (F/T) or PCA3 score) and PCA3 score in comparison with the case-finding protocol results (alone or combined with PCA3 score) was retrospectively evaluated in terms of detection rate for cancer and number of avoided biopsies.*

Results: *Prostate cancer was found in 28 (28%) patients; in the presence and absence of prostate cancer median PCA3 score was 57 versus 35 ($p < 0.05$). Using PCPT risk calculator (cut off probability of 25%) combined with PCA3 score no prostate cancer would be missed avoiding 8% of unnecessary biopsies. PCA3 score > 20 missed 7.2% of cancer; the case-finding protocol combined with PCA3 score > 35 would save 22% of avoidable biopsies, missing no cancer if all patients with PSA F/T ≤ 15% would undergo prostate biopsy irrespective of PCA3 values.*

Conclusions: *PCA3 score improves PCPT risk calculator accuracy in prostate cancer diagnosis; moreover, PCA3 score combined with PSA F/T reduce number of unnecessary biopsies (about 20%).*

Key Words: PCPT risk calculator, PCA3, PSA free/total, saturation prostate biopsy, case-finding protocol, prostate cancer

Introduction

Prostate cancer is the second most frequent tumor diagnosed after introduction of prostate-specific antigen (PSA) in clinical practice; today, the main goal is to improve PSA accuracy, especially in presence of values below 10 ng/mL, in diagnosing clinically significant prostate cancer reducing the risk of overdiagnosis and number of unnecessary biopsies. Repeat biopsy constitutes one third of all biopsy procedures and many clinical findings (PSA free/total, PCA3 score) have been introduced to improve prostate cancer detection rate and reduce false positive rate.[1]

Accepted for publication December 2012

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Recently, prostate cancer risk calculators incorporating many factors have been proposed to evaluate the individual's risk for cancer and the results have been compared with PSA accuracy, especially, in patients enrolled in screening programs.[2-8] Although many nomograms and artificial neural network lack external validation[2,3] the majority of them improved the performance of PSA alone in diagnosing prostate cancer; otherwise, before introducing a nomogram or a risk calculator in clinical practice it is mandatory to evaluate the accuracy in our population.

The Prostate Cancer Prevention Trial (PCPT) risk calculator[4] is based on age, race, PSA value, digital rectal examination (DRE), family history and history of a previous negative biopsy; recently, other parameters (i.e., PSA free/total, PCA3 score, pro2PSA) have been added to improve the calculator's accuracy.[5] We evaluated and compared the accuracy of PCPT risk calculator in

diagnosing prostate cancer with that obtained using PCA3 score or a case-finding protocol (results have been previously published)[9] in patients with PSA below 10 ng/mL submitted to repeat saturation biopsy.

Materials and methods

From December 2010 to December 2011, 100 patients, all of Caucasian origin and between the ages of 52 and 72 years (median 66 years) with primary negative extended biopsy (median 18 cores) and negative family history for prostate cancer, underwent a saturation prostate biopsy (SPBx) (median 30; range: 24-38 cores) for persistent suspicious of cancer. The patients underwent DRE and a blood sample was taken for total and free PSA assay (Roche Diagnostics; Mannheim, Germany) and measurement of the PSA free/total (F/T) ratio. The indications for repeat biopsy were those of a case-finding protocol for early prostate cancer diagnosis:[9] abnormal DRE and persistently high or increasing PSA values between 4.1 ng/mL-10 ng/mL or 2.6 ng/mL-4 ng/mL with F/T PSA ≤ 25% and ≤ 20%, respectively. SPBx was performed transperineally using a tru-cut 18 gauge needle (Bard; Covington, Georgia, USA), a GE Logiq 500 PRO ecograph (General Electric; Milwaukee, Wisconsin, USA) supplied with a biplanar transrectal probe (5 MHz-6.5 MHz) under sedation and antibiotic prophylaxis. The prostate biopsy protocol included at least 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone.[10]

All patients had negative DRE and median PSA was 7.9 ng/mL (range: 3.7 ng/mL-10 ng/mL): 95 (95%) between 4 ng/mL-10 ng/mL and 5 (5%) between 2.6 ng/mL-4 ng/mL, respectively. From 3 to 10 days prior to performing SPBx, first-catch urine samples were collected following DRE (three strokes per lobe) and processed to quantify PCA3 and PSA mRNA concentrations using the PROGENSA PCA3 assay (Gen-Prob Inc. San Diego, California, USA); PCA3 score was calculated using the following equation: (PCA3 mRNA/PSA mRNA) x 1000.[11]

PCPT risk calculation was performed using the available formula.[12] The results obtained using the case-finding protocol were retrospectively compared with those of the PCPT risk calculator alone (age, race, PSA value, DRE, family history and history of a previous negative biopsy) or combined with PSA F/T values or PCA3 score. Decision curve analysis[13] was used to explore the clinical effects of the calculator; the method estimated a net benefit for prediction model by summing the benefits (true positives) and subtracting the false positives (avoidable biopsy). The best model displays the higher net benefit (true positives) throughout a range of threshold probabilities; the large majority of the patients would have a cut off probability to undergo prostate biopsy between 10% and 40%,[14] so this range was chosen for analysis.

The performance of PCPT risk calculator (alone, combined with PSA F/T or PCA3 score) and PCA3 score (cut off > 20 versus > 35) in comparison with the case-finding protocol results (alone or combined with PCA3 score) was retrospectively evaluated in terms of detection rate for cancer, number of avoided biopsies and missed prostate cancer; moreover, a probability (p) level of less than 0.05 was considered statistically significant.

Results

All patients had adequate concentrations of PCA3 and PSA mRNA to calculate PCA3 score which was equal to 45 (median; range 3-228); 86 (86%) and 77 (77%) patients had a PCA3 score greater than 20 and 35, respectively. The median PSA F/T value was 13.5% (range: 4%-25%): 100 (100%), 58 (58%) and 45 (45%) patients had a PSA F/T ≤ 25%, ≤ 20% and ≤ 15%, respectively.

A T1c prostate cancer was found in 28 patients (28%); median PSA was 8.3 ng/mL (range: 4.5 ng/mL-10 ng/mL) and Gleason score was 6 in 20 (71.4%) and 7 in 8 (28.6%) cases, respectively. Median positive cores were 2 (range: 1-14); greatest percentage of cancer was ≤ 50 and > 50% in 18 (64.2%) and 10 (35.8%) cases, respectively. The remaining 63 men (63%) had normal parenchyma, 3 (3%) had an ASAP and 6 (6%) an HGPIN.

PCA3 score was 57 (median; range: 7-201) in the presence of prostate cancer and 35 (median; range: 3-228) in the absence of cancer ($p < 0.05$). Prostate cancer detection rate increased from 14.2% with PCA3 score of less than 20 to 42.5% with scores greater than 100, Figure 1.

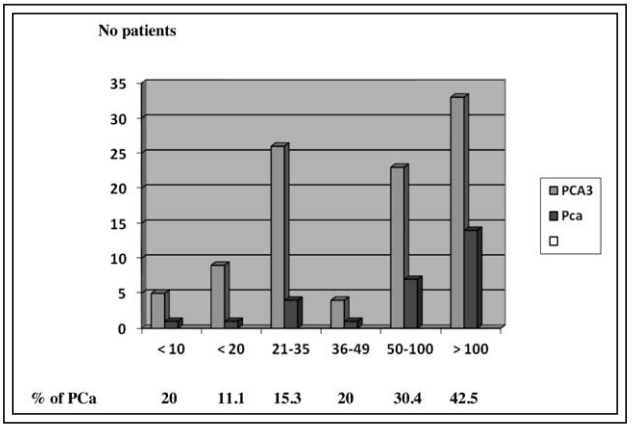

Figure 1. Prostate cancer (PCa) detection by PCA3 score range in 100 patients submitted to repeat saturation biopsy.

TABLE 1. **Detection rate for prostate cancer, number of avoided biopsies and missed prostate cancer according to threshold probability in the range of 10%-40% for the PCPT risk calculator**

Cut off probability	Detection rate for prostate cancer (%)	Avoided biopsies (%)	Missed prostate cancer (%)
*a vs b vs c	*a vs b vs c	*a vs b vs c	*a vs b vs c
*10%	100 vs 100 vs 100	0 vs 0 vs 0	0 vs 0 vs 0
*15%	100 vs 100 vs 100	0 vs 0 vs 1	0 vs 0 vs 0
*20%	100 vs 100 vs 100	0 vs 1 vs 3	0 vs 0 vs 0
*25%	100 vs 89.2 vs 100	1 vs 3 vs 8	0 vs 11.8 vs 0
*30%	96.5 vs 85.8 vs 89.3	7 vs 23 vs 9	3.5 vs 14.2 vs 10.7
*35%	96.5 vs 64.3 vs 85.8	10 vs 28 vs 17	3.5 vs 35.7 vs 14.2
*40%	75 vs 64.3 vs 85.8	26 vs 39 vs 25	25 vs 35.7 vs 14.2

*a = PCPT (Prostate Cancer Prevention Trial); b = PCPT + PSA F/T; c = PCPT + PCA3 score;
PCA3 = prostate cancer gene 3

The median PSA F/T was 13.5% (range: 5%-25%): 12% versus 14% ($p > 0.05$) in the presence or absence of prostate cancer, respectively. In the 28 patients with prostate cancer, 18 (66.7%), 24 (85.7%) and 28 (100%) had a PSA F/T ≤ 15%, ≤ 20% and ≤ 25%, respectively.

The detection rate for prostate cancer, number of avoided biopsies and missed prostate cancer according to threshold probability in the range of 10%-40% for the PCPT risk calculator are listed in Table 1.

Overall, the PCPT calculator estimated prebiopsy risks for prostate cancer were not significantly different: median risk was equal to 43%, 41% and 46% for PCPT alone, PCPT combined with PSA F/T or PCA3 score ($p > 0.05$), respectively; moreover, in presence of prostate cancer median PCPT calculated risk was 40% (PCPT alone), 48% (PCPT combined with PSA F/T) and 44% (PCPT combined with PCA3 score) ($p > 0.05$), respectively. The detection rate for prostate cancer, number of avoidable biopsies and missed cancer using the PCPT risk calculator (cut off probability of 25%) versus PCA3 score versus the case finding protocol are listed in Table 2. In the defined range of interest (10%-40% probability) using a cut off of 25% no prostate cancer would be missed (PCPT and PCPT + PCA3 score) avoiding 1% (PCPT) and 8% (PCPT + PCA3 score) of unnecessary biopsies, respectively. The case-finding protocol combined with

TABLE 2. **PCPT risk calculator (cut off probability 25%) versus PCA3 score versus case-finding protocol accuracy in prostate cancer diagnosis**

	Detection rate for prostate cancer, %	Avoided biopsies, %	Missed prostate cancer, %
Case-finding protocol	100	0	0
PCPT risk calculator (cut off 25%) + PCA3	100	8	0
PCA3 > 20	92.8	14	7.2
PCA3 > 35	78.5	22	21.5
case-finding protocol + PCA3 > 20*	100	14	0
case-finding protocol + PCA3 > 35*	100	22	0

PCPT= Prostate Cancer Prevention Trial; PCA3 = prostate cancer gene 3;
*prostate biopsy performed in presence of PSA F/T < 15% irrespective of PCA3 values

PCA3 score > 20 and > 35 would save 12% and 22% of avoidable biopsies, missing 2 (7.1%) and 6 (21.5%) out of 28 prostate cancers, respectively; on the contrary, all cancer would be found performing SPBx in presence of PSA F/T ≤ 15% irrespective of PCA3 values, Table 2.

Discussion

To better predict an individual's risk for prostate cancer statistical and computational models (risk calculators, artificial neural network, nomograms) online available[7,15] including multiple variables (age, race, DRE, family history and number of previous negative biopsy) and clinical findings (PSA F/T, PCA3 score) were developed because PSA accuracy was shown to be limited; a PSA F/T cut off of 25% in men with PSA values of 4.0 ng/mL to 9.9 ng/mL allows to avoid 20% of biopsies missing only 8% of prostate cancer[16] and a PCA3 cut off of 20 and 35 spare 67% and 44% of unnecessary biopsies missing 9% and 21% on significant prostate cancer, respectively.[17]

Schoder and Kattan[2] in a systematic review of 36 predictive models reported a benefit from nomograms and artificial neural network over PSA ranging between 2% and 26%; the majority of the models demonstrated a clinical benefit for risk thresholds greater than 30%[6] and Cavadas et al[8] in a screened cohort showed that ERSPC calculator outperformed the PCPT model allowing to avoid 9% and 23% of unnecessary biopsies using a cut off of 20% and 30%, respectively. PCPT risk calculator has improved accuracy incorporating PSA F/T and PCA3 values; Perdonà et al[5] in 218 men with PSA below 10 ng/mL submitted to initial or repeat ≥ 12 cores biopsy compared PCPT risk calculator and Chun's nomogram accuracy and demonstrated that PCPT calculator including PCA3 values and using a probability cut off of 25% would save 11% of biopsies, missing no cancer. Recently, Ankerst et al[18] underlined that PCPT risk calculator accuracy highly dependent on the different criteria for and work up before biopsy.

The urine-based testing is non-invasive and represents a rich source of novel biomarkers for prostate cancer; although urine demonstrates promise in detecting cancer, the ability to identify aggressive subsets of prostate cancer needs further development.[19] In this light, PCA3 score using different cut off has been introduced in clinical practice[20] and in risk calculator models to improve prostate cancer detection rate and reduce number of unnecessary biopsies. Crawford et al[21] in 1962 patients who underwent prostate biopsy found that PCA3 cutoff of 35 reduced the number of false-positive from 1089 to 249 (a 77.1% reduction); however, false-negative (missed cancer) increased significantly from 17 to 413. Lowering the PCA3 cut off to 10 reduced the number of false-positive 35.4% and false-negative only increased 5.6%. Recently, Goode et al[22] in 456 patients demonstrated that PCA3 score was a better predictor of prostate cancer than PSA in the population as well as the initial biopsy population, but was not superior to PSA in the repeat biopsy population.

Overall, the majority of the papers[4-8] refer to patients enrolled in screening program who underwent initial or repeat biopsy (including different PSA values) and sextant or extended scheme biopsy, but no data are known about computed models accuracy in patients submitted to repeat SPBx, especially in presence of PSA below 10 ng/mL.

In our series, we compared PCPT risk calculator results incorporating PSA F/T or PCA3 values with those obtained through the case-finding protocol for early diagnosis of prostate cancer introduced since 2002 in our clinical practice to select patients to undergo prostate biopsy; the protocol,[9] in 13,782 patients with PSA below 10 ng/mL using different PSA F/T cut offs found prostate cancer in 459 (28.8%) of 1589 men submitted to biopsy allowing to spare 33.3% biopsies (PSA F/T versus PSA cut off of 4 ng/mL) in case of repeat biopsy.

PCPT risk calculator (cut off of 25%) combined with PSA F/T demonstrated a lower accuracy in cancer diagnosis in comparison with the case-finding protocol (11.8% of undetected prostate cancer); on the contrary, PCPT risk calculator incorporating PCA3 score showed the best performance diagnosing all cancer and avoiding 8% of unnecessary biopsies. The highest percentage of avoided unnecessary SPBx without missing prostate cancer diagnosis would be achieved using the case-finding protocol combined with PCA3 cut off of 35 (22% of avoided biopsies if all patients with PSA F/T ≤ 15% would be submitted to SPBx irrespective of PCA3 score).

In definitive, in case of repeat SPBx the adjunct of PCA3 score improves PCPT calculator accuracy in diagnosing prostate cancer; moreover, a combined use of PSA F/T and PCA3 score enhances number of avoided biopsies. These data are in agreement with those previously reported on 74 patients with PSA included 4-10 ng/mL submitted to repeat SPBx in whom a PSA F/T cut off ≤ 15% combined with a PCA3 score > 35 allowed to spare about one third of unnecessary biopsy without missing significant prostate cancer.[1]

Some limitations and considerations of the present study deserve mention. First, due to the limited number of cases submitted to repeat SPBx further studies need to confirm our results. Secondly, PCPT risk calculator results were retrospectively compared with those of

the case-finding protocol based on differentiated PSA F/T cut offs, but no data about PSA accuracy were reported. Finally, the option to use contemporary PSA F/T and PCA3 value could improve PCPT calculator accuracy.

In conclusion, PCA3 score improves PCPT risk calculator accuracy in prostate cancer diagnosis detecting 100% of the cancers; on the other hand, PCA3 score combined with the case-finding protocol based on PSA F/T values significantly reduce number of unnecessary biopsies (more than 20%). □

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