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DIAGNOSTICS OF PROSTATE CANCER: A 10 YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *Prostate cancer ranks as the second most common malignancy in men globally, following lung cancer. The present method of diagnosing prostate cancer is marked by a significant level of diagnostic uncertainty. This uncertainty has led to both overtreating and undertreating, leaving the medical community unsure about the most effective approach for prostate cancer diagnosis. This study aims to to provide a 10 year systematic review of prostate cancer diagnosis.*

Methods: *This systematic review adhered to the PRISMA 2020 standards and included full-text English literature published between 2014 and 2024. Exclusion criteria involved editorials, review articles from the same journal, and submissions lacking a DOI. Literature was gathered from online sources such as PubMed and SagePub.*

Result: *Our search in PubMed yielded 24,278 articles, while SagePub produced 5,016 articles. Focusing on the year 2014, PubMed had 270 articles, and SagePub had 502. Ultimately we selected 5 papers that met our criteria, 3 from PubMed and 2 from SagePub.*

Conclusion: *This study concludes that prostate cancer diagnosis can be done with biopsy in combinations to other modalities such as vibrational spectroscopy, PSA level and PSA-density, mpMRI, and biomarkers such as PCA3 and AMACR.*

Keyword: *Prostate cancer, diagnosis, detection*

INTRODUCTION

Globally, prostate cancer is the second most common malignancy in men, following lung cancer in the first place. In 2017, 160,000 men received a diagnosis, contributing to a total of 3.3 million survivors. According to GLOBOCAN 2018, there were 1,276,106 new cases leading to 358,989 deaths. Prostate cancer accounts for 3.8% of all cancer-related deaths in men.[1]

Prostate cancer in its initial stages is often asymptomatic and tends to progress slowly with a non-aggressive course, requiring minimal or no treatment. However, potential symptoms may involve challenges with urination, increased frequency, and nocturia, which can also suggest prostatic hypertrophy. As the disease advances, more severe stages may manifest with urinary retention and back pain, particularly as the axial skeleton becomes the primary site for bony metastases.[2]

Globally, prostate cancer incidence and mortality are closely tied to advancing age, with an average diagnosis age of 66. African-American men show higher incidence rates than White men, with 158.3 new cases per 100,000 men and a mortality rate approximately double that of White men. Various risk factors, including genetic predisposition, family history, and race/ethnicity, contribute to prostate cancer development. Individual, environmental, and occupational factors further explain epidemiological variations. Disparities are associated with social, environmental, and genetic factors. While an estimated 2,293,818 new cases are projected by 2040, a minimal increase in mortality (1.05%) is expected.[1,3]

Diagnosing prostate cancer can be done with digital rectal examination (DRE) and a blood test for prostate-specific antigen (PSA), followed by a biopsy guided by transrectal ultrasound (TRUS). PSA is a glycoprotein produced by the prostate tissue. Elevated PSA levels (PSA > 4 ng/mL) are often indicative of prostate cancer. However, as increased PSA levels can also occur in men without cancer. A tissue biopsy is the standard procedure to conclusively confirm the presence of cancer.[2,4]

Despite its widespread occurrence, prostate cancer still poses a significant risk to long-term health, ranking as the third-leading cause of cancer-related deaths in men. Current technologies and advancement has allowed progress in prostate cancer diagnosis.[3] This study aims to to provide a 10 year systematic review of prostate cancer diagnosis.

METHODS

Protocol

The author followed the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 to ensure that this study adhered to the requirements. This method was chosen to guarantee the accuracy of the conclusions drawn from the inquiry.

Criteria for Eligibility

This systematic review was done by assessing evidence on post vaccination immune response in children with IBS. Evidence was compiled and analyzed thoroughly to provide an explanation and enhance the handling of patients' treatments. The primary objective of this paper is to demonstrate the relevance of the identified main points as a whole.

The inclusion criteria for this study are as follows: 1) The paper must be written in English, and 2) The studied papers include several that were published between 2014 and 2024. The exclusion criteria for this study are: 1) Editorials; 2) Submissions without a DOI; 3) Review articles that have already been published; and 4) Identical entries in published journals.

Search Strategy

We used “prostate cancer” and “diagnosis” as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields]) AND ("diagnosable"[All Fields] OR "diagnosi"[All Fields] OR "diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnose"[All Fields] OR "diagnosed"[All Fields] OR "diagnoses"[All Fields] OR "diagnosing"[All Fields] OR "diagnosis"[MeSH Subheading])) AND ((ffrft[Filter]) AND (fft[Filter]) AND (2014:2024[pdat]))*.

Data retrieval

The authors assessed studies by reviewing their abstracts and titles to determine their eligibility. We selected relevant studies based on their inclusion criteria, focusing on research that aligned with their article's objectives. A consistent trend across multiple studies led to a conclusive finding. The selected submissions were required to be in English and previously unpublished.

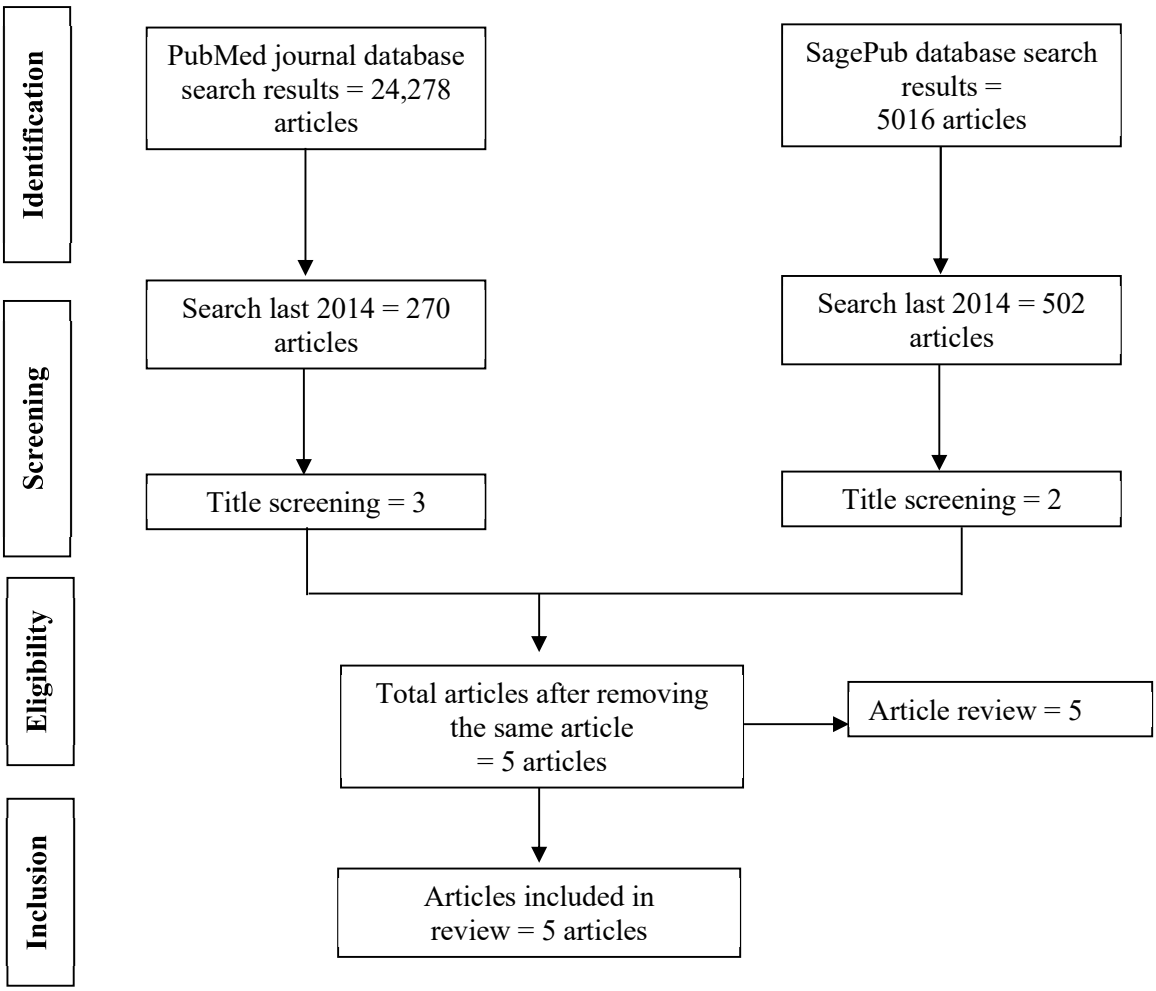

Figure 1. Article search flowchart

This systematic review only considered literatures that met all inclusion criteria and relevance to the topic. Studies not meeting these criteria were excluded, and their conclusions were not considered. The subsequent analysis delved into various details uncovered during the research inquiry, including names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author individually examined the research mentioned in the publication's title and abstract before deciding which publications to explore further. The next step involves evaluating all articles that meet the criteria set for inclusion in the review. Based on the uncovered findings, decisions will be made regarding which articles to include in the review. This criteria streamlines the process of selecting papers for further assessment, discussing the earlier investigations conducted and the elements that make them suitable for inclusion in the review.

RESULT

In our search on the PubMed database, we found 24,278 articles, while on SagePub, the search yielded 5,016 articles. Specifically, for the year 2014, PubMed produced 270 articles, and SagePub had 502. Ultimately, we selected a total of 5 papers, with 3 from PubMed and 2 from SagePub. The study includes six literatures that met the criteria, and Table 1 displays the literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Ahdoot et al., 2018.[5]	Multicenter	Clinical study	2,103 patients	In a study involving 2,103 men, both biopsy methods were

				administered, with cancer diagnosed in 62.4% through a combination of the two methods (combined biopsy), and 19.2% undergoing radical prostatectomy. MRI-targeted biopsy displayed lower cancer detection rates for grade group 1 cancers and higher rates for grade groups 3 through 5 compared to systematic biopsy. Combined biopsy led to cancer diagnoses in 9.9% more men than with either method alone and resulted in upgrading to a higher grade group in 21.8% of cases. However, relying solely on MRI-targeted biopsies would have misclassified 8.8% of clinically significant cancers (grade group ≥3). Among the men who underwent radical prostatectomy, combined biopsy was associated with the fewest upgrades to grade group 3 or higher on histopathological analysis (3.5%), compared to MRI-targeted biopsy (8.7%) and systematic biopsy (16.8%).
Medipally et al., 2020.[6]	Ireland	Cohort study	76 patients	The study utilized PCA to distinguish between the infrared and Raman spectra of plasma and lymphocytes from both healthy donors and prostate cancer patients. Differentiating signatures were observed in plasma and lymphocytes, particularly in patients with varying Gleason scores. A PLS-DA model effectively discriminated these groups, achieving sensitivity and specificity rates between 90% and 99%. CLS fitting analysis identified essential analytes associated with

				the development and progression of prostate cancer.
Chau et al., 2023.[7]	Memphis, Tennessee	Retrospective study	506 patients	The analysis involved 506 men with a median age of 66 (interquartile range (IQR) = 60–69). The median PSA was 6.6 ng/mL (IQR = 4.72–9.26). PIRADS ⩾ 3 was reported in 387 (76.4%) cases. Detection rates for Grade Group ⩾ 2 were 227 (44.9%), and for any cancer, it was 318 (62.8%). The MRI-based nomogram exhibited a performance with an area under the curve (AUC) of 0.84 (95% confidence interval (CI) = 0.81–0.88) for Grade Group ⩾ 2% and 0.85 (95% CI = 0.82–0.88) for any prostate cancer.
Nordstrom et al, 2017.[8]	Stockholm, Sweden	Prospective study	58,818 patients	The median PSA-density was 0.10 ng/ml² (IQR 0.075–0.14). PSA-density was linked to the risk of detecting clinically significant prostate cancer (csPCa), both with and without adjustments for additional clinical factors such as age, family history, previous biopsies, total PSA, and free/total PSA (OR 1.06; 95% CI: 1.05–1.07 and OR 1.07, 95% CI 1.06–1.08). Including PSA density in a model with additional clinical information improved discrimination for csPCa (AUC 0.75 vs. 0.73, P < 0.05). The proportion of men with Gleason Score 6 (ISUP 1) remained similar across different PSA-density strata. Omitting prostate biopsy for men with PSA-density ≤0.07 ng/ml² could save 19.7% of biopsy procedures, while missing 6.9% of csPCa. PSA-density cutoffs of 0.10 ng/ml² and 0.15

				ng/ml² resulted in the detection of 77% (729/947) and 49% (461/947) of Gleason Score ≥7 tumors, respectively.
Ji et al., 2019.[9]	Single center	Retrospective Study	292 patients	This study involves 292 urine sediment samples collected after digital rectal examination, levels of AMACR and prostate-specific antigen (PSA) messenger RNA (mRNAs) were assessed using quantitative real-time polymerase chain reaction. The diagnostic effectiveness of the AMACR score was evaluated through various analyses, including ROC, Mann-Whitney test, logistic regression, and decision curve analysis. For all patients, the area under the curve (AUC) for serum PSA, AMACR score, and a combined model of both parameters were 0.745, 0.753, and 0.784, respectively. The combined model outperformed the AMACR score significantly. Among patients with serum PSA levels of 4 to 10 ng/mL, the AMACR score was significantly higher in those with prostate cancer (PCa), while serum PSA showed no difference. The AMACR score and the combined model demonstrated better diagnostic value than serum PSA, particularly in patients with PSA levels between 4 to 10 ng/mL. Decision curve analysis suggested that a biopsy prediction model incorporating the AMACR score provides a superior net benefit when the threshold probability is greater than 20%.

Ahdoot, et al.[5] (2018) showed that in patients with visible lesions on MRI, utilizing a combined biopsy approach resulted in a higher overall detection of prostate cancers. Relying solely on MRI-targeted biopsy led to an underestimation of the histologic grade for certain tumors. Following radical prostatectomy, there were significantly fewer upgrades to grade group 3 or higher in histopathological analysis when a combined biopsy approach was employed.

Medipally, et al.[6] (2020) demonstrated that Raman and Fourier Transform Infrared (FTIR) can be used as a first stage diagnostic modality for prostrate cance. FTIR can be easily adaptable to many other bodily fluids and could be useful for translation of liquid biopsy-based diagnostics into the clinic.

Chau, et al.[7] (2023) demonstrated a high accuracy for prostate cancer prediction using age, PSA density, and mpMRI PIRADSv2 score as prognostic variables. This study supports the use of risk calculators in the decision-making process of whether or not to perform prostate biopsy and can be used for both TRUS and transperineal approaches.

Nordstrom, et al.[8] (2017) showed that PSA density proves as a dependable marker before proceeding to biopsy in prostate cancer diagnosis. Integrating PSA density into the diagnostic algorithm has the potential to spare men from the associated morbidity of undergoing a prostate biopsy and being diagnosed with low-grade prostate cancer.

Ji, et al.[9] (2019) also demonstrated that the diagnostic model combing serum PSA and AMACR score has a better diagnostic value in patients with abnormal PSA level (including PSA level ranging from 4-10 ng/mL). The use of this modalities in prostate cancer diagnosis could reduce unnecessary prostate biopsy in clinical use.

DISCUSSION

The present method of diagnosing prostate cancer is marked by a significant level of diagnostic uncertainty. This uncertainty has led to both overtreating and undertreating, leaving the medical community unsure about the most effective approach for prostate cancer diagnosis.[5] The diagnosis of prostate cancer is based on the microscopic evaluation of prostate tissue obtained via needle biopsy. Biopsy modality was site dependent and consisted of both transrectal ultrasound (TRUS) and transperineal approaches. Traditionally, a systematic prostate biopsy used TRUS to collect 10 to 12 tissue samples arranged in a grid-like pattern. A pathologist evaluates these samples and assigns a primary Gleason grade for the predominant histological pattern and a secondary grade for the highest pattern. The grading is done on a scale of 1 to 5, determined by the microscopic architecture and appearance of the cells.[3]

Prostate cancer is often identified in its early stages before spreading to other areas of the body. Initial assessments involve a prostate-specific antigen (PSA) blood test and a digital rectal examination (DRE). However, the widespread utilization of PSA has generated controversy due to its limited sensitivity and specificity, making it susceptible to false positives and false negatives, especially in men displaying symptoms that suggest a potential diagnosis of prostate cancer.[6] This confusion can be aided by utilizing PSA density analysis. Previous study showed that PSA density performed better than only PSA in detecting prostate cancer. The decision to perform a biopsy can be recommended for patients with low PSA density levels (<0.07 ng/ml^2).[8]

Vibrational spectroscopy methods such as Raman and infrared (IR) spectroscopy are nondestructive, non-invasive, and reagent-free diagnostic methods in detecting prostate cancer. This technique are also able to detect biochemical profiles of cells, tissues, and biofluids. Infrared (IR) spectroscopy relies on the sample's absorption of infrared radiation in which specific frequencies reflect the molecular structure. On the other hands, Raman spectroscopy used inelastic scattering of monochromatic light which alters photon frequencies upon interacting with the sample. Vibrational spectroscopy has been applied to biofluids (serum or plasma) and it has effectively distinguished non-cancer controls and patients with head and neck cancer, breast cancer, cervical cancer, and prostate cancer with sensitivities and specificities surpassing 75%.[6]

Recent developments in multiparametric magnetic resonance imaging (mpMRI) for the prostate allows targeted biopsies based on suspicious imaging findings. Studies indicate that MRI-targeted biopsies have a higher detection rate for high-grade cancers compared to systematic biopsy. There is ongoing debate regarding whether MRI-targeted biopsy should replace systematic biopsy or be used in conjunction with it, despite the improved identification of clinically significant cancers. However, Ahdoot et al.[5] (2020) showed that that MRI targeted biopsy alone underestimated the histologic degree of some tumors and combined biopsy would led to more prostate cancer detection. Chau et al.[7] (2023) stated that PIRADSv2 score in mpMRI can be used as a supplementary diagnostic modalities along with age and PSA density in the decision making process of doing both TRUS and transperineal biopsy in diagnosing prostate cancer.[5,7]

Newfound studies also demonstrated that molecular biomarkers can be used to distinguish prostate cancer from benign disease. Identifying potential urine molecular biomarkers for prostate cancer can be a non-invasive diagnostic method given that prostatic secretion products and shedding tumor cells are found in urine. Numerous biomarkers for prostate

cancer have been identified in urine, including the TMPRSS2:ETS fusion gene, prostate cancer antigen 3 (PCA3), glutathione S-transferase P1, vascular endothelial growth factor (VEGF), matrix metalloproteinases-9, and annexin A3.

PCA3 is the most commonly used in current clinical practice since PCA3 is located on chromosome 9 (9q21-22) and is exclusively expressed in prostate cancer tissues. Other biomarker such as Alpha-methylacyl-CoA racemase (AMACR) is also highly expressed in prostate cancer tissues and shows 82-100% sensitivity and 79-100% specificity. The combination of PSA and AMACR score can be a distinct diagnostic value in patients with abnormal PSA level. The use of biomarkers in detecting prostate cancer can reduce the needs of unnecessary biopsy in clinical setting.[9]

CONCLUSION

The diagnosis of prostate cancer can be ardious. Advancement in prostate cancer diagnosis with the use of recent technology has improved the predictability of treatment. Prostate cancer diagnosis can be done with biopsy in combinations to other modalities such as vibrational spectroscopy, PSA level and PSA-density, mpMRI, and biomarkers such as PCA3 and AMACR.

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