Early Screening of Prostate Cancer Using Molecular Approaches in Hospitals' Patients' Families: Systematic Review

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ABSTRACT

Prostate cancer is a major global health concern, with Saudi Arabia reporting an incidence rate of 6.1 per 100,000 individuals. This study investigates molecular screening methods for prostate cancer, particularly in familial populations, to improve early detection and management within Saudi Arabian hospitals. A systematic review was conducted using a structured methodology that adhered to PRISMA guidelines, focusing on peer-reviewed human studies and excluding non-clinical and animal studies. Out of 225 identified articles, 35 were evaluated in detail, and 32 were included in the final qualitative synthesis. The included studies highlighted the accuracy, sensitivity, and specificity of molecular screening approaches, emphasizing biomarkers such as PSMA-RGS, ctDNA, PTEN, ERG, SPINK1, and TFF3. These findings underscore the importance of integrating molecular markers into diagnostic, prognostic, and therapeutic strategies to enhance patient outcomes and support personalized treatment approaches.

1. Introduction

Prostate cancer [PCa] is a predominant cancer among males worldwide and has the third highest mortality rate[1]. There are international variations in PCa prevelance rates. PCa in the United States is more rated among African Americans race than in Caucasians or Hispanics race and is also more affected in males who had a positive family history [2]. Due to inadequate epidemiological estimation reports, there is a dearth of information regarding the prevalence of PCa in Saudi males. Nonetheless, the prevalent clinical perception is that Saudi Arabia has a far lower frequency of PCa than developed nations.[3]. According to geographical regions the rate of prostate cacner in Saudi arabia is variable but is estimated to be 6.1 per 100,000 individuals [4]. According to a 2019 study by Almutairi et al., the prevalence of PCa in Saudi males is higher than that calculated by the Saudi Cancer Registry and is on par with that of affluent nations.[5]. A routine screening for prostate-specific antigen (PSA) among Saudi males patients is recommended[1].

Numerous investigations conducted throughout the world have revealed that PCa is related to family history and may have a genetic or hereditary origin. Hereditary PCa types can arise as a result of genetic mutations in the DNA damage repair genes [BRCA1, BRCA2, CHEK2, ATM, and PLB2] and DNA mismatch repair genes [MLH1, MSH2, MSH6, and PMS2]. [6]. Yadav et al. examined normal tissue samples from African Americans and Caucasians with exome sequencing of 124 DNA damage repair and response genes in malignancies from formalin-fixed, paraffin-embedded tissues.[7]. They found 762 somatic mutations in Caucasian malignancies and 671 somatic mutations in African American tumors. For African American men, the most common mutations were in the EXO1, ATR, POLQ, NEIL3, ERCC6, BRCA2, BRCA1, XPC, JAG1, RPA1, POLE, ATM, and LIG1 genes; for Caucasians, the most common mutations were in the POLQ, NEIL3, POLB, BRCA2, EXO1, ERCC6, ATR, RBBP8, BRCA1, ATM, JAG1, XPC, and POLE genes. [8].

Single nucleotide polymorphisms [SNPs] have been implicated in the development of PCa, according to multiple genome-wide association studies. [9]. It was discovered that individuals with the homozygous

T allele of the rs10993994 SNP were more likely to develop PCa than those with the homozygous C allele. .[10]

The incidence of SNP in Saudi Arabia has not been sufficiently investigated before, even though there aren't many studies on the genetics and epidemiology of PCa in the Middle East and Arab nations. In order to ascertain a potential link with PCa in Saudi patients, a set of SNPs [Table 1] based on global and regional studies..[1].

Table 1: Set Of Snps:Represent General Trends And Potential Links Based On Previous Studies.

SNP ID	Gene Name/Region	Chromosome Location	Allele	Frequency Range	Potential Role in PCa	Reference
rs4430796	TCF2	17q12	A > G	Moderate	Associated with prostate cancer susceptibility.	Zheng et al. 11
rs1859962	CASC17	17q24.3	T > G	Moderate	Implicated in gene regulation affecting PCa.	Zheng et al. 11
rs16901979	Intergenic	8q24	C > T	Low	Common in prostate cancer risk loci.	Zheng et al. 11
rs6983267	CASC8, CCAT2	8q24	G > T	Moderate	Linked to genomic instability and PCa.	Wokolorczyk et al. 12
rs1447295	CASC8	8q24	C > A	Low	Related to non-coding regulatory functions.	Zheng et al. 11
rs1571801	DAB2IP	9	C > A	Low	Tumor suppressor gene affecting cancer spread.	Duggan et al. 13
rs1545985	FYCO1	3	A > G	Low	Related to cellular transport mechanisms.	Duggan et al.13
rs7652331	FYCO1	3	C > T	Low	Similar role as rs1545985 in PCa progression.	Duggan et al.13
rs629242	KIAA1211	4	C > T	Moderate	Implicated in DNA repair and genomic integrity.	Duggan et al.13

SNP, single nucleotide polymorphism

Benefits of molecular approach:

1- EARLY DETECTION

Finding individuals with prostate cancer who are asymptomatic for a prostate core biopsy and identifying which men will benefit from final therapy are the two primary objectives of current prostate cancer early detection programs.[14,15].

2- DIAGNOSIS

Tissue-based molecular biomarkers for prostate cancer diagnosis include RB1 and cyclin D1 IHC for neuroendocrine prostate cancer [NEPC], PTEN immunohistochemistry [IHC] for intraductal carcinoma of the prostate [IDC-P], PIN-4 cocktail and ERG IHC for atypical small acinar proliferation [ASAP], and a polymerase chain reaction [PCR]-based methylation assay [Confirm MDx] for negative core

biopsies.[16].

3- PROGNOSIS

The current prognosis for prostate cancer is based on easily accessible clinical data [e.g., age, serum total PSA, etc.] and histopathologic analysis of tissue from either radical prostatectomy or prostate core biopsy [e.g., GS, clinical or pathologic stage, etc.] only a small number of single-gene and multigene assays have been identified as potentially clinically beneficial.[16].

Prostate cancer molecular biomarkers for prognosis. Both single and multiple biomarker assays are tissue-based tumor biomarkers for prognosticationof prostate cancer. Clinically useful mono biomarker study such as PTEN DNA fluorescent in situ hybridization [FISH] or immunohistochemistry [IHC] and SChLAP1 RNA microarray or in situ hybridization [ISH].quantitative multiplex proteomics imaging [[QMPI] as published by Blume-Jensen et al. 2015], multiplex reverse transcription polymerase chain reaction [RT-PCR] assays [Oncotype Dx Prostate and Prolaris], and RNA microarray [GenomeDx Decipher]. are some tests for biomarkers that have therapeutic value..[16,17].

4- TARGETED THERAPEUTICS

Molecular biomarkers for prostate cancer-targeted therapies include AR-V7 transcripts [androgen receptor signaling], somatic mutations, PTEN alterations, and gene fusions [recurrent molecular alterations], DNA repair mutations [PARP1 inhibition and immunotherapy], and PD-L1 immunohistochemistry [IHC] [immunotherapy].[17].

CONCLUDING REMARKS

Recent advancements in technology have led to the creation of sophisticated molecular biomarker tests that can evaluate a vast number of biomarkers at once. For instance, next-generation sequencing has made it possible to develop multiplex targeted DNA and RNA sequencing tests that can simultaneously analyze somatic variants, copy number changes, and gene expression from small clinical tissue samples, such as prostate biopsies and tiny metastatic tissue areas [15,18,19].

Assays for molecular alterations in tumors offer a comprehensive overview, enhancing prognostication and risk stratification. Clinical trials offer unique opportunities to evaluate biomarker combinations. Advances in molecular biomarkers will influence prostate cancer care and management. However, rigorous studies are needed to demonstrate their cost-effectiveness in treatment decisions.[16].

This review study seeks to investigate molecular screening methods for PCa, particularly in familial populations, to enhance early detection and management in Saudi Arabian hospitals.

Methodology

1. Research Question and Objectives

- **Question**: What molecular approaches are being used for early screening of prostate cancer, particularly in patients' families, in Saudi Arabia hospitals

- **Objective**: To systematically identify and evaluate molecular screening methods for prostate cancer in familial populations

2. Eligibility Criteria

Inclusion Criteria:

- Studies published in peer-reviewed journals.
- Types of articles: RCT-Multicenter study-Clinical trial
- Human studies involving molecular approaches to prostate cancer screening.
- Studies focusing on familial cases of prostate cancer or patients with a family history of prostate cancer.

3. Search Strategy

Search Terms and Keywords: To ensure comprehensive coverage, we combined the following terms : [Prostate Cancer]] AND [[Molecular Screening]]] OR [Saudi Arabia]

4. Study Selection Process

First, we conducted a preliminary PubMed search. Step 2: After that, download all of the references and import them into Mendeley for categorization. Step 3: Duplicate articles were eliminated. Step 4: Using the inclusion and exclusion criteria as a guide, we screened abstracts and titles. Step 5: Retrieve full-text publications of relevant research for in-depth analysis. Step 6: Strict application of the qualifying requirements led to the final selection, which was based on a full-text review.

5. Data Extraction

We developed a data extraction form to collect relevant information from each selected study.

8. Reporting and PRISMA Flow Diagram

From the number of publications found in the search to the final number of studies included in the review, we demonstrated the selection process of studies by adhering to the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] standards figure 1 .

Results:

A total of 225 publications about prostate cancer and molecular screening were first found by the systematic review [200 from PubMed and 25 from Scopus]. 225 papers were screened for titles and abstracts after duplicates were eliminated. Due to their lack of relevance to the study's focus on early prostate cancer detection utilizing molecular techniques in Saudi Arabian familial populations, a sizable number of the papers 191were eliminated. Three of the 35 papers that were left for full-text review were disqualified because they did not satisfy the study's inclusion requirements. In the end, the final qualitative synthesis had 32 studies. The accuracy, sensitivity, and specificity of molecular screening techniques in the Saudi Arabian setting were all shown by this research, which ranged in design from cohort studies to case-control and clinical trials .

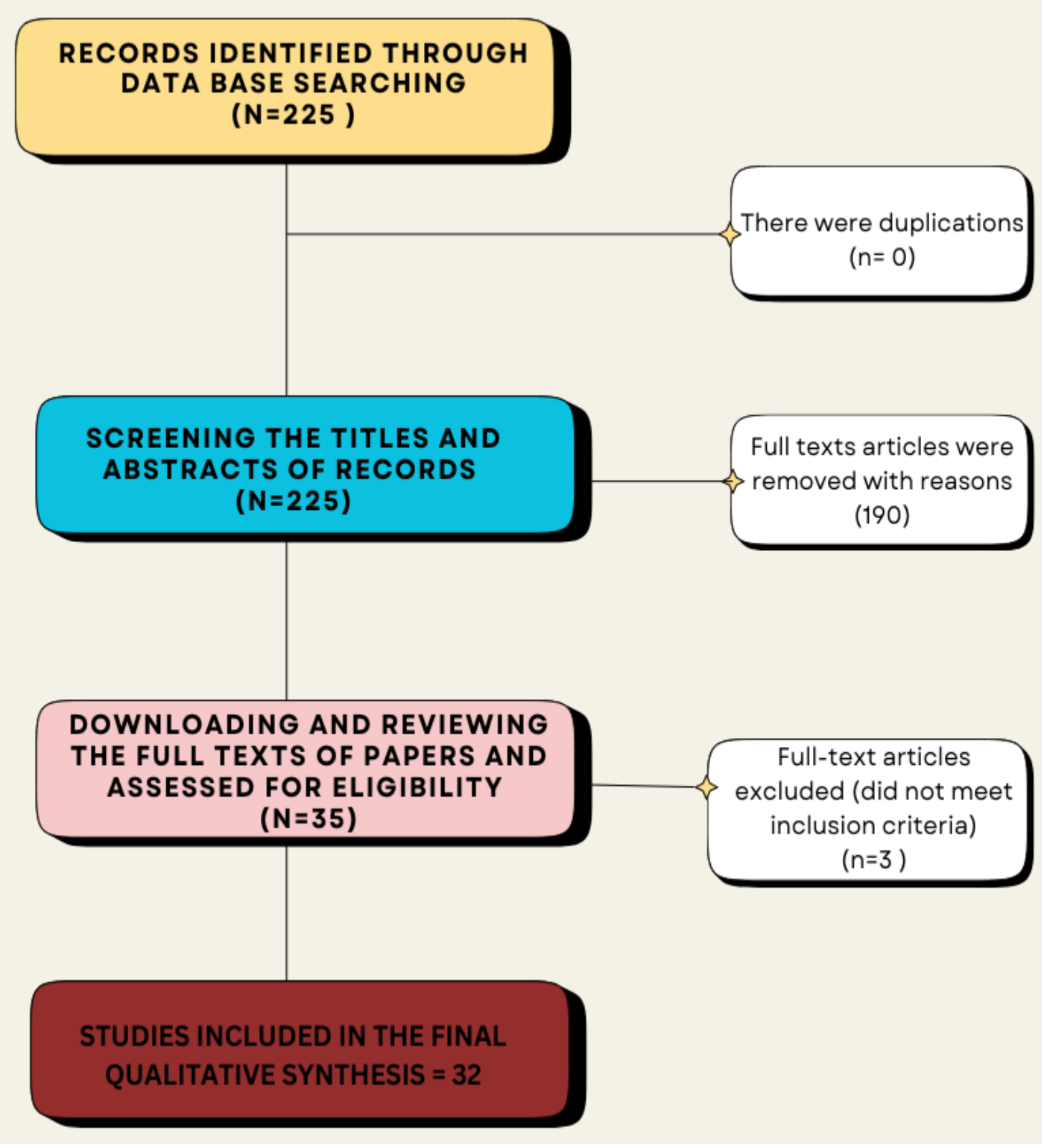

Figure 1:Results were displayed using a PRISMA flow diagram:

Discussion :

The results of 32 studies on the early detection of prostate cancer in hospitals were included in this systematic review. In high-risk groups, the analysis emphasizes the importance of early screening, especially in familial clusters where genetic predispositions may raise the risk of prostate cancer.

Molecular methods, including genetic testing, biomarker assays, and epigenetic profiling, were widely used in the research and showed differing levels of sensitivity and specificity in the early identification of cancer.

Both PSA and MRI have recently been investigated as methods for enhancing prostate cancer detection, either alone or in conjunction with other techniques, to improve accuracy and cut down on pointless treatments. There have also been comparative studies in which PSA was paired with either MRI or the Stockholm3 biomarker test. Similar detection rates for major tumors were found in the results. However, the biomarker-based strategy increased the number of biopsies, indicating that it would be a good substitute in places with limited access to MRIs.[20,21]. Additionally, recent research has contrasted transrectal [TRUSBx] and transperineal [TPBx] biopsy methods. Despite taking longer to perform, studies in Saudi Arabia have shown that TPBx has a far greater detection rate for clinically relevant prostate cancer than TRUSBx [22].

To further improve prostate cancer detection methods, systematic versus targeted biopsy procedures have also been assessed. For instance, in men with MRI-visible lesions, the STHLM3MRI pilot research examined the combination of targeted and systematic biopsies [CBx]. According to the study, CBx identified more significant cancers than targeted biopsy alone [43.6% vs. 39.2%], but it also found more non-significant cancers in cases where the MRI results were unclear.[23].

In prostate cancer detection, risk assessment, and staging, the use of sophisticated imaging methods like MRI and PSMA PET/CT has grown in significance, especially for high-risk or recurrent patients. According to the following studies, PSMA PET/CT greatly improves the ability to detect both localized and systemic disease, enabling more individualized treatment plans and more precise evaluations of the risk and progression of prostate cancer.

Even for individuals on 5-alpha-reductase inhibitors [5-ARI], research shows that MRI is a useful tool for prostate cancer screening and therapy planning. For example, despite 5-ARI exposure, MRI maintained high detection rates for clinically significant prostate cancer [csPCa], with aggressive cases often manifesting as PIRADS 4 or 5 lesions, according to multicenter research involving data from 24 institutions.[24]. Furthermore, MRI-based models like PLUM and RPCRC-MRI are diagnostically accurate in a variety of populations by multi-institutional research, indicating their applicability in clinical settings where MRI is essential for prostate cancer screening.[25].

Prostate cancer management has also benefited greatly from PSMA PET imaging, especially for accurate risk assessment and staging. Using the PROMISE nomograms, retrospective research with 2,414 patients showed that PSMA PET could successfully classify patients into high- and low-risk groups, providing better predictive accuracy than traditional techniques across different stages of prostate cancer.[26]. PSMA PET's prognostic usefulness in identifying aggressive disease types was highlighted by another study on high-risk nonmetastatic prostate cancer, which indicated that in 39% of instances, it discovered distant metastases not detected by traditional imaging.[27].

Furthermore, PSMA PET/CT is superior to traditional imaging modalities [such as CT and MRI] in detecting lymph node involvement [LNI] and forecasting systemic progression in patients with prostate cancer following radical prostatectomy [RP]. For instance, PSMA PET/CT performed better than routine imaging in identifying high-risk lymph node involvement in a cohort analysis of 1,163 patients,

confirming its use in precise staging and high-risk case decision-making.[28]. Furthermore, PSMA PET/CT demonstrated moderate-to-substantial accuracy in predicting tumor extent in a trial of 600 patients undergoing staging before prostatectomy, highlighting its usefulness in local tumor staging and treatment planning.[29].

Radiolabeled PSMA PET/CT has demonstrated potential in identifying residual or metastatic disease in cases of biochemical recurrence following prostatectomy, which is essential for directing salvage therapy. In patients with high PSA levels, a retrospective analysis validated the targeted method of PSMA PET/CT, enabling precise identification of recurrence sites [Table 2]. This feature facilitates prompt interventions and individualized treatment modifications to efficiently control the course of the disease.[30].

Table 2: Results of PSMA PET/CT according to low and high-risk BCR groups [30].

	Low-risk BCR group [%]	High-risk BCR group [%]	p-value
PSMA PET/CT positivity	38.0	72.4	0.026
Pelvis-confined disease	23.1	24.1	0.935
Metastatic disease	15.4	51.7	0.017
Prostate bed recurrence	15.4	19.0	1.0
Lymph node metastasis	23.1	41.4	0.219
Bone metastasis	7.7	37.8	0.048

68Ga-PSMA and 18 F-flotufolastat PET/CT are effective imaging modalities for prostate cancer detection and staging, particularly in cases of recurrence and bone metastasis. A study on 140 Saudi patients showed 68Ga-PSMA PET/CT superior in detecting skeletal lesions, correlating with PSA levels and bone metastases. [31].

In two phase 3 studies, 18 F-flotufolastat PET/CT showed high interreader and intrareader reproducibility, with agreement rates over 95% in newly diagnosed cases and over 75% in recurrent cases, reinforcing its consistency across different clinical scenarios[32]. In 171 patients with negative baseline imaging, 18 F-flotufolastat PET/CT had a 95% detection rate [DR] in another phase 3 investigation, detecting true-positive lesions in 64% of cases. Recurrence localization was improved by finding detections in the prostate bed, pelvic lymph nodes, and other areas in patients who had undergone prostatectomy. [33].

A European study on robot-assisted radical prostatectomy outcomes found high cancer-specific survival [CSS] and overall survival rates at 15 years, particularly among low- and intermediate-risk patients, emphasizing the importance of precise risk stratification.[34].

More tailored patient care is now possible because of tissue microarray analysis, which revealed that markers including PTEN, ERG, SPINK1, and TFF3 are connected to particular clinical outcomes. With a tumor-to-background [TtB] ratio of ≥2, PSMA-RGS has also demonstrated promise in identifying lymph node invasion, potentially minimizing needless prolonged pelvic lymph node dissections.[35]. Studies on urine-based biomarkers and circulating tumor DNA [ctDNA] further highlight the relevance of molecular diagnostics in improving the management of prostate cancer. Studies on genetics, specifically X chromosome STR markers, suggest potential links to prostate cancer risk, which may increase the precision of screening in particular populations, such as Saudi Arabians.[36].

The Middle East's prostate cancer awareness and early detection practices are varying, highlighting the growing disease burden and the need for effective screening programs due to demographic factors and steady mortality rates. The Global Burden of Disease 2019 study revealed a 77% rise in incidence and a 144% increase in the prevalence of prostate cancer in North Africa and the Middle East since 1990. This trend emphasizes the urgent need for effective prevention and treatment strategies in the region[37].

A retrospective study in Lebanon, Saudi Arabia, Iraq, and Kuwait found that 57.7% of prostate cancer patients had localized or advanced cancer, while only 4.1% had metastatic castration-resistant cancer. Underscoring the critical issue of late-stage diagnosis[38]. A similar study in Aseer, Saudi Arabia, which evaluated 883 patients, identified an 8.7% prevalence of prostate cancer, particularly among men over 60 with elevated PSA levels, further highlighting the disease's public health impact[39].

Statistics from studies on particular subtypes of prostate cancer in Saudi individuals were alarming. 5.8% of patients had prostate ductal adenocarcinoma [PDA], which is mostly linked to high-grade malignancies and has a 15.8% fatality rate, especially in the Kingdom's western region. More targeted studies on treatment outcomes for these subtypes are necessary since, on the other hand, adenocarcinoma with transitional cell features was found in 0.44% of cases, resulting in a mortality rate of 56.3% without any significant tumor or demographic variables associated with mortality.[40].

A cross-sectional survey of 372 healthcare professionals found disparities in screening practices, even though 91.4 percent of them were aware of the significance of cancer screening. Notably, older male healthcare practitioners favored PSA screening and fewer performed colonoscopies. These results highlight the urgent need to improve cancer screening practices in medical facilities.[41].

In a quasi-experimental study aimed at improving prostate cancer knowledge, participants demonstrated significant gains in awareness and intentions to undergo screening, highlighting the effectiveness of educational programs in bolstering early detection[42]. However according to a questionnaire of 1,212 males in Medina, Jeddah, and Makkah, 77% of them had heard of prostate cancer, but only 52.5% knew how to get screened for it, and just 3.9% had received a PSA test. This striking disparity emphasizes the need for strong public health initiatives to raise awareness and educate people about the advantages of early detection.[37].

Lastly, advancements in screening technologies, including machine-learning algorithms like Random Forest [RF] and XGBoost [XGB], have shown promise in enhancing the accuracy of prostate cancer predictions in patients with elevated PSA levels. This technological approach could play a crucial role in improving screening outcomes and reducing missed diagnoses[43].

Limitations and Recommendations

In our review,there were several limitations should be addressed. First, it is difficult to generalize results due to the diversity of study methodologies. For instance, it is difficult to compare sensitivity and specificity rates directly since different research use different molecular methodologies and imaging modalities. Second, a thorough grasp of prostate cancer trends in these regions is hampered by the underrepresentation of regional data, particularly in the Middle East. Last but not least, early identification and prompt interventions are hampered by the general public's and healthcare practitioners' uneven screening procedures and lack of awareness in Saudi Arabia.

Future research should place an emphasis on extensive, multicenter relationships with a broad population, especially from the Middle East and other underrepresented regions, in order to overcome such limitations. To ensure the viability and affordability of molecular biomarkers and advanced imaging techniques, research should concentrate on verifying them in real-world contexts. Future studies require to examine the long-term effects of combining different diagnostic techniques as well as how they affect patient survival and quality of life.

Conclusion

In summary, prostate cancer research has made significant strides, particularly in diagnostic and prognostic tools, through advancements in molecular markers and imaging modalities like PSMA PET/CT and MRI. These innovations offer a more precise approach to disease detection and staging, enabling tailored treatment strategies. Additionally, the integration of machine learning and the development of region-specific biomarkers hold promise for further enhancing early detection and risk stratification.

However, addressing limitations such as inconsistent methodologies, limited regional data, and awareness gaps is crucial to maximizing these advancements' impact. Collaborative research, public health initiatives, and technological innovations will be key in improving prostate cancer outcomes, particularly in regions like the Middle East.

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