

The Clinical Efficacy of Prostate Cancer Screening in Worldwide and Iran: Narrative Review

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Abstract

Prostate cancer (CaP) imposes a great health burden on men, while its incidence has significantly increased in recent years. The screening program for CaP is still controversial and recent large trials have failed to present a significant reduction in prostate-specific mortality and all-cause mortality. An entire body of data obtained from worldwide studies conducted on CaP screening is required to better evaluate health policy decisions and patient decision-making. In current review, the clinical efficacy of screening programs on CaP was discussed in numerous parts of the world, such as in the US, Europe, and Asia, to provide an updated screening recommendation. Finally, we discuss about CaP screening status in Iran and update the screening recommendation in Iran.

Keywords: Prostate cancer; Screening program; Digital rectal examination; Prostate-specific antigen; Iran

Introduction

As a most prevalent form of cancer in men, prostate cancer (CaP) is known to be a serious health threatening disease worldwide. According to the latest estimates of global cancer incidence, CaP is the third and sixth most common cancer in men and in the world (numerated by new cases), respectively. Nearly 10% of all cancers in men have appeared in North America, Europe, and some parts of Africa with annual 500,000 new cases [1, 2]. Some reports on its malignant form indicate it as the second cause of deaths in the world. Its risk of occurrence is enhanced by such factors as being from a black

race and having a positive family history or prostate intraepithelial neoplasia displayed in the previous biopsies [3].

A gradual increase is being witnessed for CaP incidence and rate of mortality among world's population. The incidence of CaP has undergone a high geographical variability. North America, as well as northern and western Europe countries have shown higher incidence rates of the disease compared to those of Asian countries, while south America and Europe have undergone an intermediate rate of incidence [4]. CaP has less frequently occurred in Japanese and Chinese men [5], whereas it has been reckoned to be the third most common cancer among men in Iran. Such differences are seemingly related to ethnic traits [6].

Although it has a high incidence and prevalence, its progression from an early to advanced disease takes a longer time compared to other malignant types of cancer, thus showing a rather slow growth rate [7]. For this reason, to promptly and potentially conduct a life-saving treatment for this disease, a reliable way for its detection in an early stage has been attempted to be found by Lamb et al [8] with the two goals of alleviating significant morbidities associated with the advanced prostate disease and its mortalities [9].

Cancer has been diagnosed with higher probability in the developed compared to developing countries. Due to early detections through some screening programs, the relevant mortality has been reported to be lower in the developed countries. The higher rates of morbidity and mortality in the developing countries are due to cancer detection in late stages and older ages, thus showing that screening programs are important since they lead to reduced diseases and mortalities and improved life qualities. Studies are indicative of probable live-saving in case of an early detection via CaP screening. Thus, it is highly important to use screening methods for cancer detection at curable stages.

The screening options for CaP include digital rectal examination (DRE) and blood test of prostate-specific antigen (PSA). For men of 50 - 69 years old, PSA and DRE screening of CaP have shown the overall \$3,574 - 4,627 costs per year of life-saving. For PSA alone, these figures for men of 50 - 70 years old have been \$3,822 - 4,956 [10].

No uniform recommendations for the current screening of CaP have been offered by National Health Organizations [11]. Controversial attitudes towards using DRE and PSA tests for the early detection of CaP have resulted from the recent guidelines and recommendations presented [12]. Yet, an entire body of data obtained from the studies conducted on CaP screening worldwide is required to provide individual patients

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with better information for decision-making and health policy decisions. Therefore, finding the clinical efficacy of screening programs for CaP in the US, Europe, and Asia was aimed at in this article. Finally, the screening status of CaP in Iran was discussed and updated as a screening recommendation.

Screening CaP in the US and Canada

Although no evidence exists based on large randomized trials to produce a net benefit in the US, most men over 50 years old were found to have undergone a PSA test [13]. Moreover, male urologists (95%) and primary care physicians (78%) with an age of 50 years or more were found to have practiced the PSA test [14]. Indeed, 5 years after PSA test introduction in 1992, the death rates due to CaP declined to nearly 4% per year in the US [15].

Since conflicting results were observed to be obtained from the largest trials on CaP based on a randomized controlled screening in the US [16], no consensus on the net benefit of its early detection was discovered. Thus, no final evidence for or against the screening as a method of reducing the mortality rates of CaP was achieved in the US. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial showed no success though expected. In fact, no unequivocal benefit was obtained from PSA screening in this large study [17]. During a median 11-year follow-up, no mortality benefit was arrived at through a combined screening with PSA test and DRE in the PLCO Cancer Screening Trial, which might have been practiced within a too short period for providing reliable data on the relevant mortality. Nevertheless, a wide confidence interval was deduced from the rather low number of end-points for CaP mortality regardless of the insignificant effect of PLCO trial assessed so far. The possible explanations for the negative results are high pre-screening levels in the PLCO population and the control group contamination [18].

According to the current guidelines presented for CaP screening in the US, no best tradeoff between harms and benefits has been achieved through a consensus. Considering the updated recommendations of the US Preventive Services Task Force (USPSTF) against PSA screening for CaP provided in 2012 (grade D recommendation), a moderate certainty on the fact that such screening benefits do not outweigh the harms has been achieved [19]. In fact, not sufficient evidence has been found by the USPSTF for evaluating the screening risks and benefits in the men younger than 75 years. It is commonly stated that a strong recommendation for patients' informed decisions from all the groups should be preceded with regard to the increasing number of men diagnosed with an early non-metastatic disease during screening as a prevailing benefit of the clinical over-diagnosis and overtreatment of insignificant cancers. The USPSTF recommends providing an informed choice for patients when physicians are to offer PSA screening since some uncertainties may be associated [20]. The updated screening guideline for CaP released by American Urological Association (AUA) in 2013 is indicative of no such recommendations for men younger than 40 years, routine screening for those aged between 40 and 54 showing an average risk,

and those older than 70 or guessed to have a life expectancy of less than 10 - 15 years. As noted by the AUA, an individual decision-making should be considered for higher-risk men aged between 40 and 54 years, while screening benefits may belong to those over an age of 70 years and who are in excellent health. Furthermore, a shared decision-making for PSA screening in the men aged between 55 and 69 years has been strongly recommended by the AUA [21].

As shown in another study performed on 1,067 US counties by Howrey et al, PSA testing rate was significantly related to both rates of CaP treatment and mortality for men ($P < 0.001$ for both rates), while no other causes were found for mortality. The mortality rate related to CaP demonstrated a reduction via PSA testing at the county level, while the number of over-diagnosed and over-treated men significantly increased [22].

Some guidelines for CaP screening through PSA has been recently published by the Canadian Urological Association (CUA), thus recommending beginning screening for all men with at least 10 years of life expectancy at the age 50 and repeating it every 1 - 2 years. Also, starting screening at the age of 40 has been recommended for "high-risk" men. This is while PSA testing for men has been suggested by Towards Optimized Practice (TOP) to be commenced at the age of 50. The relative risk of mortality from CaP in a screened population was reported to be improved by 67% in another randomized study carried out in the area of Quebec City [23]. Nevertheless, the study was methodologically criticized [23, 24] and thus a re-analysis plan is being currently pursued.

Noticeably, minor to major severity of harms and duration of screening were resulted. A short-term anxiety associated with bruising and bleeding was some common minor harm resulting from screening, while blood loss, infection, pneumonia, erectile dysfunction, and incontinence were some common major harms caused by over-diagnosis and overtreatment. Screening through PSA could lead to false-positive results and subsequent over-diagnosis. Biopsies guided through transrectal ultrasound (TRUS) could result in such adverse events as bleeding, pain, and infection. No detailed or comprehensive assessments were provided by the studies in terms of the screening effects on life quality or resource utilization [25].

Nonetheless, CaP screening should not be completely considered as non-beneficial when regarding all the above considerations. Hence, after informing the patient and his clinician and weighing his risk factors, decisions can be made about screening.

Screening CaP in Europe

The ultimate evidence for or against CaP screening as an approach to alleviate its mortality rate was expected to be provided by the European Randomized Screening for Prostate Cancer (ERSPC) as a multicenter trial in Netherlands, Switzerland, Sweden, Belgium, Finland, Italy, and Spain. Based on a randomized controlled trial (RCT), 82,816 and 99,184 men participated in the intervention and control groups (total of 182,000) for the screening procedure, respectively. PSA without DRE was reported by Schroder et al to lead to a

relatively reduced mortality rate of 20% during the average 9 years of follow-up. The absolute reduction of deaths from CaP was nearly seven men per 10,000 men screened. Therefore, it was recommended that this screening be weighed for additional interventions based on the burdens imposed only when the results are real and not yielded by chance or through bias. The side effects were estimated to be rather higher though the screening benefits were somewhat greater for men undergoing an actual testing without compliance compared to the untested ones. Overall, assessments of life quality and cost-effectiveness are the promising issues to be addressed by ERSPC in the future analyses. Although chance alone may be involved in the higher mortality of CaP induced by screening the subgroup of men over 69 years old, ERSPC has re-emphasized a necessarily cautious approach towards this decision. Assuming its correct point estimate, ERSPC recommended the necessity of screening 1,410 men and treating 48 additional men to prevent one death due to CaP within a period of 10 years [26].

GOTEBORG Randomized Prostate Cancer Screening (GRPCS) began another European prospective study on 19,904 men aged between 50 and 64 years at the time of randomization in 1995. A 14-year follow-up revealed a 44% reduction of mortality rate in CaP screening compared to the control group. Upon finding a statistically significant difference between the screening and control arms in terms of the relative risk of CaP mortality in a clinical trial, GOTEBORG reached a life-saving result obtained from an organized screening based on PSA and early intervention for treatment [27].

The results of both ERSPC and GOTEBORG Swedish trials on prostate screening demonstrated reduced mortalities from CaP [27, 28]. All the groups have highlighted the common themes of patients' necessarily informed decisions and increased number of men diagnosed with an early non-metastatic disease in the screening process. These are the benefits, which can be weighed against the present restrictions of potential downsides resulting from over-diagnosis and overtreatment of clinically insignificant cancers [29].

Another RCT was conducted by the Department of Urology and the South-East Region Prostate Cancer Register in Norrköping, Sweden, to evaluate the probability of mortality specific to CaP caused by screening. A total of 9,026 men aged between 50 and 69 years were identified by the National Population Register in the city of Norrköping, Sweden, in 1987. However, the men in the screening and control groups showed no significant differences in terms of mortality rate due to CaP after a 20-year follow-up program [30].

In 1988, 2,400 men aged between 55 and 70 years were randomly selected for CaP screening in Sweden and 65 men were detected to have CaP. Then, CaP diagnosis via screening and survival rate in the entire source population of 27,204 men in addition to 618 non-attendees for 15 years revealed no beneficial effects on the possible risk of death related to the disease or any other causes following their comparison with the mentioned invited men. However, the screening program could lead to a significantly reduced risk of death from any other causes [31].

Although the UK's National Screening Committee (UKNSC) has offered no universal recommendation for CaP screening, a decline of CaP mortality in the UK [32] and the Neth-

erlands [33] has been evidenced. Thus, an informed shared decision-making program has been provided for those requesting PSA testing after exchanging detailed information [34].

Also, an individualized approach based on a shared decision-making instead of a population-based screening has been recommended by the European Society for Medical Oncology (ESMO). As stated by ESMO, incongruent evidence has been discovered for screening the men younger than 50 years old and aged between 70 and 75 years, while its harms for those older than 75 years outweigh its benefits [35]. However, one has to acknowledge that despite all these efforts, the insights into the dynamics of collective decision-making in political science have yet remained far from complete.

In short, studies in Europe acknowledge that making decisions about existing CaP screening should consider the age of men and the risks of existing screening methods.

Screening CaP in Asia

There are unclear benefits of population-based screening based on PSA in the Asia-Pacific region since having a very low rate compared to those of Western countries.

In 2012, a total of 191,054 incidences and 81,229 mortalities related to CaP were recorded in Asian countries. Turkey, Lebanon, Israel, Singapore, and Japan were the five Asian countries with the highest standardized incidence rates, while Lebanon, Turkey, Armenia, Timor-Leste, and the Philippines were the five countries with the highest standardized mortality rates [34].

There are no available official guidelines on CaP screening in Asian countries, except in Japan, and thus, there is an urgent need to develop general guidelines for screening CaP for Asian individuals [36]. Screening through PSA has been recommended by the Japanese Urological Association (JUA) only for 50-year-old men or older. The recommendation is based on the merits and demerits of CaP screening in Japan with regard to the present and future perspectives. Therefore, the best screening system available for men who wish to be screened is provided by JUA [37].

The only known controlled study on CaP screening in Asia is the Japanese Prospective Screening for Prostate Cancer (JPSPC), which began in 2002 and ended in 2014. The study aimed at comparing the mortality rate of CaP between the screening and control cohorts. A total of 200,000 men aged between 50 and 79 years, who were from the prefectures of Gunma, Hokkaido, Hiroshima, and Nagasaki participated in this research. During 1992 - 2006, the compliance rate of PSA and contamination to CaP screening cohorts in Isesaki and Kiryu cities were almost 75% over 5 years and as low as 8%, respectively [36]. Since no opportunistic screening for CaP could be detected in Japan, a significantly low rate of contamination was expected for the whole control cohort. The outcome of the study is being well awaited to understand any possible potentiality for screening based on PSA in Asia [36].

Another large study conducted on CaP screening in Japan is a screening cohort study based on Kanazawa population. During the period of 2000 - 2006, 32,769 men aged

between 55 and 69 years took part in the program and 249 cases (0.76%) were diagnosed with CaP. A radical treatment was conducted for 75% of the patients. The overall survivals and cause-specific mortalities after 8 years were 93.3% and 97.5%, respectively. Four patients diagnosed to be involved in an advanced CaP died from the disease. Thus, the screening system effectiveness of this study, as well as its good clinical outcomes detected in the CaP patients was so well shown [38].

Assessment of the tendency and quality control of CaP screening was serially performed in the study of Okihara et al in an area of Japan for 10 years. Since 1995, 39,213 men older than 55 years have totally participated in the mass CaP screening in Otokuni District. In Japan, the primary screening of CaP has been widely recognized and the screening rate has thus increased through the basic health screening system. An extremely high rate of PSA exposure was found to have been practiced in Otokuni District; yet, it must be evaluated if such a procedure has reduced the mortality rate related to CaP. The need for prostate biopsy is substantially lowered by using prostate-specific antigen density (PSAD) in the secondary screening; yet, the quality of the screening system can be maintained only when the PSA-positive individuals are encouraged to be periodically screened for CaP [39].

The relationship between PSA screening and CaP mortality was investigated in South Korea. A total of 118,665 men participated in the study during 1994 - 2004 and then followed up to 2011. During the follow-up period, 56 and 6,036 men died for CaP and any other causes, respectively. A statistically significant enhancement of the multivariate-adjusted hazard ratio was found for CaP mortality with more concentrations of PSA (P trend < 0.0001) in a way that 1 ng/mL increase in PSA led to 7% enhancement of the hazard ratio. A stronger relationship was seen between CaP mortality and PSA concentration in younger and heavier men than in older and leaner ones. In this study, some implications were provided for biopsy recommendation through the development of targeted cut-points of PSA [40].

The impact of CaP mass screening in Vietnam has been evaluated in a study conducted in Binh Dan Hospital in Ho Chi Minh City since January 2008. During CaP program, 408 patients were totally screened. Generally, a low CaP prevalence (2.5%) and a high occurrence of medium-grade lesions (Gleason 7) among CaP-positive subjects were discovered via the initial outcomes. Although the value of CaP screening programs for the patients and doctors was highlighted through this observation and more cases were detected in the early stages of development, the mass screening benefits of CaP program were not proven. Nonetheless, prostate cancer diagnosis and treatment in Vietnam revealed to be promising via a selective CaP screening [41].

To explore CaP status in a healthy population in Nepal, 1,521 men aged over 50 years were evaluated from July of 2010 to June of 2011. In this study, the overall rate of locally advanced cancer detection was 0.73%. DRE specificity, sensitivity, and positive predictive value were 66.0%, 90.9%, and 38.5%, respectively. For detecting prostate carcinoma, the PSA sensitivity of higher than 4 ng/mL and the positive predictive value for serum PSA were 100% and 19.0%, respectively. A higher guarantee must be provided for larger studies based

on community, especially for high-risk groups [42].

Screening of 12,027 Chinese men for CaP was performed in Changchun in a Chinese cohort study in Changchun through the total PSA of serum and TRUS-guided systematic biopsies. Forty-one cases out of 12,027 cases were found to have prostatic carcinoma and moderately differentiated carcinoma as the most common type of CaP was revealed by the results. Also, an association between the total PSA value of serum in CaP, Gleason score, and tumor size was discovered through this study.

To evaluate the practicability of a potential screening program in Saudi Arabia, CaP prevalence was investigated in a healthy cohort of men through a small study of CaP screening. A total of 2,100 healthy subjects participated in the study from January to December of 2008. An elevated PSA value (≥ 4 ng/mL) was seen among 223 men, while 132 men were prepared for prostate biopsy. Fifty-two men were diagnosed to have CaP, while almost half of them had been already involved in locally advanced or metastatic cancers. A higher rate of prevalence of an advanced disease than what was expected was detected through screening.

Racial differences between Saudi and Canadian populations were studied in terms of the detection rate of CaP in a study conducted by Al-Abdin et al. The data prospectively obtained by the Urology Clinics of McGill University Health Center and King Saud University Hospital over 5 consecutive years were retrospectively analyzed. In this study, 414 Saudi and 1403 Canadian patients with a median age of 64 - 68 years were assessed. Compared to Western populations, Arabic populations demonstrated a significantly lower prevalence of CaP, for which there was no explanation. As a valuable marker for performing prostate biopsy, PSA is recommended to be adjustably applied with regard to the geographic and/or ethnic differences in the study populations. Also, a different set of PSA cut-offs compared to the current standards used in North America may be needed for an Arabic population. Furthermore, to determine this cut-off and provide a better definition of the optimal PSA values usable for the Arab world, more prospective analyses are required [43].

The most common non-cutaneous malignancy and third most common cause of death in men after bowel and lung cancers in New Zealand is prostate cancer [41]. An inquiry was conducted into the early detection and management of CaP by the Health Committee in New Zealand in search of screening advantages or disadvantages for the disease and its early diagnosis. Seventeen recommendations were included in the report of the Inquiry into an Early Detection and Treatment of Prostate Cancer presented to the House in July 2011. The Health Committee stated the necessity of clear evidence on any possible harms caused by over-diagnosis and overtreatment before establishing any organized national screening program besides outweighing its reduced morbidity and mortality. However, no conclusive evidence has been currently acquired in this issue. The Health Committee recommended a Quality Improvement Program (QIP) based on equity though no national prostate screening programs are available at present. According to this program, men must receive CaP information based on evidence to make informed decisions for testing and treatment, during which timely access to high-quality care can be ensured. In

New Zealand, inconsistent quality and equity of services has been noted by the Ministry of Health for an early detection and treatment of CaP. Currently, evidence-based information is not accessible to all men for making informed decisions. A framework within the existing resources was definitely developed by the Ministry of Health for the QIP [44].

In brief, it is still not clear that screening based on PSA can reduce deaths from CaP in Asia. Currently no official guidelines on screening for CaP in Asian countries are available, except in Japan [37]. Therefore, all the mentioned data suggest a need for developing a population-specific guideline since CaP features are diverse among different races in Asia. Notably, unlike the PLCO or ERSPC studies mentioned above, no large controlled trials can be easily organized for CaP screening in Asia due to the significant differences in the political systems, economic climates, and health policies of the countries involved. Therefore, there should be an option for applying a pre-determined statistical modeling and combining the available results of various Asian screening trials.

Yet, an optimal and standard screening system adjusted for Asian individuals through history can be established based on the PSA-related indices, serum PSA kinetics in middle-aged men, and new biomarkers discovered for CaP screening through the recent evidence [36].

Screening CaP in Iran

Cancer distribution significantly varies from country to country in the world. It can be said that the third and sixth most common cancer in men and in Iran is CaP, respectively [45]. Iran is a sovereign state in Western Asia. With over 79.92 million inhabitants (as of March 2017), Iran is the world's 18th most populous country. Comprising a land area of 1,648,195 km² (636,372 sq mi), it is the second largest country in the Middle East and the 18th largest in the world. During 2003 - 2008, the trend of CaP incidence was investigated in Iran. Totally, 16,071 CaP cases were identified in Iran. A significantly increasing incidence of the disease, especially for older men, with an annual percentage change of 17.3% was found. It is essential to conduct etiological and epidemiological studies and planning evaluation of CaP besides detecting and screening it at an early stage due to the changing lifestyles and population aging [46].

A significantly lower rate of CaP incidence has been detected in Iran compared to Western countries like the US. A combination of genetic and environmental factors can be the reason for this large disparity in CaP incidence. The high rates of CaP incidence reported in the Western countries may be partly due to people's increased awareness of prostate screening conditions and nationwide programs [47].

Consequently, the detection of localized latent cancer lesions in an attempt to detect CaP at an early stage through PSA screening has enhanced CaP incidence. In contrast, only clinically obvious diseases have been detected in Iran as reflected by the data on CaP incidence. This is certainly due to lacking any screening and early detection programs for CaP in this country. Moreover, high life expectancy in Western popu-

lations has resulted in the greater proportion of elderly men in those countries and consequent differences considering CaP occurrence mainly in higher ages. Some other reasons may be the Western risk factors of high-fat diet, sexual behavior, infectious agents, smoking, occupational exposure, and socioeconomic status. Finally, the number of people affected in Iran has been undoubtedly underestimated due to the lack of a registration system of high quality for CaP, whereas it has provided the most precise data in the Western world [47].

Only two large RCTs were found to be conducted on PSA screening in Iran since CaP has not been a suitable candidate for providing a national screening program in this country. A total of 3,758 Iranian males aged over 40 years were mass screened through PSA testing by Hosseini et al (2007). An extended prostate biopsy through TRUS-guided was practiced on the men having a total serum PSA level of higher than 4 ng/mL and undergoing an abnormal DRE. In this study, 65.9% of the cancers detected were clinically significant. Quite a common CaP development would occur to the Iranian male population if they had a serum PSA level of higher than 4.0 ng/mL [45].

Another study conducted by Safarinejad (2006), a large population-based study of screening using total prostate-specific antigen (tPSA) and percent free PSA (fPSA) as the initial test was performed. A total of 3,670 Iranian men aged over 40 years were mass screened with PSA in Tehran during 1996 - 2004. The subjects were invited for a DRE, PSA assay of serum, and TRUS-guided. The detection rate of clinically significant organ-confined CaP with potential curability is increased by screening via PSA associated with its low values of cut-off points [48].

A shared decision-making has been emphasized by the current guidelines though contradictory data have been obtained on CaP screening in the available research. This informed decision-making must be motivated by the physicians who are in charge of helping patients. On this basis, 184 urologists were invited by Ali Asgari et al (2015) to take part in a survey on CaP screening through a questionnaire. They showed that most Iranian urologists (76.8%) prefer to perform CaP screening despite the controversy on PSA testing. Many Iranian urologists with different backgrounds have been in favor of CaP screening regardless of their ages, years of experience, fellowship statuses, and types of medical practice. Of the urologists, 35.8% and 62.8% preferred biopsies and serial PSA screening in case of higher PSA levels than normal ranges in their follow-up plans, respectively. Therefore, PSA screening has been favored by Iranian urologists although its usefulness has still remained controversial. DRE has not been chosen by most Iranian urologists as part of a screening program. However, to investigate a rationale behind their decisions on CaP screening, large high-quality studies are required [49].

Clinically insignificant cancers may be over-diagnosed during an early detection of CaP and the subsequent overtreatment can reduce the life qualities of patients who inevitably experience untoward side effects. In any case, fighting against cancer as a priority, especially CaP, is highly recommended to be supported by Iranian government through the Comprehensive National Cancer Control Program (CNCCP). CaP prevention and early detection should be controlled via this program. Early detection of symptomatic benign prostatic hy-

perplasia (BPH) is also recommended for men over 40 years old though population screening is infeasible based on the currently available evidence. Nonetheless, population-based studies are needed for defining the PSA cut-off point and early detection method besides clarifying the suspected cases. Prior to the integration of this program into the CNCCP, assessment of the cost effectiveness of this method should be done through pilot studies. To take an urgent strategy and provide evidence on CaP treatment and a national guideline protocol for it for the next 5 - 10 years by using the existing experts' consensus, the local clinical trials should be supported [50] though unnecessary costs and burdens may be imposed on our health care system.

The two above-mentioned studies could not determine CaP screening effectiveness in Iran. Further research associated with additional follow-up years is required based on the existing RCTs to designate population screening advantage by reducing mortality. There are no available official guidelines on CaP screening in Iran. Nevertheless in Iran most urologists preferred biopsies and serial PSA screening in case of higher PSA levels. Yet, it must be evaluated if such a procedure has reduced the mortality rate related to CaP.

Although an early detection or symptomatic BPH for those aged over 40 years is highly recommended in Iran, population screening is not suitably feasible based on the currently available evidence. A clarified method of early detection of suspected cases should be provided for Iranian population by defining the PSA cut-off point. Before integrating this program into the CNCCP, evaluation of the cost-effectiveness of this approach should be done via pilot studies. Finally, to provide an urgent strategy based on the national guideline protocol for CaP treatment by using the current experts' consensus, the local clinical trials should be supported so as to achieve elaborate evidence in this area for the next 5 - 10 years [50].

Conclusion

Although various studies have been conducted on the effectiveness of CaP screening in different countries all over the world, the conflicting recommendations have further highlighted its uncertainty. In some areas, screening for CaP is recommended for a specific age range, and for other age, the cost and clinical beneficence should be considered. In some other areas, screening for CaP is recommended based on the life expectancy which is difficult to determine. Some population-based investigations have revealed need for defining the PSA cut-off point for each region. Some researchers believed that advantage and disadvantages of screening program should be clarified for the related offices of decision-making, but unfortunately in most cases comprehensive data are not available for them. Some studies have revealed that mortality reduced by screening program and generally recommended it, while some say there is no difference. Some researchers believed that along with the over-diagnostic disadvantage and unnecessary treatments, the novel method with higher sensitivity and specificity must be invented.

The best screening method for CaP is unknown though

both morbidity and mortality are probably reduced by screening. It may promote unwarranted treatment procedures or adversely affect the patients' health outcomes with an equal result of no net benefit or harm. It can be only justified if the potential follow-up tests and treatments are cost-effective though there is not a known economic implication for CaP screening.

Still, it is not clear that CaP mortality can be lowered by screening. A high over-diagnosis rate may be resulted by applying PSA screening policies to asymptomatic men. It is not certain that more benefit than damage is achieved through the best screening and treatment methods. Finally, well-informed patients can be screened upon request. For this purpose, validated tools of information should be developed and the men willing to be screened should be provided with clear information. Fortunately, these issues are being addressed through recent increasing reports [51].

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Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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