Accuracy of PSA versus PCA3 in the Indication of Biopsy for the Diagnosis of Prostate Cancer

Acurácia do PSA versus PCA3 na indicação do diagnóstico de câncer de próstata

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Abstract

Prostate cancer is the most common neoplasm in men and the second largest cause of mortality due to neoplastic disease in this population. This study aims to analyze the biomarker that presents the highest accuracy for indication of prostate biopsy, between serum PSA and urine PCA3, aimed at the diagnosis of prostate cancer. It was performed a systematic review with the search for scientific studies in the PubMed, Bireme, Scielo, Cochrane Library, Health System Evidence, Epistemonikos databases and Capes thesis and dissertations from 2007 to 2017 using the descriptors "prostatic neoplasms", “prostate cancer”, “PCA3”, “DD3”, “prostate cancer antigen gene 3”, “PSA”, “prostate-specific antigen", "biopsy" and "diagnosis". The included studies were analyzed for risk of bias and applicability through the QUADAS-2 questionnaire. Nine articles were selected to compose this study. PCA3 was more accurate than PSA in predicting the biopsy result. The PCA3 sensitivity was between 53% and 94% and specificity between 36% and 86.7%, positive predictive value between 54% and 72% and negative predictive value over 60%. Eight of the nine articles included showed that the PCA3 accuracy decreases the indication of unnecessary prostate biopsies, presenting specificity higher than PSA. However, due to the risk of bias in the included studies, it was not possible to affirm that PCA3 is superior to PSA in the diagnosis of prostate cancer.

Keywords: Prostate cancer. Biopsy. Diagnosis. Prostate-specific antigen. Prostate cancer Gene 3.

Resumo

O câncer de próstata é a neoplasia mais comum no sexo masculino e a segunda maior causa de mortalidade por doença neoplásica nesta população. Este estudo visa analisar o biomarcador que apresenta maior acurácia para a indicação de biópsia prostática, entre o PSA sérico e o PCA3 urinário, visando o diagnóstico de câncer de próstata. Para tanto, realizou-se uma revisão sistemática, com a

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busca de estudos científicos nas bases de dados PubMed, Bireme, Scielo, Cochrane Library, Health System Evidence, Epistemonikos e Banco de teses e dissertações da Capes no período de 2007 a 2017, utilizando os descritores "prostatic neoplasms", "prostate cancer", "PCA3", "DD3","prostate cancer antigen gene 3" , "PSA", prostate-specific antigen", "biopsy" e "diagnosis". Os estudos incluídos foram analisados quanto ao risco de viés e aplicabilidade por meio do questionário QUADAS-2. Nove artigos foram selecionados para compor este estudo. A acurácia do PCA3 mostrou-se superior ao PSA na predição do resultado da biópsia. A sensibilidade do PCA3 foi entre 53% e 94%, especificidade entre 36% e 86,7%, valor preditivo positivo entre 54% e 72% e valor preditivo negativo superior a 60%. Oito dos nove artigos incluídos demonstraram que a acurácia do PCA3 diminui a indicação de biópsias prostáticas desnecessárias, apresentando especificidade superior ao PSA. No entanto, devido ao risco de viés nos estudos incluídos, não é possível afirmar que o PCA3 é superior ao PSA no diagnóstico de câncer de próstata.

Palavras-chave: Câncer de próstata. Biópsia. Diagnóstico. Antígeno prostático específico. Gene 3 do câncer de próstata.

Introduction

Prostate adenocarcinoma or prostate cancer (PCa) is the most common neoplasm in males, only supplanted by non-melanoma skin tumors, and the second largest cause of mortality due to neoplastic disease in males [1]. The National Cancer Institute (INCA) estimated the incidence of 61.82 cases of PCa per 100,000 men in 2016, with the highest rate being found in the southern region, with about 95.63 new cases [1]. Patients over 65 years of age make up more than 75% of diagnoses, indicating an increase in PCa incidence with advancing age [1,2].

The main risk factors related to PCa are age 50 or older, African ancestry, obesity, and family history of father or sibling who presented the disease before the age of 60 years [1,2]. Other factors are associated with lifestyle habits, such as high-fat diet, abusive consumption of alcoholic beverages and smoking, which are potential mutagens for the development of this type of cancer [3].

CaP suspicious is performed with Prostatic Specific Antigen (PSA) and digital rectal examination (DRE) [4,5]. Historically, the first prostatic malignant indicator marker to be studied was Prostate Acid Phosphatase (PAP) [6]. However, its applicability is controversial due to its low specificity, and its use was replaced with the discovery of PSA in 1970, with approval by the Food and Drug Administration (FDA) in 1994 [6].

The Ministry of Health does not recommend measuring PSA and DRE in asymptomatic patients aged over 75 years, since their damages outweigh the benefits [4].

For asymptomatic patients younger than 75 years of age, there is insufficient evidence to support the recommendation against or in favor of this procedure [4]. This fact is based on the limitations of PSA for clinical decision-making [2,3,5].

PSA is a glycoprotein produced by the epithelium of the prostate gland that acts on the liquefaction of semen, preventing its obstruction in the course [7,8]. Prostatic changes (benign or malignant), which change the architecture of PSA secreting gland cells, increase the permeability of this protein and raise its serum levels [7]. Value up to 4 ng / ml is considered a normal result; however, some types of PCa can occur with PSA below this level [9].

The formal indication for biopsy is advocated with PSA above 10 ng/ml [10]. Values between 4-10 ng/ml are considered in the "gray area" or "borderline PSA", considered benign prostatic hyperplasia (BPH) [10]. For these cases, the analysis of the PSA increase rate and the free/total PSA ratio is considered as an investigational complement [10]. The number of false positive PSA tests is estimated at 75.9% [9,10].

It is emphasized that each gram of BPH elevates serum PSA by 0.3 ng/mL, while each gram of adenocarcinoma is capable of elevating it to 3.0 ng/ml [8]. Its basal level increases proportionally with age [8,9]. Thus, it is verified that PSA is tissue-specific and not tumor-specific [4].

In view of these characteristics, it is observed that PSA is a serum marker used with divergence in current clinical practice [6]. This antigen is associated with considerable rates of overdiagnosis, unnecessary interventions and overtraining, since it can detect a clinically irrelevant cancer for the patient's life expectancy [2,3,5].

PCa is usually asymptomatic [5]. The definitive diagnosis is made by transrectal prostate biopsy, considered the gold standard, indicated by PSA levels and DRE alterations [2,5]. The main adverse effects of the biopsy are hematochezia, hematospermia, hematuria, dysuria, as well as retention and urinary infection [2]. According to histopathological analysis, the most commonly prostatic tumor variant is acinar adenocarcinoma, responsible for almost 95% of these tumors [11].

In 1999, a new biomarker was created to aid in the diagnosis of PCa: the Prostate Cancer Antigen gene 3 (PCA3), also known as DD3 [12]. It is a gene located on chromosome 9q21-22 that codes for lncRNA (long non coding RNA), which is composed of four exons with alternative polyadenylation at three different positions in exon 4 [12,13]. It was discovered through a method to compare mRNA expression between malignant and benign prostatic tissues [12]. Reverse transcription real-time polymerase chain reaction (RT-qPCR) was the method of choice used for its analysis, presenting significantly increased PCA3 expression in PCa in relation

to healthy prostate [12,13]. In the initial studies on this biomarker, it was verified that PCA3 is undetectable in other tissues and tumors, with a low expression in BPH 12,13,14.

The only FDA-approved test for PCA3 detection is Progensa®, which consists of an *in vitro* nucleic acid amplification method [15]. Its function is to measure the concentration of RNA molecules of PCA3 and PSA by calculating the rate of RNA molecules of each of these markers in urine samples after the patient undergoes digital rectal examination[15]. Progensa® is indicated for patients with suspected PCa due to PSA levels and/or DRE alteration and/or with one or more negative biopsy results [15]. The PCA3 score represents the ratio of RNA molecules of PCA3 by the number of RNA molecules of PCA and the value established as limiting for the PCa diagnosis was 25 [14]. However, later studies have certified that the cutoff point from 10 to 35 reduces the number of false positives by about 34.5%, and the value of 35 has been recognized as the best validity in clinical practice [14,16,17]. The use of PCA3 for improving accuracy in PCa detection at repeat biopsy is accepted by urologic community, but it is more expensive and is not a consensus that PCA3 is better than total PSA or that the relation free/total PSA in the first biopsy [14,16,17].

Based on the assumption that there are divergences regarding the more specific noninvasive test for the prediction of the biopsy result that confirms the diagnosis of prostate adenocarcinoma, the present systematic review seeks to answer the following question: Which biomarker has the highest accuracy for the indication of prostatic biopsy, aiming at PCa diagnosis: serum PSA or urine PCA3?

Methodology

The present study consists of a systematic literature review according to the following research protocol.

Search strategy

The search for PubMed, Bireme, Scielo, Cochrane Library, Health System Evidence, Epistemonikos databases and Bank of thesis and dissertations of Capes, from 2007 to 2017. It was not possible to carry out the survey of articles indexed in the Embase database due to its restricted and paid access. The combination of descriptors in English language "prostatic neoplasms", "prostate cancer", "prostate cancer antigen gene", “prostate-specific antigen and "diagnosis", contained in the title and / or abstract and validated by Descriptors in Health Sciences (DeHS/MeSH). All articles on the use of PCA3 and PSA markers in the indication of biopsy for the diagnosis of prostate adenocarcinoma were reviewed.

Selection Criteria

Articles identified in the initial search strategy were independently assessed by two

examiners according to the following inclusion criteria: 1) Type of study: observational and interventional; 2) Population: adult men submitted to prostate adenocarcinoma screening, without previous biopsy; 3) Intervention: quantitative detection of the PCA3 gene in urine samples using the biological-molecular method, and collection of blood samples for the quantitative PSA evaluation associated to initial biopsy, defined as gold standard for prostate cancer diagnosis; 4) Outcome: comparison of accuracy between PCA3 and PSA markers for indication of prostate biopsy, showing sensitivity (S), specificity (E), ROC curve and Area Under Curve (AUC) value.

Exclusion criteria were: review articles; case reports; studies including only patients submitted to repeat biopsies, and those in which intervention evaluated other types of samples or material of non-human origin for the detection of both markers.

Data collection

Data collection was performed by two examiners based on the established selection criteria. The following characteristics were collected: name of the first author, year of publication, type of study, country of origin, mean age, type of PCA3 test used, means of urine PCA3 and total serum PSA, cutoff point (score) of PCA3, PSA and PCA3 AUC, sensitivity, specificity and positive and negative predictive PCA3 values.

Disagreements in data extraction were solved with discussion of the topic among examiners and subsequent consensus.

Analysis of studies

The risk of bias and applicability of studies were evaluated with the Quality Assessment of Diagnostic Accuracy Studies-2 questionnaire (QUADAS-2) [18].

Results

In the initial search strategy, 245 articles were found, nine of which presented criteria for inclusion in this systematic review (Figure 1).

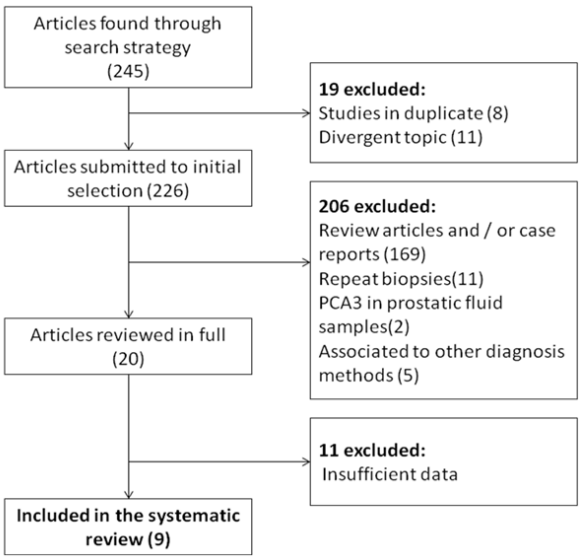

Figure 1 - Flowchart of selection of articles

Initially, studies in duplicate and those whose topics were not in accordance with the search objective were excluded. After being submitted to the selection criteria, this systematic review excluded review articles,

case reports and studies in which the methodology was presented with intervention only in patients submitted to repeat prostate biopsies, with analysis of PCA3 from prostatic fluid sample and using the association of magnetic resonance imaging and nomograms for the diagnosis of prostate adenocarcinoma.

Twenty articles were selected for full review, and studies with insufficient data were excluded, that is, they failed to meet at least one of the following criteria: 1) without PSA analysis; 2) did not evaluate PCA3 at score 35; 3) did not present data for the analysis of the accuracy of markers such as sensitivity, specificity or AUC. Studies that included patients who underwent initial and repeated biopsy in their samples, but presenting isolated statistical data on the relationship between markers and initial biopsy were included.

It should be observed that the standard choice of cutoff point 35 of PCA 3 was made from the observation of its statistical validity well described in literature [19].

The nine studies of diagnostic accuracy contained in this review were evaluated for their risk of bias and applicability concerns, according to the QUADAS-2 questionnaire. Studies classified as low risk on all bias or applicability criteria were classified as "low risk of bias" or "low applicability concern". However, when they presented high risk or uncertain risk in one or more criteria, they were considered as "at risk of bias" or with "applicability concerns".

All studies were at risk of bias and with applicability concerns. Regarding patient selection, Ochiai et al [20] (2013) and Adam et al [21] demonstrated a risk of bias due to their heterogeneous populations with patients submitted to initial biopsy and repeat biopsy.

Among selected studies, only Taille et al [14] reported that the results of PCA3 and PSA analysis were interpreted without prior knowledge of the biopsy result. However, they did not report whether the researchers performed biopsies with blinding relative to the levels of markers, resulting in risk of bias for the reference standard. Chevli et al [22], Ochiai et al [20] and Vlaeminck-Guillem et al [23] did not perform blinding in relation to tests and biopsies. Schilling et al [24] only conducted biopsy for 32 patients from a population of 103, and used magnetic resonance guided biopsy in two patients, increasing the risk of bias in this criterion.

In contrast, Ruffion et al [25], Ramos et al [26], Adam et al [21] and Deras et al [27] received the low risk status for the reference standard, since their investigators were unaware of the PCA3 and PSA values at the time of histopathological collection.

All studies presented low risk in the flow and timing criteria, since they described patients who were excluded from the study and the interval between collection of marker samples and prostate biopsy.

The selected studies were published in the period from 2008 to 2014 and all were

performed according to the observational design, longitudinal type, being seven prospective and two retrospective. Of the nine articles, four were carried out, South Africa, Chile, Germany and Japan one in each, three in France and two in the United States of America. Their general characteristics are described in Table 1.

Table 1. General characteristics of the nine studies included in the review

Authors	Year	Study	Country	Population (n)	Mean age group (years)	PCA3 Test	Urine PCA3 score	Mean PCA3 values	Mean PSA values (ng/mL)
Chevli KK	2014	OR	USA	3073	64.8	Progensa®	35	38.3	6.4
Ruffion A	2014	OP	France	595	63	Progensa®	35	29	5.9
Ochiai A	2013	OP	Japan	476	69	Progensa®	35	49	7.6
Ramos CG	2013	OP	Chile	64	64	Progensa®	35	31.7	5.8
Adam A	2011	OP	South Africa	86	67	Progensa®	35	72	27.5
Taille A	2011	OP	France	516	63	Progensa®	35	69.6	5.6
Vlaeminck-Guillem V	2011	OP	France	240	63	Progensa®	35	33	5.05
Schilling D	2010	OR	Germany	103	67	Progensa®	35	32	6.3
Deras IL	2008	OP	USA	570	64	Progensa®	35	38	7.8

OR = Observational retrospective; OP = Observational prospective; USA = United States of America

The study population consisted of patients with indication for initial prostate biopsy, aiming at the diagnosis of prostate adenocarcinoma. The intervention presented in all included articles consisted of blood collection to evaluate total PSA levels and urine sample, after performing prostatic massage, to measure PCA3. The standard used for PCA3 dosing was Progensa®. Subsequently, researchers performed the standardized collection of material for histopathological examination. The aim of this study was to evaluate the accuracy of these two biomarkers in predicting the biopsy result. Its diagnostic results are shown in Table 2.

Table 2. Diagnostic results presented in the nine studies included in the review

Authors	Year	PCA3					PSA
		S* (%)	E*(%)	PPV (%)	NPV (%)	AUC**	AUC**
Chevli KK	2014	53	75	62	67	0,697	0,599
Ruffion A	2014	63	72	ND	ND	0,740	0,509
Ochiai A	2013	66,5	71,6	58,1	78,3	0,742	0,647
Ramos CG	2013	57,9	86,7	72	74	0,77	0,57
Adam A	2011	77,7	50	54	75	0,7054	0,8443
Taille A	2011	64	76	ND	ND	0,703	0,577
Vlaeminck-Guillem V	2011	60	68	67	61	0,70	0,53
Schilling D	2010	94	36	65	83	0,81	0,61
Deras IL	2008	54	74	ND	ND	0,703	0,618

S = Sensitivity; E = Specificity; PPV = Positive predictive value; NPV = Negative predictive value; OR = Odds ratio; AUC = Area under curve; ND = Not described; * Values at cutoff point 35; ** 95% confidence interval

The comparison of the accuracy between PCA3 and PSA markers in the biopsy indication for the diagnosis of prostatic neoplasia was performed using AUC values in all studies, using a 95% confidence interval (CI). Eight studies had AUC values of PCA3 (between 0.69 and 0.81) higher than that of PSA (range from 0.50 to 0.64) [14,20,22,24,25,26,27]. Only one of them showed AUC of PCA3 lower than PSA (0.70 versus 0.84) [21].

Regarding PCA3, sensitivity ranged from 53% to 94% and specificity from 36% to 86.7%, with cutoff point of 35 being referenced for such determination in all studies. Six studies evaluated positive predictive value (PPV) and negative predictive value (NPV), ranging from 58.1 to 72% and 61 to 83%, respectively [20,21,22,24,25]. All articles presented sensitivity and specificity results for the PCA3 score of 35.

Only Vlaeminck-Guillem [23] presented sensitivity, specificity, PPV and NPV of total PSA values, which limits the detailed comparative evaluation between markers. In this study, PSA (> 4ng / mL) had PPV and NPV equal to 52% and 46%, respectively, sensitivity of 63% and specificity of 32%.

Discussion

It was verified that the accuracy of PCA3 biomarker in predicting the biopsy result is higher than that of PSA, considering cutoff point equal to 35. According to the review data, it was identified that the PCA3 sensitivity varied from 53% to 94%, with average of 65.5%. Regarding specificity, the lowest value was 36% and the highest was 86.7%, with an average value of 67.7%. These results denote adequate values for the diagnostic relevance. The best result was the negative predictive value, above 60% in all studies that analyzed this variable. Positive predictive value ranged from 54% to 72%.

The analysis of the Receiver Operational Curves (ROC curves) was used by all studies, which is a tool to evaluate the performance of diagnostic tests [12,16]. The ROC curve is the representation of pairs (specificity, sensitivity) obtained when considering all possible cutoff values, that is, it evaluates the efficiency of the test from the effect of the different cutoff points in relation to sensitivity and specificity [16]. Its purpose is to analyze the certainty that a patient to have the disease or not and, for this, the result of the gold-standard test is used as reference (prostate biopsy) [12]. Thus, the area under the curve (AUC) is used

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as discrimination between diseased and healthy patients. In an ideal test, the AUC value is equal to 1, and value equal to or less than 0.5 indicates inability to distinguish the test between study groups.

All studies presented AUC area for PCA3 above 0.6, being the highest value 0.81, indicating adequate performance and close to the ideal in the study by Schilling et al [24]. This study, despite showing favorable results for PCA3, has a significant selection bias. Of the 103 patients submitted to the tests to analyze biomarkers, only 32 with PCA3 score > 35 were selected for biopsy. Of these, 14 had already performed at least one prior biopsy with negative result, and of the total, 56.2% had positive result for prostate adenocarcinoma. This study showed the lowest specificity (36%), with the highest NPV (83%) and high PPV (65%). It is concluded that there was a selection of patients who were more likely to be ill, increasing their sensitivity to the detriment of specificity.

The only study that presented PSA sensitivity, specificity, PPV and NPV was Vlaeminck-Guillem [23], presenting values of 63%, 32%, 52% and 46%, respectively, corroborating values lower than PCA3 for specificity in biopsy indication for the diagnosis of prostate adenocarcinoma.

The AUC of PSA resulted in 0.5 in five studies, pointing out its poor performance to distinguish patients with prostate neoplasia from healthy individuals [14,22,23,25,26]. However, the study by Adam et al [21] points out AUC of PSA equal to 0.84, exceeding the highest result found for PCA3. It is hypothesized that this overestimated prediction of PSA is related to risk stratification between groups. In the aforementioned study, 68.6% of the population sample was composed of black patients, and 49.5% of the total had PSA values above 10 ng/mL. The mean total PSA of patients in this study was more than double that of other studies, also showing the highest mean urine PCA3 value.

The pioneering study by O'Malley et al [28] on the interracial variation in the results of urinary biomarkers corroborates the study by Adam et al [21] regarding elevated PCA3 levels in black patients when compared to non-black patients. The prospective observational study by Smith et al [29] on racial differences in the prostate adenocarcinoma screening tests confirmed that the total PSA value is higher in black individuals, presenting higher positive predictive value in relation to Caucasians. In the latter study, the authors reported that 32% of black men in the study without prostate adenocarcinoma had already undergone unnecessary prostate biopsy, indicated from PSA levels alone.

Studies with larger samples demonstrated agreement regarding the higher accuracy of PCA3 in the prediction of prostatic biopsy, as well as its sensitivity and specificity [14,20,22,25,27]. Considering their data, the PCA3 values were: sensitivity between 53% and

66.5% (mean = 60.1%), specificity between 72% and 76% (mean = 73.7%), AUC between 0.69 and 0.74 (mean = 0.71). As for PSA, the AUC variation was from 0.50 to 0.64 (mean = 0.59).

In this review, the existence of heterogeneity regarding the performance of PCA3 in relation to PSA levels was evidenced. Thus, there was no consensus as to which PSA level the PCA3 score is more accurate.

Five studies showed a relationship between the PCA3 and Gleason score in positive results for neoplasia in prostatic biopsies [14,20,22,25,27]. Specifically, PCA3 score from 38 correlated with Gleason score > 6, indicating that this biomarker may be useful in estimating the adenocarcinoma severity and to perform the differential diagnosis with other pathologies of the gland. The articles included were consistent that the prostate volume does not interfere with increased PCA3 levels.

Ruffion et al [25] were the only to analyze the performance of the PCA3 (PCA3D) and PSA (PSAD) densities in predicting the biopsy. Density values were obtained by dividing prostatic volume (in milliliters) by total serum PSA (ng/mL) and by PCA3 score, separately. The authors found higher performance of PCA3D compared to serum PSA and PCA3 score. Its AUC was 0.773, with sensitivity of 64%, specificity of 76% and accuracy of 71% for cutoff point 1. The PCA3 score and total PSA AUC values in the same analysis were 0.740 and 0.509, respectively. Thus, they concluded that the prostate volume in the analysis of PCA3 and PSA is superior to the isolated interpretation of the results of these markers.

These authors formulated some considerations that increase the test specificity: 1) the number of positive results in the histopathological study increases proportionally to the increase of PCA3D; 2) if PCA3D is greater than 1, the risk of positive biopsy result is > 70%; 3) there is a lower risk of positive biopsy if PCA3D is <0.5. Therefore, the PCA3 density has a significant statistical relevance in order to reduce the number of unnecessary biopsies and avoid the loss of follow-up of patients with prostate adenocarcinoma.

Applicability

The studies included in this review show populations from Europe, Asia, Africa, North America and Latin America, the latter represented by Chile [26]. Considering the miscegenation of the Brazilian population and its striking feature of Afrodescendant ancestry, the performance of urine PCA3 may be different from that observed by Adam et al [21], since prostate adenocarcinoma is more common in black men than in white men, and these individuals have higher PSA and PCA3 levels [28,29]. In addition, the population samples studied come from medical and academic centers of urological reference, treating patients with high total PSA levels and risk

factors such as family history of prostate adenocarcinoma, altered digital rectal examination and submitted to previous biopsies. There is a need for future studies investigating a sample with a broad population representation in order to reduce the possibility of selection bias and investigating the variation in PCA3 expression among the different ancestries.

Its applicability is also dependent on the level of its acceptance by healthcare professionals and patients as well as its financial cost. Although urine PCA3 showed greater accuracy in relation to PSA at biopsy indication, it did not show high performance. In addition, studies have demonstrated the risk of bias, according to QUADAS-2, which may compromise the level of clinical evidence and its practical application.

This review also emphasizes the significant performance of PCA3 density to guide the medical decision of the histopathological examination, pointing out the need for clinical studies that certify its accuracy in representative populations.

Study Limitations

The limiting factor of this research was the definition of cutoff point of 35 for urine PCA3, which made impossible an extended analysis of the sensitivity and specificity of this marker, although the validity of this score for the test is already established in literature.

Among the 20 articles classified as eligible to be included in this review, 8 were excluded due to insufficient data regarding the PCA3 test. The use of TaqMan® and mirVana® tests did not generate sufficient data to construct the ROC curve or even consistent information for comparison between PSA and PCA3 accuracy. A study using the TRANSPLEX® test presented only an isolated AUC value for PCA3, without further specification. Although SYBR® was shown to be useful in generating data to compare accuracy between markers, it used PCA3 score of 114.8.

In eight studies, the only comparative parameter of accuracy between PSA and PCA3 was the AUC, which is sufficient for this purpose. However, the lack of data such as sensitivity, specificity, PPV and NPV of total PSA limits the analysis of risk of bias regarding patient selection and the elaboration of possible correlations with the characteristics of individuals.

Conclusion

Eight of the nine articles analyzed demonstrated that the accuracy of PCA3 is favorable to reduce the indication of unnecessary prostate biopsies, presenting specificity higher than PSA. However, due to the risk of bias in these studies, it was not possible to show that PCA3 is superior to PSA in the diagnosis of prostate adenocarcinoma.

Comparatively, PSA and PCA3 levels were higher in black individuals than in non-black individuals, which could overestimate the indication of biopsy for such population, indicating the need for future research analyzing the variation in the expression of these markers between the different ancestries in order to verify if it is possible to establish specific cutoff points for the indication of biopsy, considering its genomic characteristics.

This review emphasizes the significant performance of PCA3 density to guide the medical decision of the histopathological examination, suggesting the conduction of further clinical studies certifying its accuracy in representative populations.

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