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Prostate cancer risk prediction in a urology clinic in Mexico

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Abstract

Objectives—To evaluate factors affecting the risk of prostate cancer (PCa) and high-grade disease (HGPCa, Gleason score ≥ 7) in a Mexican referral population, with comparison to the Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator (PCPTRC).

Methods and Materials—From a retrospective study of 826 patients who underwent prostate biopsy between January 2005 and December 2009 at the Instituto Nacional de Cancerología, Mexico, logistic regression was used to assess the effects of age, prostate-specific antigen (PSA), digital rectal exam (DRE), first-degree family history of PCa, and history of a prior prostate biopsy on PCa and HGPCa separately. Internal discrimination, goodness-of-fit and clinical utility of the resulting models were assessed with comparison to the PCPTRC.

Results—Rates of both PCa (73.2%) and HGPCa (33.3%) were high among referral patients in this Mexican urology clinic. The PCPTRC generally underestimated the risk of PCa but overestimated the risk of HGPCa. Four factors influencing PCa on biopsy were logPSA, DRE, family history and a prior biopsy history (all $p < 0.001$). The internal AUC of the logistic model was 0.823 compared to 0.785 of the PCPTRC for PCa ($p < 0.001$). The same four factors were significantly associated with HGPCa as well and the AUC was 0.779 compared to 0.766 of the PCPTRC for HGPCa ($p = 0.13$).

Conclusions—Lack of screening programs or regular urological checkups in Mexico imply that men typically first reach specialized clinics with a high cancer risk. This renders diagnostic tools developed on comparatively healthy populations, such as the PCPTRC, of lesser utility. Continued efforts are needed to develop and externally validate new clinical diagnostic tools specific to high-risk referral populations incorporating new biomarkers and more clinical characteristics.

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Keywords

Prostate Specific Antigen (PSA); Prostate Cancer Prevention Trial Risk Calculator (PCPTRC); prostate cancer; high-grade prostate cancer; Mexico

1. Introduction

Mexico is one of the most important regional neighbors of the U.S. and, especially among southern U.S. states, shares many ethnic and racial characteristics. Although prostate-specific antigen (PSA) testing is increasingly implemented in Mexico, the bulk of men undergoing prostate biopsy in the country are referred to urology clinics with higher levels of prostate cancer (PCa) risk than in the U.S.[1] These patients generally have higher PSA levels and more frequent abnormalities on digital rectal examination (DRE). While integration of PSA and DRE with other risk factors for PCa, such as family history in a first-degree relative, has resulted in increased accuracy of diagnostic testing for PCa in the U.S., it is not clear that integration of multiple risk factors will have a similar benefit in a referral population in Mexico.[2–11]

The Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) provides individualized risk estimates of PCa and high-grade prostate cancer (HGPCa, Gleason score ≥ 7) on prostate biopsy and is recommended by the American Cancer Society for early detection of PCa and, most importantly, HGPCa. [3, 12] A limitation of the PCPTRC is that it was developed in a lower-risk cohort of men from the U.S., all with an initial PSA of 3.0 ng/ml or less, normal DRE and 55 years or older at enrollment to the Prostate Cancer Prevention Trial (PCPT), so the validity of this tool in screening higher risk men in other countries remains unproven. A strength of the PCPTRC is that all men without PCa after seven years of follow-up underwent an end-of-study prostate biopsy, substantially reducing ascertainment bias, a problem of all other risk assessment tools.[3] The PCPTRC has been validated in several U.S. screening/unreferred populations including a recent study of a high-risk young screening cohort with a majority of African American participants.[13] The usefulness of the PCPTRC in higher-risk clinical/referred populations in the U.S. remains controversial.[8, 14–15] No study has been done to examine the utility of the PCPTRC in the contemporary urology practice in Mexico.

The purpose of this study was two-fold, first to determine whether the same factors included in the PCPTRC influence PCa or HGPCa risk in a contemporary clinical cohort of Mexican referral patients and second, to determine whether the PCPTRC would be of benefit in triaging these high-risk men for prostate biopsy.

2. Materials and Methods

2. 1. Subjects

The Instituto Nacional de Cancerología is the largest oncology hospital in Mexico and patients with an elevated PSA or other suspicious clinical findings were referred to this clinic from family clinics and general hospitals all over the Mexico. A retrospective chart review of all patients who underwent 9–12 core transrectal prostate biopsy between January 2005 and December 2009 was conducted. Patients were excluded if they had a previous diagnosis of PCa, atypical acinar proliferation, high grade prostate intraepithelial neoplasia, or were taking finasteride. A total of 826 patients were identified and reasons for biopsy included high PSA levels (>2 ng/mL) or abnormal DRE. The majority of the patients in this study underwent 9-core biopsies (including all patients biopsied between 2005 and 2008 and some patients biopsied in 2009). For each patient, age, PSA (within 8 weeks prior to

biopsy), DRE (within 8 weeks prior to biopsy), first-degree family history of PCa and whether or not the patient had ever had a prior prostate biopsy were recorded. All pathological results were reviewed by a single genitourinary pathologist. The study was approved by the Ethical and Research Committee at the Instituto Nacional de Cancerología, Secretaría de Salud.

2.2. Statistical analyses

Descriptive statistics were used to summarize clinical risk factors, including age, PSA, DRE, family history, and prior biopsy, and Fisher's exact test used to compare these factors between the Mexican and the PCPT cohorts. Multivariable logistic regression was performed to assess the independent predictive effect of the risk factors on PCa and HGPCa in the Mexican cohort and the resulting coefficients were compared to the coefficients in the PCPTRC. Risk curves for the Mexican cohort were overlaid on PCPTRC risk curves for comparison of estimated risk. As the PCPTRC is only computable for men over 55 years of age, for men who were younger than 55, an age of 55 was implemented in the calculation of PCPTRC risks. A sensitivity analysis of using this imputation versus discarding these men from analysis produced no qualitative differences.

Discrimination was assessed using the area underneath the receiver operating characteristic (ROC) curve (AUC). AUCs were calculated using the Wilcoxon statistics and differences between AUCs were performed using a nonparametric U-statistic method.[16] Differences in AUCs between two independent subgroups were tested using a Z-statistic.[17] Calibration of the PCPTRC and goodness-of-fit of fitted Mexican models were assessed by comparing average PCa and HGPCa risks based on the PCPTRC and fitted Mexican models to the observed PCa and HGPCa rates, respectively, for the sample as a whole and among subgroups. The net benefit were computed by adding the benefits (true positive biopsies) and subtracting the harms (false positive biopsies) weighted by a factor that is related to the relative harm of a missed PCa versus an unnecessary biopsy (risk threshold).[18] Clinical net benefit curves were calculated for the PCPTRC and fitted Mexican models for PCa and HGPCa separately as plots of risk thresholds for referral to biopsy varying from 0 to 100% on the x-axis versus net benefit, $(\text{True positive biopsies} - [\text{Risk threshold}/(1 - \text{Risk threshold})] \times \text{False positive biopsies})/\text{sample size}$, on the y-axis, and compared to the strategy of biopsying all men.

All statistical tests were performed at a two-sided significance level of 0.05 and all analyses were performed using the R statistical software (Version 2.12.2).

3. Results

Patient characteristics are summarized in Table 1. Compared to PCPT, patients from Mexico were significantly younger (19.1% younger than 60 versus 0.7% younger than 60; $p < 0.001$), more likely had a family history of PCa (19.5% versus 16.7%; $p = 0.047$), more often had a $\text{PSA} > 4 \text{ ng/mL}$ (93.9% versus 11.4%; $p < 0.001$), and more often had an abnormal DRE (56.7% versus 10%; $p < 0.001$). In these men, 73.2% had PCa and 33.3% had HGPCa, compared to 21.9% and 4.7%, respectively, in the PCPT (both $p < 0.001$). Among patients with PCa, 45.5% had high-grade cancers compared to the PCPT's 21.2% ($p < 0.001$). 748 patients (90.6%) never previously had a prostate biopsy; and 54 patients (6.5%) were younger than 55. Ten men with HGPCa had a low PSA ($< 4 \text{ ng/mL}$) and 9 of them had a PSA no more than 2.5 ng/mL, confirming the need for improved test sensitivity by the use of multiple risk factors including PSA.

The average PCPTRC PCa risk for the entire study cohort was significantly lower than the observed incidence of PCa (67.5% versus 73.2%; $p < 0.001$). In all subgroups, the estimated

average risk of PCa calculated by the PCPTRC was lower than the observed incidence (Table 2:A). This was most pronounced in the subgroup of men with PSA ≤ 10 ng/mL, with an abnormal DRE, or a family history of PCa; this is not surprising as the proportion of patients with PCa was high (73.2%). The diagnostic performance of the PCPTRC was good in some subgroups, despite the underestimation of risk, including men with PSA >10 ng/mL (AUC=0.864; 95% CI: 0.821 to 0.906). However, the average PCPTRC HGPCa risk for the entire study cohort was significantly higher than the observed incidence of HGPCa (43.7% versus 33.3%; $p<0.001$); in all subgroups estimated risk of HGPCa was higher than the observed incidence (Table 2:B). In the present study of Mexican men, the PCPTRC generally underestimated the risk of PCa but overestimated the risk of HGPCa (Figure 1 A and B). Based on poor calibration of the PCPTRC for detecting cancer and HGPCa, new Mexican models were developed for PCa and HGPCa separately from this cohort of patients.

Results of multivariable logistic regression are displayed in Table 3 and compared to coefficients and odds ratios (ORs) of the PCPTRC. Four factors were statistically significantly associated with risk of PCa on biopsy: logPSA (OR=1.80; 95% CI:1.46, 2.21; $p<0.001$), abnormal DRE (OR=4.22; 95% CI:2.91, 6.14; $p<0.001$), a family history of PCa (OR=3.23; 95% CI:1.89, 5.54; $p<0.001$) and having a previous negative biopsy history (reducing risk: OR=0.13; 95% CI:0.07, 0.23; $p<0.001$). For HGPCa, the same four risk factors were significant but age (a significant risk factor in the PCPTRC) was not significant in the Mexican model. Risk curves as a function of PSA for Mexican men who did not have a previous prostate biopsy are shown in Figure 2. Figure 2A shows that family history and DRE result led to substantial differences in predictive value beyond use of the PSA level alone for an individual patient, and the PCPTRC risk predictions (dotted lines) were well below the Mexican model (solid lines) especially when PSA <10 ng/mL. For HGPCa, the PCPTRC risk predictions were generally higher than the Mexican model when PSA >10 ng/mL (Figure 2B). Discrimination and goodness-of-fit were examined for the fitted Mexican model for prediction of PCa and HGPCa (Table 2; Figure 1 C and D). Operating characteristics for the fitted Mexican model are over-optimistic since the same data set was used to train and test the model. Nevertheless it is common to report such statistics and they serve as a benchmark for external evaluation of the PCPTRC on the Mexican cohort.

ROC curves (Figure 3) illustrate the improved ability of the Mexican model in discriminating patients with cancer from those without cancer as well the discriminating patients with high grade cancers from all others compared to the PCPTRC and PSA alone. The AUC for the detection of PCa was 0.823 for the Mexican model compared to 0.785 for the PCPTRC ($p<0.001$) and 0.683 for PSA ($p<0.001$). For HGPCa, the AUC of the new model was 0.779 compared to 0.766 for the PCPTRC ($p=0.13$) and 0.683 for PSA ($p<0.001$).

Net benefit curves in Figure 4 show that, compared with biopsying all men, the net benefit would be larger for the Mexican or PCPTRC models for higher threshold values of risk for PCa or HGPCa. However, the decision curves in Figure 4A indicated no clear net benefit of using the fitted Mexican model or the PCPTRC over the strategy of biopsying all men in this Mexican cohort in the region of the threshold risk between 10% and 40%, the range most relevant to men considering prostate biopsy.[19] However, as seen in Table 4, if a threshold risk of PCa of 40% is chosen to recommend biopsy, using the Mexican model, 9% (=1–752/826) patients would have been spared from a biopsy, which could have a significant impact on public health and health care cost at a cost that 3% (=19/605) cancers and 0.7% (=2/275) high grade cancers would be missed. For the Mexican model, the net benefit was 0.575, higher than the net benefit if all men underwent biopsy (0.554), and the PCPTRC (0.529).

Discussion

In Hispanic men PCa is the most common cancer and it is the second leading cause of cancer death.[20] An increasing incidence of PCa is expected in Latin American countries as life expectancy increases. [1] While PCa incidence is lower in Hispanic men, the stage of the disease is generally more advanced at diagnosis.[1, 21–22] It is for this reason that PSA testing of Hispanic men may be preferred. However with PSA screening, interpreting the results of the PSA and determining risk of prostate cancer, and more specifically HGPCa are paramount in order to appropriately recommend biopsy to the correct subset of high risk patients. Given the poor calibration of the PCPTRC in the cohort of Mexican patients, a fitted Mexican model was developed for PCa and HGPCa separately using this dataset.

In Mexico, PCa epidemiologic data are limited, mainly reporting descriptive statistics with respect to the epidemiology of this disease, often based on older data.[21–22] A recent study described the results of three consecutive PCa screenings between 2004 and 2006 in Monterrey, Mexico. Of 125 men who were recommended to have a biopsy, only 55 (44%) men underwent biopsy, and 15 (27%) of these biopsied men were diagnosed with PCa; 93% of these men had Gleason scores>6.[1] A few PCa studies have been performed among Hispanics in the U.S.[23–25] Recently, a population-based PCa screening in San Antonio area, TX, found that the PCPTRC performed significantly better for PCa detection than PSA alone for Hispanic men (AUC=0.84 vs. AUC=0.79; $p=0.017$; $n=727$).[25] The present study is the first to examine the use of PCa and HGPCa risk assessment tools in Mexico.

Both the Mexican model and the PCPTRC were a superior diagnostic tool compared with PSA for predicting men with PCa and more importantly, for predicting men with HGPCa. In the present study of Mexican men, the PCPTRC generally underestimated the risk of PCa but overestimated the risk of HGPCa. This was not surprising as the study sample were drawn from a referral population in a Mexican Urologic clinic and the overall risk range for this population was significantly greater than that used to build the PCPTRC, likely due to the lower rate of PSA screening in Mexico. While other PCa risk calculators may be beneficial in this population, they generally involve more specialized measures that are not routinely collected during screening, such as prostate volume [4, 7, 10], prostate cancer gene 3 [6–7, 11], freePSA and/or proPSA [4, 26]. The advantages of the Mexican model and the PCPTRC are that they only need information that is routinely collected in the clinic and both perform significantly better than PSA alone. Even in this very high-risk population, when compared with performing biopsy in all men studied in this series, the new model can reduce unnecessary biopsies with a relatively small risk of missing both cancer and high grade tumors (Table 4).

A challenge to the use of risk assessment tools for PCa is how to translate an estimate of cancer risk into a clinical recommendation by a physician or a decision by a patient.[27] Data summarized in Table 4 may help physicians counsel men regarding whether to perform a prostate biopsy. At any given threshold of risk, there is a tradeoff between missing PCa particularly HGPCa and the risk of an unnecessary biopsy. For example, if a threshold PCa risk of 40% is used to pursue a biopsy, about 9% patients would be spared from biopsy which could have a significant impact on public health and health care cost. Clinicians must weigh the risk versus the potential therapeutic benefit of diagnosing PCa to determine whether a biopsy should be recommended or not. This must take into account not only the threshold risk of the patient for PCa, and more specifically HGPCa, but also the overall health status and life expectancy of the patient to determine if biopsy should be recommended.

While it is clear that multivariable models like the PCPTRC significantly improve a physician's assessment of a patient's risk of PCa, these data demonstrate that the accuracy of the risk estimate for a patient in Mexico undergoing PCa testing is substantially different than in the U.S. Multiple factors including underlying risk as well as prior population screening intensity may be operational. For the present, the PCPTRC or the Mexican model may help physicians and patients in Mexico, especially for detecting high grade disease. Ideally, with more clinical data and other promising biomarkers such as freePSA, we would recommend development of a new risk assessment tool for other countries such as Mexico where screening practices may have been different and, as a result, disease prevalence at a referral clinic is higher. However the current Mexican model includes clinical data that would be readily available to most clinicians in Mexico, thereby increasing the general applicability of this model in Mexican patients.

A limitation of the study is that data was collected from a retrospective chart review with limited clinical data. As a result, data on the number of biopsy cores, prostate volume, and results on other biomarkers such as freePSA were not available. Continued efforts are needed to develop new models incorporating new biomarkers and more clinical characteristics in a large prospective study. Another limitation of the study is that the same data set was used to train and test the Mexican model, therefore operating characteristics for the fitted Mexican model are over-optimistic. We decided not to split data into training and test sets because we tried to avoid developing a new model based on an even smaller dataset. Further external validation studies are needed to confirm the general applicability of the Mexican model. In addition, this Mexican cohort represents a referral population to a specialty clinic and may not reflect the Mexican population in a screening setting.

Conclusions

Risk of biopsy-detectable PCa in a clinical prostate biopsy cohort in Mexico was high; about half of patients with PCa had HGPCa. The risks of PCa or HGPCa calculated by the PCPTRC were not well calibrated for this cohort and a fitted multivariable logistic regression provides a tool for future external validation in Mexican high-risk referral centers. Continued efforts are needed to develop new clinical diagnostic tools specific to high-risk referral populations incorporating new biomarkers and more clinical characteristics in a large prospective study.

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Abbreviations

AUC	Area Under the ROC Curve
DRE	Digital Rectal Exam
HGPCa	High-Grade Prostate Cancer
PCa	Prostate Cancer
PCPT	Prostate Cancer Prevention Trial
PCPTRC	Prostate Cancer Prevention Trial Risk Calculator

PSA	Prostate Specific Antigen
ROC	Receiver Operating Characteristic

References

1. Gomez-Guerra LS, et al. Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases. *BMC Cancer*. 2009; 9:91. [PubMed: 19317909]
2. Parekh DJ, et al. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. *Urology*. 2006; 68(6):1152–1155. [PubMed: 17169636]
3. Thompson IM, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2006; 98(8):529–534. [PubMed: 16622122]
4. Nam RK, et al. Assessing individual risk for prostate cancer. *J Clin Oncol*. 2007; 25(24):3582–3588. [PubMed: 17704405]
5. Thompson IM, et al. Prediction of prostate cancer for patients receiving finasteride: results from the Prostate Cancer Prevention Trial. *J Clin Oncol*. 2007; 25(21):3076–3081. [PubMed: 17634486]
6. Ankerst DP, et al. Predicting Prostate Cancer Risk Through Incorporation of Prostate Cancer Gene 3. *The Journal of urology*. 2008; 180(4):1303–1308. [PubMed: 18707724]
7. Chun FK, et al. Prostate Cancer Gene 3 (PCA3): Development and Internal Validation of a Novel Biopsy Nomogram. *European urology*. 2009; 56(4):659–668. [PubMed: 19304372]
8. Eyre SJ, et al. Validation in a Multiple Urology Practice Cohort of the Prostate Cancer Prevention Trial Calculator for Predicting Prostate Cancer Detection. *The Journal of urology*. 2009; 182(6): 2653–2658. [PubMed: 19836788]
9. Liang Y, et al. Body Mass Index Adjusted Prostate-specific Antigen and Its Application for Prostate Cancer Screening. *Urology*. 2010; 76(5):1268, e1–e6. [PubMed: 20739049]
10. Roobol MJ, et al. A Risk-Based Strategy Improves Prostate-Specific Antigen-Driven Detection of Prostate Cancer. *European urology*. 2010; 57(1):79–85. [PubMed: 19733959]
11. Cao D-L, et al. A multiplex model of combining gene-based, protein-based, and metabolite-based with positive and negative markers in urine for the early diagnosis of prostate cancer. *The Prostate*. 2011; 71(7):700–710. [PubMed: 20957673]
12. Wolf AMD, et al. American Cancer Society Guideline for the Early Detection of Prostate Cancer: Update 2010. *CA Cancer J Clin*. 2010 caac.20066.
13. Kaplan DJ, et al. Evaluation of the Prostate Cancer Prevention Trial Risk calculator in a high-risk screening population. *BJU International*. 2010; 105(3):334–337. [PubMed: 19709072]
14. Nguyen CT, et al. Performance of prostate cancer prevention trial risk calculator in a contemporary cohort screened for prostate cancer and diagnosed by extended prostate biopsy. *J Urol*. 2010; 183(2):529–533. [PubMed: 20006887]
15. Ngo TC, et al. The Prostate Cancer Risk Calculator From the Prostate Cancer Prevention Trial Underestimates the Risk of High Grade Cancer in Contemporary Referral Patients. *The Journal of urology*. 2011; 185(2):483–488. [PubMed: 21167519]
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988; 44(3):837–845. [PubMed: 3203132]
17. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982; 143(1):29–36. [PubMed: 7063747]
18. Vickers AJ. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. *Am Stat*. 2008; 62(4):314–320. [PubMed: 19132141]
19. Steyerberg EW, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010; 21(1):128–138. [PubMed: 20010215]
20. O'Brien K, et al. Cancer Statistics for Hispanics, 2003. *CA Cancer J Clin*. 2003; 53(4):208–226. [PubMed: 12924775]

21. Gilliland F, et al. Trends in prostate cancer incidence and mortality in New Mexico are consistent with an increase in effective screening. *Cancer Epidemiol Biomarkers Prev.* 1994; 3(2):105–111. [PubMed: 8049631]
22. Tovar-Guzman V, et al. Prostate cancer mortality trends in Mexico, 1980–1995. *Prostate.* 1999; 39(1):23–27. [PubMed: 10221262]
23. Stone SN, et al. Family history, Hispanic ethnicity, and prostate cancer risk. *Ethn Dis.* 2003; 13(2): 233–239. [PubMed: 12785421]
24. Strom SS, et al. Prostate cancer in Mexican-Americans: Identification of risk factors. *The Prostate.* 2008; 68(5):563–570. [PubMed: 18247399]
25. Liang Y, et al. Population-based screening for prostate cancer: Improved outcomes in African American men. *Annals of Urology.* 2011 Epub Feb 2011.
26. Ankerst DP, et al. Updating risk prediction tools: A case study in prostate cancer. *Biometrical Journal.* (Accepted).
27. Liang Y, et al. Likelihood of Detectable Prostate Cancer in the General Population: Implications for Prostate Cancer Screening. *Cancer Epidemiology, Biomarkers & Prevention.* (under review).

Figure 1.

Calibration plots for PCPTRC and goodness-of-fit plots for Mexican model: (A) PCPTRC PCa risk vs. observed PCa rate; (B) PCPTRC HGPCa risk vs. observed HGPCa rate; (C) Mexican model predicted PCa risk vs. observed PCa rate; and (D) Mexican model predicted HGPCa risk vs. observed HGPCa rate. The histogram of predicted risk and the number of patients within each risk interval are displayed as well.

Figure 2.

Risk curves for Mexican men who had no previous negative prostate biopsy (A: risk of PCa; B: risk of HGPCa). DRE+=abnormal DRE; DRE-=normal DRE; FAM HIST+= family history of PCa; FAM HIST-= no family history of PCa. The solid lines are estimated risks based on Mexican model and the dotted lines are estimated risks based on PCPTRC.

Figure 3. ROC curves for discrimination of patients with PCa from those without PCa (A) and for discrimination of patients with HGPCa from those without HGPCa (B)

Figure 4.

Net benefit curves for fitted Mexican model, PCPTRC and biopsying all men based on different threshold risks of PCa (A) and HGPCa (B). A threshold risk is a probability of disease for opting for biopsy.

Table 1

Comparison of participant characteristics between Mexican and PCPT cohorts

	Mexican Cohort N=826	PCPT Cohort N=5519	P Value ^I
Age (year)			<0.001
Younger than 55	54 (6.5)	0 (0)	
55–59	104 (12.6)	38 (0.7)	
60–64	168 (20.3)	1,143 (20.7)	
65–69	184 (22.3)	1,741 (31.5)	
70 or Older	316 (38.3)	2,597 (47.1)	
Family History ²			0.047
No	665 (80.5)	4,599 (83.3)	
Yes	161 (19.5)	920 (16.7)	
PSA (ng/mL)			<0.001
Less than 2	23 (2.8)	3,603 (65.3)	
2–4	27 (3.3)	1,285 (23.3)	
Greater than 4	776 (93.9)	631 (11.4)	
DRE			<0.001
Normal	358 (43.3)	4,968 (90)	
Abnormal/Suspicious	468 (56.7)	551 (10)	
Prior negative biopsy			0.06
Never	748 (90.6)	4873 (88.3)	
At least one	78 (9.4)	646 (11.7)	
Cancer			<0.001
	605 (73.2)	1,211 (21.9)	
Gleason 7–10 Cancer			
Out of all pts	275 (33.3)	257 (4.7)	<0.001
Out of pts with Cancer	275 (45.5)	257 (21.2)	<0.001

Entries are count (%)

^IDifferences between Mexican and PCPT cohorts using Fisher's exact test.²Defined as a father, brother or son having had prostate cancer.

Comparison of observed PCa (HGPCa) incidence rates to average PCa (HGPCa) risks based on PCPTRC or new Mexican model in various subgroups

Table 2

A: Risk of PCa									
Subgroup	N	Obs. PCa n (%)	Mexican Model ¹			PCPTRC ¹			P Value ²
			Ave. Risk (%)	AUC	P Value ²	Ave. Risk (%)	AUC	P Value ²	
All	826	605 (73.2)	73.2	0.823		67.5	0.785		
PSA 10 ng/mL or less	362	223 (61.6)	61.6	0.727	<0.001	51.7	0.652	<0.001	
PSA greater than 10 ng/mL	464	382 (82.3)	82.3	0.872		79.9	0.864		
Normal DRE	358	197 (55)	55	0.703	<0.001	52.7	0.616	<0.001	
Abnormal DRE	468	408 (87.2)	87.2	0.829		78.9	0.788		
Age: 65 yrs or older	500	385 (77)	75	0.826	0.72	69.3	0.787	0.76	
Age: younger than 65	326	220 (67.5)	70.6	0.815		64.9	0.777		
No Family History	665	465 (69.9)	69.9	0.816	0.42	66.7	0.794	0.08	
Family History	161	140 (87)	87	0.779		70.8	0.705		
B: Risk of HGPCa									
Subgroup	N	Obs. HGPCa n (%)	Mexican Model ¹			PCPTRC ¹			P Value ²
			Ave. Risk (%)	AUC	P Value ²	Ave. Risk (%)	AUC	P Value ²	
All	826	275 (33.3)	33.3	0.779		43.7	0.766		
PSA 10 ng/mL or less	362	62 (17.1)	18	0.708	0.64	20.5	0.63	0.03	
PSA greater than 10 ng/mL	464	213 (45.9)	45.3	0.728		61.9	0.732		
Normal DRE	358	62 (17.3)	17.3	0.756	0.46	24.8	0.699	0.72	
Abnormal DRE	468	213 (45.5)	45.5	0.727		58.2	0.716		
Age: 65 yrs or older	500	188 (37.6)	35.4	0.766	0.42	49.5	0.761	0.97	
Age: younger than 65	326	87 (26.7)	30	0.793		34.9	0.763		
No Family History	665	212 (31.9)	31.9	0.813	<0.001	44.5	0.811	<0.001	
Family History	161	63 (39.1)	39.1	0.616		40.3	0.596		

¹Description of the Mexican model and the PCPTRC model was given in Table 3.

²Difference in AUC between two independent subgroups (current row vs. the row below it) using a z statistic.

Table 3

Summary of Mexican model versus PCPTRC model

Outcome	Mexican Model [/]				PCPTRC		
	Risk Factors	Coef.	OR (95% CI)	P Value	Coef.	OR (95% CI)	P Value
PCa	Intercept	-1.03	-	<0.001	-1.8	-	<0.001
	log(PSA)	0.59	1.8 (1.46, 2.21)	<0.001	0.85	2.34 (2.13, 2.56)	<0.001
	DRE	1.44	4.22 (2.91, 6.14)	<0.001	0.91	2.47 (2.03, 3.01)	<0.001
	Previous Negative Biopsy	-2.06	0.13 (0.07, 0.23)	<0.001	-0.45	0.64 (0.53, 0.78)	<0.001
	Family History	1.17	3.23 (1.89, 5.54)	<0.001	0.27	1.31 (1.11, 1.55)	0.002
HGPCa	Intercept	-3.34	-	<0.001	-6.25	-	<0.001
	log(PSA)	0.76	2.14 (1.79, 2.56)	<0.001	1.29	3.64 (3.04, 4.37)	<0.001
	Age	-	-	-	0.03	1.03 (1.01, 1.06)	0.01
	DRE	0.93	2.55 (1.78, 3.63)	<0.001	1	2.72 (1.96, 3.77)	<0.001
	Previous Negative Biopsy	-2.07	0.13 (0.04, 0.41)	0.001	-0.36	0.7 (0.49, 0.99)	0.04
	Family History	0.47	1.6 (1.08, 2.37)	0.02	-	-	-
	African American	-	-	-	0.96	2.61 (1.55, 4.41)	<0.001

[/] The results of the final model for all cancers and for high-grade cancers were displayed respectively. The covariates considered in the full model include logPSA, age, DRE, previous negative biopsy, and family history.

Coef.: coefficients of logistic regression

OR: odds ratio

95% CI: 95% confidence interval

Table 4

Number of biopsies would have been performed and numbers of PCa and HGPCa cases would have been missed if a specific threshold risk estimated by Mexican model had been used to recommend prostate biopsy

Threshold risk of PCa	Mexican Model			
	# of biopsies recommended (%)	# of PCa missed (%)	# of HGPCa missed (%)	# of unnecessary biopsies (%)
10%	824 (99.76)	1 (0.17)	0 (0)	220 (26.7)
15%	792 (95.88)	6 (0.99)	0 (0)	193 (24.37)
20%	776 (93.95)	10 (1.65)	0 (0)	181 (23.32)
25%	768 (92.98)	13 (2.15)	1 (0.36)	176 (22.92)
30%	766 (92.74)	14 (2.31)	1 (0.36)	175 (22.85)
35%	760 (92.01)	14 (2.31)	1 (0.36)	169 (22.24)
40%	752 (91.04)	19 (3.14)	2 (0.73)	166 (22.07)

Threshold risk of PCa	Mexican Model			
	# of biopsies recommended (%)	# of PCa missed (%)	# of HGPCa missed (%)	# of unnecessary biopsies (%)
10%	721 (87.29)	39 (6.45)	6 (2.18)	155 (21.5)
15%	626 (75.79)	89 (14.71)	12 (4.36)	110 (17.57)
20%	543 (65.74)	129 (21.32)	25 (9.09)	67 (12.34)
25%	474 (57.38)	179 (29.59)	48 (17.45)	48 (10.13)
30%	400 (48.43)	233 (38.51)	68 (24.73)	28 (7)
35%	352 (42.62)	273 (45.12)	82 (29.82)	20 (5.68)
40%	288 (34.87)	330 (54.55)	109 (39.64)	13 (4.51)