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PROSTATE SPECIFIC ANTIGEN [PSA] AS EARLY DETECTION APPROACH FOR PROSTATE CANCER: SYSTEMIC REVIEW IN LITERATURE

Zead Alhussain[1]*, Ali Alghamdi[2], Husam Alamri[3], Rawan Alyami[4], Suliman Alnamlah[3], Ibrahiem Mutaki[5], Samar Alkhaldi[6], Saad Mushni[7], Mohammad Alelyani[2], Khalid Alamri[8]

[1]Arabian Gulf University, Medical College of Arabian Gulf University, Manama, Bahrain
[2]Albaha University Medical College of Albaha University, Albaha, Saudi Arabia
[3]Imam Mohammed Bin Saud Islamic University, Medical College, Riyadh, Saudi Arabia
[4]Tabuk University, Medical College of Tabuk University, Tabuk, Saudi Arabia
[5]King Faisal University, Medical College of King Faisal University, AL-Ahsa, Saudi Arabia
[6]Taif university, Medical College of Taif University, Taif, Saudi Arabia
[7]Imam Abdulrahman bin Faisal University, Medical College, Dammam, Saudi Arabia
[8]King Khalid University, Medical College of King Khalid University, Abha, Saudi Arabia

Abstract:
This review is aiming to discuss the prostate Specific Antigen [PSA] As Early Detection Approach for Prostate Cancer. A systemic search for the terms: Prostate Cancer, prevention, methods for early detection and screening using prostate specific antigen [PSA] was done up to 2018 in the period between the first of September to the 6th of October in different databases including Google Scholar, Science Direct and NCBI including PubMed, Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and its levels of evidence. Out of the five trials and studies, only the PLCO trial concluded to the fact that the prostate cancer screening using the prostate specific antigen shows no evidence in reducing the mortality from the disease after the follow-up period. This review concluded to the importance of using the PSA as a screening tool in reducing prostate mortality although more researches need to be done.

Keywords: *prostate specific antigen, early detection, screening.*

Corresponding author:
Dr. Zead Alhussain,
Arabian Gulf University,
Medical College of Arabian Gulf University,
Manama, Bahrain
Email: Alhussainzead@hotmail.com

QR code

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INTRODUCTION:

Prostate Cancer is the second most common cancer and the sixth leading cause of cancer death among men worldwide, with an estimated recorded amount of 1.1 million cases and 307,000 deaths in 2012. [1] [2]

Approximately 42% of prostate cancer occurs in men over the ages of 50 years old and the majority of them are often seen after 60 years. [3]

Screening for prostate cancer with serum prostate-specific antigen aims to detect prostate cancer at an early Intervenable stage amenable to curative treatment and reduction in overall and disease-specific mortality. [4][5]

The guidelines on prostate cancer screening that have been issues by :American Cancer Society [ACS], National Comprehensive Cancer Network [NCCN],American Urological Association[AUA], U.S Preventive Services Task Force [USPSTF], American College of Physicians[ACP] and European Association of Urology/European Society for Radiotherapy and Oncology/International Society Of Geriatric Oncology [EAU/ESTRO/SIOG] differ in their recommendations regarding whether or not to provide a routine prostate-Specific-Antigen [PSA]-based prostate cancer screening, in what age group and life expectancies, and at what intervals. So the method of screening for prostate cancer remains a controversial issue in medical community. [6].

The risk factors for developing prostate cancer can be divided into modifiable and non-modifiable risk factors.

The non-modifiable risk factors include:

Age: Study of age-specific incidence curves reveals that prostate cancer risk begins to rise sharply after age 55 years and peaks at age 70-74, declining slightly thereafter. [7].

Race/ethnicity: prostate cancer occurs more often in African-American men and in Caribbean men of African ancestry than in men of other races. [8]

Genetic factors: segregation studies have identified familial clustering patterns of prostate cancer that are consistent with the presence of high penetrance genetic mutations that confer a Mendelian pattern of inheritance. [9]

Family history: The relative risk [RR] for developing prostate cancer is higher in men who have a first-degree relative with prostate cancer [RR 2.48, 95% CI 2.25-2.74] than men without a first-degree relative with prostate cancer. [10]

The non-modifiable risk factors include the following:

Smoking: smoking is associated with a moderate increase in the risk of prostate cancer. This association is much stronger and the increase more pronounced for aggressive or fatal cancers particularly in current or heavy smokers who could have double or more risk as non-smokers. [11] [12].

Lifestyle and dietary factors: accumulating evidence indicates that obesity may have a dual effect in prostate cancer: an increased risk of aggressive prostate cancer and decreased risk of localized prostate cancer. Although no clear links with specific dietary factors have been established, red meat, dairy fat and coffee have been mentioned as factors. [13]

External exposure: both ultraviolet radiation and ionizing radiation have been linked to prostate cancer. [14] [15].

Urinary tract infections: A number of separate lines of researches have pointed to a potential role of for inflammation in prostatic carcinogenesis and tumor

progression. [16].

METHODS:

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[PRISRM] declaration standard for systematic reviews. A systemic search for the terms: Prostate Cancer, prevention, methods for early detection and screening using prostate specific antigen [PSA] was done up to 2018 in the period between the first of September to the 6th of October in different databases including Google Scholar, Science Direct and NCBI including PubMed.

Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and it's based on the level of evidence as following:

Level 1 [likely reliable] evidence: representing research results addressing clinical outcomes and meeting an extensive set of quality criteria which minimize bias. example: Randomized controlled trial/meta-analysis.

Level 2 [mid-level] evidence: representing results addressing clinical outcomes, and using some methods of scientific investigation but not meeting the quality criteria to achieve level 1 evidence labeling. Example: well-designed non-randomized clinical trials.

Level 3 [lacking direct] evidence: representing reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion and conclusions extrapolated indirectly from scientific studies.

Inclusion Criteria:

Inclusion criteria were:

Age: Above 50 years.

Race: All races.

Prostate cancer.

Exclusion Criteria:

Exclusion criteria were:

Conditions other than prostate cancer like: prostatitis "Inflammation of the prostate" and Benign tumors of the prostate like benign prostatic hyperplasia.

Data extraction and analysis

Information's relating to the systemic review question elements was extracted from the studies and collated in quantitative tables.

The selected studies were summarized and unreproducible studies were excluded. Selected data is shown in the Table 1

RESULTS:

After the exclusion of the inadequate studies and trials and the inclusion of the trials and studies with a higher methodological quality, these five trials have reported different outcomes possibly because of the different research design.

The European Randomized Study of Screening for Prostate Cancer [ERSPC] at a 13 years of follow up in a multi-Centre randomized trial with a pre-defined centralized database, analysis plan and core age group [55-69 years] in eight different European countries concluded that a substantial reduction in prostate cancer mortality attributed to testing of PSA with a substantiality increased absolute effect at 13 years compared with findings after 11 and 12 years of age. [17]

In contrast the Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial which undertaken to determine whether there is reduction in prostate cancer mortality from screening using prostate Specific Antigen[PSA] ,concluded the following results: At 13 years 4250 participants had been diagnosed with prostate cancer in the intervention arm compared with 3815 in control arm, and after the 13 years of follow-up, the cumulative mortality rates

from prostate cancer in the intervention and control arms were 3.7 and 3.4 deaths by 10,000 person-years respectively with a final conclusion of that there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with the opportunistic screening.[18]

In the third randomized population-based prostate cancer screening trial with a total of eighteen year follow up with an objective of determining whether previously reported results indicating that PSA screening can reduce prostate cancer mortality regardless of the sociodemographic inequality resulted in the following: the systematic PSA screening reduces prostate cancer mortality. [19]

In contrast the CAP randomized clinical trial that tested the effect of a low-intensity PSA-based screening intervention on prostate cancer mortality and that compared a total of 415,357 men aged 50-69 years and assigned them into an intervention group [a total of 189,386 undergoing a single PSA screening] and a control group [a total of 219,439 not undergoing a PSA screening] resulted in: Out of the 40% attended the PSA testing clinic, 36%[67,313] underwent PSA testing, and out of the [64,436] with a valid PSA test result,11%[6,857] had a PSA level between 3 ng/ml and 19.9 ng/ml, of whom 85% had a prostate biopsy, after a median follow up of 10 years 549 died of prostate cancer in the intervention group vs 647 in the control group.[20]

In more details the study founded the following: the number of diagnosed prostate cancer was higher in the intervention group[n= 8054 ,4.3%] than in the control group[n= 7853 , 3.6%] and More prostate tumors with a Gleason grade of 6 or lower were identified in the intervention group[n= 3263/189,386[1.7%]] than in the control group [n= 2440/219,439 [1.1%]], finally in the analysis of the all-causes mortality there were 25,459 deaths in intervention group vs 28,306 deaths in the control group .So the study concluded that there was no significant difference in prostate cancer mortality after the median 10 years follow-up.[20]

The final retrospective cohort study that enrolled a total of 400,887 men under 80 years with no history of prostate cancer and who had PSA testing and were followed up for 12-16 years showed that early PSA screening is beneficial. [21]

Table 1 show summary for the selected studies:

Study	Sample Size	Findings	Level of evidence
Fritz H.[17]	7408 in intervention group 6107 in Control group	Substantial reduction in prostate cancer mortality attributable to testing of PSA	Level 1 RCT
Gerald L.[18]	38,340 in intervention group 38,345 in control group	No evidence of a mortality benefit for organized annual screening in the PLCO trial .	Level 1 RCT
Jonas H.[19]	10,000 in intervention group 10,000 in control group	Systematic PSA screening reduces prostate cancer mortality	Level 1 RCT
Richard M.[20]	189,386 in intervention group 219,439 in control group	No significant difference in prostate cancer mortality .but the detection if low-risk prostate cancer cases increased.	Level 1 RCT
Paul F.[21]	400,887 men	Early PSA screening is beneficial ,reducing prostate cancer deaths by64% for men aged 55-75 years ,and all-causes mortality by 24%	Level 2

DISCUSSION:

Out of the five trials and studies, only the PLCO trial concluded to the fact that the prostate cancer screening using the prostate specific antigen shows no evidence in reducing the mortality from the disease after the follow-up period. And because both PLCO and ERSPC trials were closely similar in their design, this section is focused on those two studies.

In the ERSPC trial the approach was a multi-Centre randomized trial with a pre-defined centralized database, analysis plan and core age group [55-69 years] in eight different European countries that assigned the population under the study randomly into two groups: screening[intervention] and no intervention [control] and after a multistep approach including methods to avoid bias such as masking investigators and a secondary analysis that focused on avoiding bias due to non-participation reached a final result of the significance of prostate cancer screening. Such a big trial with a high level of evidence and the scientifically organized steps support the importance of using a PSA as a screening and early detection tool.

On the other hand, the PLCO trial stated that there's no significance in using the PSA to reduce prostate cancer mortality. The PLCO trial is a Randomized Control Trial which assigned the population under study into control[usual care and sometimes included

opportunistic screening] and intervention group[Organized screening of annual PSA testing for 6 years] and after following 92% of the study participants to 10 years and 57% to 13 years the trial concluded that :1396 men in the screening group and 962 in control group of the 77% of the Screening group attended at least once had been diagnosed with prostate cancer thus showing that there is no significance in the mortality rate.

The absence of benefit might not be entirely due to contamination [screening in the control group] in the control group because the results did not vary by PSA- screening status at baseline, but those men who were screened before recruitment had 25% lower risk of prostate cancer death than those who were not screened.

CONCLUSIONS:

This review concluded to the importance of using the PSA as a screening tool in reducing prostate mortality although more researches need to be done.

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