INTRODUCTION

Prostate cancer (PCa) is the second most common cancer globally. However, significant disparities exist in incidence and mortality between countries, especially between Western and Asian regions. This review discusses the applicability of Western-based randomized controlled trials on prostate-specific antigen-based PCa screening in other regions such as Korea, where PCa is less frequently diagnosed but tends to present more aggressive features compared to Western countries. The paper also reviews major guidelines and landmark trials, emphasizing the importance of an individualized approach in the context of regional diversity in PCa incidence and mortality.

Key Words: Prostatic neoplasms, Prostate-specific antigen, Early detection of cancer, Mass screening

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of the disparity in PCa prevalence can be attributed to the less frequent utilization of PSA testing [9].

Due to such clinical or genetic characteristics, Asian countries show a lower survival rate after diagnosis compared to Western countries [3,10,11], indicating a high potential for improving cancer management through early detection. However, the current guidelines for PCa screening using PSA testing are primarily based on prospective randomized controlled trials (RCTs) conducted in the United States and Europe in the early 2000s [12-16]. Despite RCT offering the highest level of evidence, their applicability is limited to specific study populations and intervention types. A uniform approach to PCa screening overlooks the considerable variability in cancer risk by regions and individuals. This represents the broader challenge of balancing evidence-based medicine with personalized medicine, where recommendations are customized for each individual [17]. In this context, the question arises: Should the policy for PSA-based PCa screening be uniform for all, or should it be individualized according to each country and/or race? We will review the current guidelines and their important evidences to assess whether it is appropriate to apply these guidelines uniformly, even when considering the varying characteristics across different countries and races. We will discuss it using Korean data as an example.

**MAJOR GUIDELINES REGARDING PSA-BASED PCa SCREENING**

In 2012, the US Preventive Services Task Force (USPSTF) recommended against routine PSA screening for men of all ages, a stance marked as a grade D recommendation [18]. Initial observations from this approach indicated that both the incidence of rate of PSA testing and early-stage PCa have declined [18], but a rise in more high-risk cases subsequently [19]. Predictive models have raised concerns that abandoning PSA screening entirely might reduce cases of overdiagnosis, yet could lead to an increase in patients presenting with advanced, metastatic disease, potentially boosting PCa mortality by 13% to 20% by 2025 [20]. A cohort study involving 836,282 patients with PCa, using data from the SEER (Surveillance, Epidemiology, and End Results) database spanning from 2004 to 2018, revealed that the incidence rates of metastatic PCa have increased significantly and coincide temporally with the USPSTF recommendations against PSA-based PCa screening across races and age groups [21]. Other nationwide epidemiologic study using comprehensive PCa mortality data through 2019 also demonstrated decreasing PCa mortality rates that flattened or increased after the 2012 USPSTF grade D recommendation [22]. Between 1999 and 2012, and then from 2014 to 2017, there was a significant increase in the age-adjusted incidence of metastatic PCa, particularly in men aged 60 years or older [22]. These changes were seen across ages, races and ethnicities, urbanization categories, and US Census regions. Consequently, the updated 2018 USPSTF guideline endorsed shared decision-making for men aged 55 to 69 years regarding individualized PSA-based screening, although it continued to recommend against screening in men aged 70 years and older [23].

In light of this, many professional society recommend a more nuanced, shared decision-making process, weighing the pros and cons of PSA screening, along with individual patient preferences and the uncertainties involved [13-15,24]. There remains, however, a divide in the specific guidelines about how to best implement screening for those opting in, especially concerning the ideal age for commencement and cessation, as well as the optimal screening frequency. Furthermore, the guidelines lack specific considerations for regions or ethnic groups, with the exception of African-Americans. The National Comprehensive Cancer Network emphasized the shared decision-making process and recommend PSA-based screening since 45 years of age [13,14]. They suggest testing intervals based on baseline PSA, digital rectal exams (DREs) and age. The European Association of Urology advises conducting an initial baseline PSA test in the 40s, adopting a risk-adapted strategy that takes into account factors such as family history, African-American ethnicity, and baseline PSA levels, after counseling patients about the potential risks and benefits [15]. The American Urological Association advised offering PSA screening to men between 55 and 69 years, with a more individualized approach for those aged 40 to 55, and suggests biennial screenings to mitigate potential risks [24]. In their latest revision, the guideline now supports initiating PSA-based screening for younger men aged 45 to 50 years, with
an emphasis on shared decision-making [16]. Additionally, it strongly recommends beginning PSA-based screening from age 40 to 45 years for individuals at increased risk of PCa based on the following factors: Black ancestry, germline mutations, and a strong family history of PCa, backed by evidence level grade B.

**LANDMARK TRIALS AND THEIR LIMITATIONS**

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a multicenter RCT, enrolled participants in the United States from 1993 through 2001. The study randomly assigned participants aged 55 to 74 to either a screening group (n=38,340) or a control group (n=38,345) [25]. The primary endpoint was PCa-specific mortality, compared between the 2 groups. For the screening group, PCa screening was recommended using PSA tests and DRE for the first 4 years, followed by PSA testing alone for the next 2 years. The control group received routine medical care. Individuals were recommended a prostate biopsy for a PSA>4 ng/mL or suspicious DRE.

The analysis of the PLCO trial showed no significant difference in PCa-specific mortality between the screening and control groups [25-27]. However, this outcome was anticipated, considering that about 91% of men in the usual care arm underwent PSA testing [28]. This high rate of contamination, reflected in the low incidence of advanced and metastatic PCas in both groups (1.9% and 2.7% in the screening group, 1.4% and 2.1% in the control group), undermines the study's findings. Furthermore, this trial had also other limitations. In the PLCO trial, some participating centers enrolled less than 10% of the total candidates in the study, contrasting with the European Randomized Study of Screening for Prostate Cancer (ERSPC), which included up to 75% of candidates. Additionally, prostate biopsies were recommended in cases with PSA>4 ng/mL or suspicious DRE, but only 30%–40% of these cases actually underwent biopsy. Despite these limitations, nonurological organizations interpreted the results as evidence against routine PSA screening. In contrast, specialists in urology and radiation oncology contended that the trial should not be viewed as conclusive evidence against PSA screening.

The ERSPC randomly allocated men aged 55 to 69 years to screening (N=72,891) or control (N=89,352) from 8 European countries from 1991 to 2005 [29,30]. A screening interval of 2 to 4 years using a serum PSA test was employed. For the indication of a biopsy, a PSA level of ≥3.0 ng/mL was used as the cutoff. The intention-to-screen analysis of the ERSPC indicated that PSA-based screening significantly reduced mortality about 20% over a median follow-up period upto16 years [29]. Moreover, individuals who underwent PSA test at least once showed a 25% reduction, while those who were screened more than twice demonstrated a 48% reduction in PCa mortality compared to the control group.

Analysis of Rotterdam section of the ERSPC showed very low nonattendance rate (5.4%) in the screening arm and true PSA contamination (defined as PSA testing in the absence of symptoms, 19.4%) in the control arm [31]. These indicators suggest that the quality and reliability of the ERSPC study are significantly higher compared to the PLCO study. Therefore, most guidelines on PCa screening from professional society regard the ERSPC as the only reliable large-scale RCT.

Following studies have suggested the potential benefits of initiating screening at an even earlier age. A Swedish study using stored serum samples revealed that elevated baseline PSA levels at ages 45 to 49 years were associated with an increased long-term risk of metastasis and PCa mortality [32]. Notably, 44% of all PCa mortality within 25 to 30 years occurred in men who were in the highest 10th percentile of the PSA distribution (≥1.6 ng/mL) at ages 45 to 49. In contrast, men with baseline PSA levels below the median of 0.68 ng/mL at this age range had less than a 0.1% risk of developing metastatic disease over the following 15 years. Thus, a randomized trial focusing on risk-adapted screening for PCas, known as the PROBASE trial, is currently underway. This study compares men who start screening at age 45 with those beginning at age 50. To date, 23,301 patients have participated in the first round of the trial [33].

**DIVERSITY OF PCa BY REGION**

The GLOBOCAN 2020 estimates highlight that cancer significantly contributes to morbidity and mortality globally, affecting every world region regardless of the level of human development [1]. It’s crucial to note the remarkable diversity...
of cancer by region, influenced by factors such as genetics, environment, healthcare accessibility, economic status, and the human development index. Therefore, the report also emphasizes that adopting a tailored approach to health planning at the national level can significantly reduce the future burden and suffering caused by cancer worldwide. This also implies the need for an individualized approach in the application of PCa screening plan, taking into account the differences between countries.

Incidence rates of PCa are 3 times higher in transitioned countries compared to transitioning countries (37.5 vs. 11.3 per 100,000), while mortality rates show less variation (8.1 vs. 5.9 per 100,000) (Fig. 1) [1]. The incidence rates across regions range from 6.3 to 83.4 per 100,000 men, with the highest rates observed in Northern and Western Europe, and the Caribbean, and the lowest in Asia and Northern Africa. However, the patterns of mortality rates do not mirror those of incidence; the highest mortality rates are found in the Caribbean and sub-Saharan Africa. This diversity in PCa incidence and mortality can be attributed to several factors, including advancing age, family history, specific genetic mutations (e.g., BRCA1 or BRCA2), ethnicity (e.g., African-American or Caribbean descent), and potentially lifestyle or environmental factors (e.g., smoking history or obesity). However, the most significant factor contributing to the global variation in PCa incidence is the regional differences in diagnostic practices for PCa including exposure rate of PSA testing [7,9].

We can notice that aggressiveness of the diagnosed PCa is higher in Africa and Asia, despite the higher incidence rate in Europe and America, when calculating mortality/incidence ratio (Fig. 1) [1]. In regions where the frequency of diagnosis is low and lethal cancers are more prevalent, implementing more aggressive PCa screening could potentially be more effective and cost-effective.

**EPIDEMIOLOGY AND CHARACTERISTICS OF PCa IN SOUTH KOREA**

Metastatic PCa is almost incurable and typically progress to castration-resistant PCa, ultimately leading to death. While the overall 5-year survival rate of men with PCa in Korea is 96.0%, the survival rate for those with metastatic PCa is significantly lower, at only 48.8% [34]. According to the National Cancer Registry data (2017–2021), the percentage of distant metastasis and regional disease in Korea was 10.1% and 25.6%, respectively. In comparison, data of from the Surveillance, Epidemiology, and End Results Prostate with Watchful Waiting Database in the United States (2010–2015)
showed corresponding rates of 5.8% for distant metastasis and 3.3% for pelvic lymph node metastasis [35]. In addition, in Korea, high-risk disease dominates even in localized PCa, accounting for over 60% of cases, which is significantly higher compared to about 30% in the United States [35-37]. One retrospective analysis comparing men who underwent radical prostatectomy in Korea and the United States showed that Korean patients had higher proportion of ≥T3 stage (34.8%) and Gleason score 8–10 (19.4%) compared to Caucasian (13.3% and 5.5%, respectively), and even compared to African-American (18.2% and 6.1%, respectively) [38]. These findings suggest a substantially increased risk of recurrence and progression posttreatment in Korea.

In Asia, a notable distinction in PCa compared to the Western countries is its rising incidence primarily among the elderly population. In Japan, where PCa became the most prevalent male cancer in 2016, approximately two-thirds of diagnosed patients were aged ≥75 years [39]. Similarly, in Korea, about 90% of the registered PCa patients were ≥60 years old, with about a third being ≥75 years old. In contrast, in the US, the proportion of men aged ≥75 years among PCa patients decreased from approximately 50% in 1975 to 20% in 2015 [35]. Moreover, South Korea is experiencing a rapid increase in its elderly population. South Korea ranks highly in terms of longevity, with the life expectancy of 83.7 years for both sexes in 2021 [40]. On average Korean men (80.4 years) have a 6.1-year longer lifespan compared to men in the United States (74.3 years). This indicates that Korean men, after being diagnosed with PCa, are likely to have a longer period of competing with PCa mortality against other cause mortality. Therefore, early PCa detection would be more effective than the United States.

**PSA TESTING AND SCREENING IN SOUTH KOREA**

Although many evidences suggest that PSA-based PCa screening could be effective in Korea, PCa and the PSA test awareness remains low in the country. According to a 2020 report, an online survey on awareness revealed that only 9.7% (58 out of 600 respondents) were aware of the PSA test, and a mere 16.7% had ever undergone an opportunistic PSA test in their lifetime [41]. This is significantly lower compared to the approximately 91% PSA contamination rate in the control arm of the PLCO trial [28], indicating that exposure to PSA testing in Korea is still very limited. Additionally, the frequency of PSA testing shows considerable variation between different residential areas, with disparities observed between urban and rural regions [42]. Therefore, this suggests that organized PSA screening in Korea could potentially be quite effective.

Actually, a nationwide study for PSA testing and prostate biopsy was conducted in Korea, targeting men aged 55 years or older in 2007 [43]. A total of 3,943 individuals underwent PSA testing, and among them, 719 (18.2%) were recommended for biopsy due to PSA levels >3 ng/mL. Of these, 268 (37.3%) actually underwent biopsy, and PCa was diagnosed in 76 cases (28.5%). Consequently, the estimated PCa detection rate was 3.36%, which is considerably higher compared to estimates derived from national cancer statistics [5,11].

In a study conducted in Yokosuka City, Japan, which shares demographic and genetic characteristics with Korea, the 15-year results indicated that patients diagnosed with PCa through PSA screening had a higher long-term survival rate compared to those who were not screened [44]. The hazard ratio for these screened patients was 1.58 (95% confidence interval, 1.065–2.356; p=0.023). Therefore, it can be inferred that, unlike in Western populations, PSA-based PCa screening in populations like Korea and other East Asian countries could provide a significant survival benefit.

**CONCLUSIONS**

Although RCTs provide the highest level of evidence, their applicability is often limited to specific populations and intervention types. The characteristics of PCa incidence and mortality vary widely by region. Therefore, direct adoption of the results from RCTs conducted in Western countries for PCa related policies may not be appropriate for other regions. There is substantial evidence suggesting that PSA-based PCa screening could provide significant survival benefits in Asian countries, including Korea. In this context, it is essential to establish individualized screening plans that are specifically tailored to each region. Moreover, conducting clinical trials within each region to gather more relevant and impactful
evidence is strongly recommended.

NOTES

• Author Contribution: Chang Wook Jeong is single author.

REFERENCES


