



# Should Contemporary Western Guidelines Based on Studies Conducted in the 2000s Be Adopted for the Prostate-Specific Antigen Screening Policy for Asian Men in the 2020s?

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Though prostate cancer (PCa) is the second most common cancer world widely, there exist substantial differences exist between Asia and the west. Genetic susceptibility and lifestyle may contribute to disproportionately lower incidences and mortalities of PCa in Asian countries, but the differences in diagnostic practices are also likely to contribute, and a large part of them may be explained by the lesser chance of prostate-specific antigen (PSA) testing. In the US, about half of men aged over 50 years had been exposed to the screening test in the early 2000s. The shifts in the risk stratification from the high-risk dominant disease in the late 1980s to the low-risk dominant disease in the early 2000s led to criticism regarding the unconditional nature of PSA-based screening. Based on the conflicting outcomes from the randomized clinical trials which investigated the benefit of PSA testing, US Preventive Study Task Force recommended ceasing mass screening in 2012. Accordingly, guidelines begin to emphasize shared decision-making on the PSA testing narrowing their scopes to men aged 55 to 69 years since 2013. Though most Asian countries have not begun to recognize PCa as a major agenda item until the 2010s, a clear trend of expanding incidence of it implies that the time to come to reconsider PSA testing as a higher priority in the public health sphere in the 2020s. Concerns regarding over-diagnosis and over-treatment of insignificant diseases are imperative. However, the distinctive epidemiologic characteristics of PCa in Asia areas, such as low exposure to the repetitive PSA testing, the recent increase in its incidence driven by the elderly and super-elderly, and racial differences should be considered when it comes to the establishment of screening policy utilizing PSA test.

**Keywords:** Aging; Prostate cancer; Prostate-specific antigen; Screening

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## INTRODUCTION

Cancer is a leading cause of death worldwide regardless of income level [1-4]. In 2008, it was estimated that there were about 12.7 million new cancer cases and 7.6

million cancer deaths worldwide [2]. Twelve years later, in 2020, estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) were grown up to 19.3 million new cancer cases and almost 10.0 million cancer deaths [4].

**Received:** Jan 2, 2022 **Revised:** May 23, 2022 **Accepted:** May 26, 2022 **Published online** Jul 22, 2022

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Among them, prostate cancer (PCa) is the second most frequently diagnosed cancer with an estimated 1.4 million new cases and 375,000 deaths worldwide in 2020 [4]. PCa is currently the most frequently diagnosed cancer in men in over half (112 of 185) of all countries. In terms of mortality, PCa is the leading cause of cancer death among men in 48 countries, including many countries in sub-Saharan Africa, the Caribbean, Central and South America, and Sweden [4]. However, the incidence of PCa varies by as much as 30-fold between selected registries, and mortality varies 18-fold [1]. The highest incidence rates (per 100,000 population) were observed among African Americans, followed by France (132.1) and Australia (111.1). In contrast, the lowest incidence and mortality rates were observed in Asia. The most recent data from IARC, which allows comparisons of estimated incidences between countries (2010), shows huge differences between countries (Fig. 1) and significantly lower incidences of PCa in Asia than in the west. The estimated age-

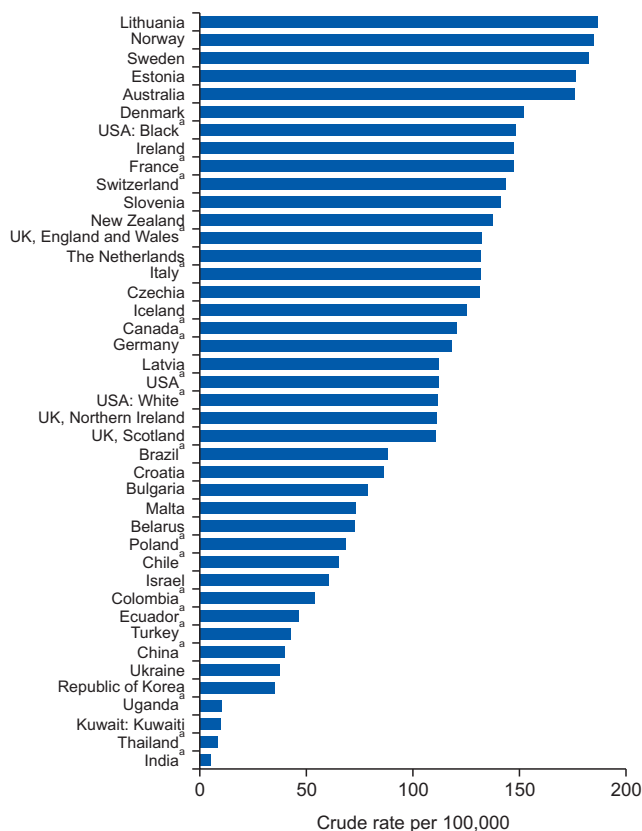
standardized mortality per 100,000 population in 2020 was also the lowest in Asia (8.4 in Western Asia, 4.7 in Eastern Asia) [4]. While several factors, such as genetic susceptibility and lifestyle generated from cultural background, may contribute to these disproportionately lower incidences and mortalities of PCa in Asian countries, international differences in diagnostic practices are likely to contribute most to the different PCa incidences reported [5], and a large part of the differences between the prevalence of PCa may be explained by the lesser use of prostate-specific antigen (PSA) testing [6].

## MAIN BODY

### 1. The observed trends of high-PSA testing among Western countries in the early 2000s

PSA test was firstly approved by the U.S. Food and Drug Administration (FDA) in 1986 for monitoring disease progression. In countries that disseminated PSA testing since then including the United States (US), Canada, and Australia, the incidence rates of PCa show similar trends of a rapid increase as more new cases with PCa were detected. In the US, it has been assumed that 1988 was the first year in which it was used for screening the population [7]. But by 1992, about 25% of men in the US aged 50 years or older had undergone at least one test [8]. This spread of PSA testing between the late 1980s and early 1990s coincided with the period of a dramatic increase in PCa. The utilization of PSA testing kept increased since 1992 when the FDA approved the PSA test for screening purposes. In 2001, 75% of men aged 50 years or older had a PSA test in the US, and 54% of them had a repeated PSA screening, in an annual population-based survey of adults conducted by the US Centers for Disease Control and Prevention (CDC) [9].

The soared incidence of PCa, however, was then followed by a sharp reduction by a precipitous decline as the pool of prevalent cases available for detection diminished [1,5,10]. The incidence curve of PCa reaches its plateau during the early 2000s followed by a period of fluctuation with a definite trend downward since then. Meanwhile, a fundamental change in the aggressiveness of detected cancers was observed in the US within just two decades, from the high-risk dominant disease in the late 1980s to low-risk dominant disease in the early 2000s [11], because of the expansion of PSA



**Fig. 1.** The crude incidence rate of prostate cancer per 100,000 of the population (incidence, males, age 0–84 y) by country in 2012. <sup>a</sup>Subnational data. Data source: GLOVOCAN 2020, Graph production: IARC/World Health Organization (<http://gco.iarc.fr/today>), Accessed December 12, 2021.

screening during this period resulted in the detection of 'insignificant' preclinical cancers. In 1989, which constituted the initial stage of PSA screening, high-risk PCa accounted for more than 40% of detected PCa cases, but in 2002, high-risk disease detections had reduced to 16% of the PCa population. The proportion of patients with an initial PSA of >20 ng/mL decreased from 27% to 8.1% during the same period [11]. These shifts in the risk stratification of PCa gave rise to criticism regarding the unconditional nature of PSA testing. To evade over-treatment of insignificant cancers and the adverse effects on quality of life caused by radical surgery or radiotherapy, watchful waiting or active surveillance (AS) strategies were adopted in the US, and the clinical merits of these approaches were amply demonstrated by milestone randomized clinical trials (RCTs), including the PROTECT trial [12] and PIVOT trials [13] undertaken in the late 2010s.

## **2. Amendments of guideline statements regarding PSA screening policies in the West in the 2010s**

Screening for malignant disease is performed to improve cancer-specific survival and prolong life expectancy. As regards the establishment of PSA-based screening policies, three key questions need to be properly answered: 1) Which patient population would receive maximum benefit from the screening strategy? 2) How frequently should serial testing be performed? 3) How can over-diagnosis and overtreatment of low-risk diseases triggered by the consequences of unconditional, single cut-off level-based, detection-oriented PSA screening practices described in many western studies in the early 2000s be prevented?

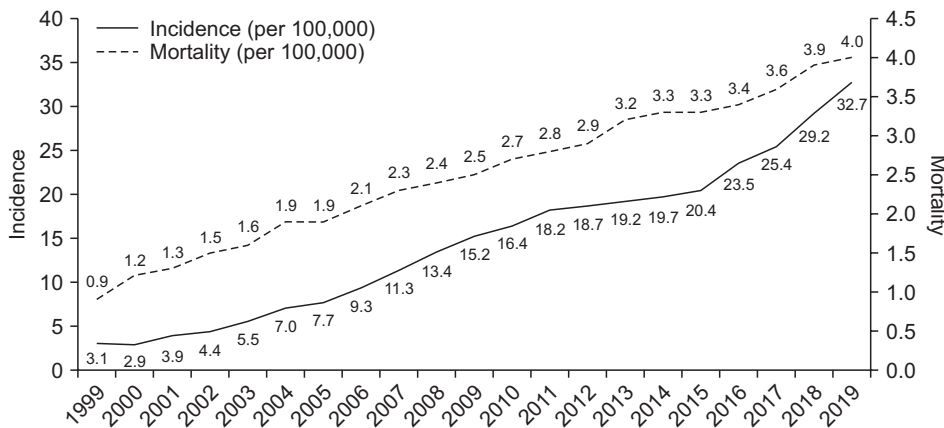
Most importantly, the benefits of a screening policy should be demonstrated by RCTs to prove its socioeconomic relevance. Two representative RCTs that differed in terms of subject age, numbers recruited, intervals between serial PSA tests, PSA cut-offs recommending a prostate biopsy, and follow-up periods were performed between the early 1990s and early 2000s in the US (the PLCO trial [14]) and Europe (the ERSPC trial [15]). However, results conflicted with respect to the effect of PSA screening on survival rates, although PCa was the most common malignant disease and the second leading cause of death in both geographical regions. Furthermore, whereas the ERSPC trial showed a 20% reduction in PCa-related death and a 41% re-

duction in metastasis at presentation, the PLCO trial failed to detect any survival benefit despite a median study period of 14 years. These contrasting results provided the most persuasive argument advanced by the US Preventive Study Task Force (USPSTF) for ceasing PSA mass screening in 2012 [16], although they later modified their position in 2018 by making recommendations for the screening of individuals aged between 55 and 69 years based on the outcomes of the ERSPC trial [17].

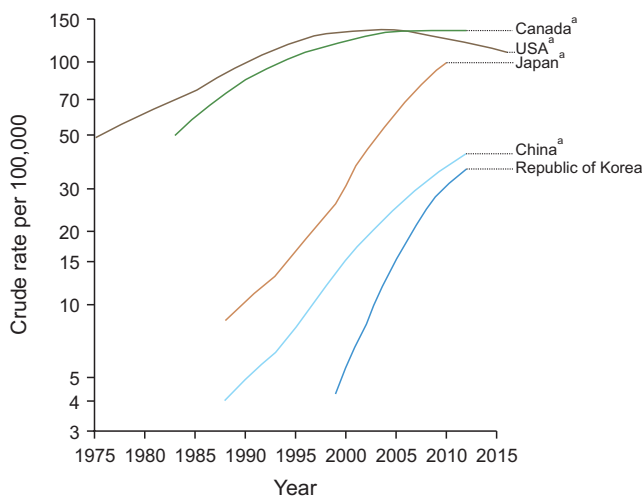
The most serious macroscopic consequence of these Western-based guidelines was the negative impact they had on the establishment of screening policies for men living in other parts of the world that might benefit from PSA testing. From the viewpoint of cost-effectiveness, the clinical relevance of PSA screening should be individualized for each country as we recommended it for the single person, given that the well-reported national differences in the incidence of PCa, availability of PSA testing, the structure of PCa risk stratification, and cultural differences that generate distinctive priorities in public health policies. In this point, how the contemporary Western guidelines on PSA screening that are strongly influenced by USPSTF revision in 2012 apply to the Asian population with a recently expanding incidence of PCa remains unclear.

## **3. The skyrocketing incidence of PCa in Asian countries since the 2010s**

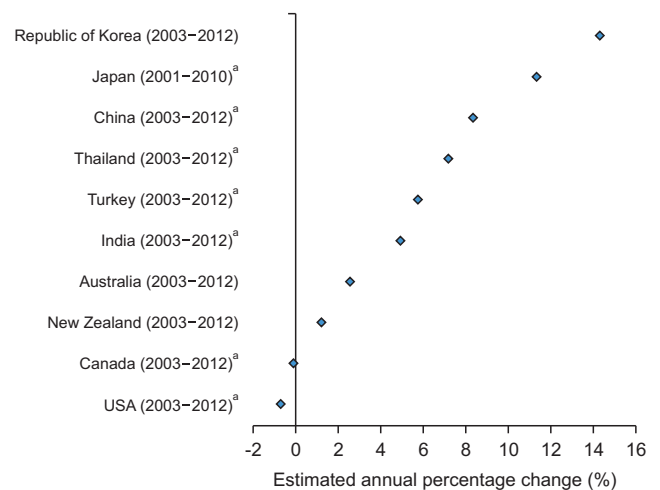
Unlike the US or Europe, which have a long history of clinical application and ready access to PSA testing as well as greater social awareness of PCa than any Asian country, the incidence of PCa in the majority of Asian countries is likely to soar just recently. For example, in Korea, PCa remained the 10th most prevalent male cancer to the end of the 20th century. However, in 2002, it was reported to be the 5th most common male malignant disease, and in 2018, it had become the 3rd most prevalent male cancer and 2nd most common cancer in men aged  $\geq 65$  years. During the last two decades, the crude incidence of PCa in Korea increased 10-fold (3.1 in 1999 to 32.7 in 2019) and mortalities increased 4-fold (0.9 in 1999 to 4.0 in 2019; Fig. 2). These increases are ascribed in part to limited social awareness dominantly caused by the absence of nationwide public screening, which contrasts starkly with the attention afforded to other prevalent male malignant diseases such as stomach, colon, liver, and



**Fig. 2.** Temporal trends of prostate cancer incidence and cancer-specific mortality in South Korea during 1999–2019. Data source: Statistics Korea, Graph production: <http://www.kostat.go.kr/portal/korea/index.action>, Accessed April 2, 2022.



**Fig. 3.** Crude incidence rates of prostate cancer per 100,000 of the population (incidence, males, age 0–84 y) during 1978–2016 between several Asian and Western countries. <sup>a</sup>Subnational data. Rates are shown on a semi-log scale. Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.5). Data source: GLOVOCAN 2020, Graph production: IARC/World Health Organization (<http://gco.iarc.fr/overtime>), Accessed December 12, 2021.



**Fig. 4.** The estimated annual changes in the crude incidence rates (per 100,000, incidence, males, age 0–84 y) of prostate cancer by countries. <sup>a</sup>Subnational data. Data source: GLOVOCAN 2020, Graph production: IARC/World Health Organization (<http://gco.iarc.fr/overtime>), Accessed December 12, 2021.

lung cancer. Indeed, in a public survey of the six-hundred Korean population in 2019, only 9.7% of men aged over 40 years were aware of PSA testing, and 83.3% of them had never received PCa screening [18]. The national-wide incidence of PSA testing during the last 10 years (2006–2016) in Korean men older than 40 years, therefore, remains very low (between 2 and 6%), though it reached 7% in 2016, which is still less than a quarter of that reported in the US [19]. During the period 2008 to 2016, only around a quarter of men with PCa underwent repeat PSA testing before a pathologic diagnosis has been confirmed [20].

By the data from IARC, the crude incidence of PCa in Asian countries, including China, Japan, and Korea,

is lower than in Western countries, such as the US and Canada (Fig. 3). However, the slope in the incidence of PCa in Asian countries is more acute than in the West, and this trend has been maintained for a decade without reaching its plateau yet. As for the annual crude incidence rates of PCa in Asia, the majority of countries have reported strong positive values, for example, Korea (14% per year), Japan (12%), China (8%), Thailand (7%), Turkey (6%), and India (5%), which stand in contrast with negative reported values in Canada and the US (-1%) during the period between the early 2000s and 2010s (Fig. 4). Though most Asian countries have not begun to recognize PCa as a major agenda item until the 2010s, this clear trend of expanding incidence of it implies that the time to come to reconsider PSA testing as a higher priority in the public health sphere

in the 2020s.

#### **4. The distinctive epidemiology of PCa in Asia: lead by the elderly population**

Another unique difference between PCa in Asia and the West is that its increasing incidence appears to be driven dominantly by the elderly and super-elderly (aged  $\geq 75$  y), which unfortunately results in low-social awareness of PSA testing and PCa and turn higher incidences of metastatic disease and lower 5-year survival outcomes than are experienced in the West. In Japan, where PCa became the most common male cancer in 2016, about two-thirds of registered patients were  $\geq 75$  years [21], and similarly, in Korea, 90% of registered PCa patients in the national database were  $\geq 60$  years old, and around a third were  $\geq 75$  years old. In contrast, in the US, the percentage of men aged  $\geq 75$  years among PCa patients diminished from  $\sim 50\%$  to  $20\%$  between 1975 and 2016 [22]. The percentage of distant metastasis and regional disease according to the most recent data (2015-2019) were  $10\%$  and  $24\%$  in Korea [23], whereas according to US (Surveillance, Epidemiology, and End Results [SEER] 18, 2012-2018) corresponding rates were  $7\%$  and  $14\%$ , respectively [24].

One of the unique characteristics of PCa that deserves special mention based on its epidemiology in Asian populations is that it tends to be more aggressive nature in the elderly. Published data indicate that men  $\geq 70$  years old present with higher disease grade and stage and larger tumors [25,26]. In the same context, studies suggest that older patients are at elevated risk of biochemical recurrence, distant metastasis, and disease-specific death [25-27]. Therefore, given the inevitability of continued global aging, there is an increasing need for optimal screening and management of PCa in the vulnerable elderly population.

Nevertheless, contemporary western guidelines have maintained their stance against public PSA screening, suggesting shared decision-making through proper counseling of the patients on the potential risks and benefits of the PSA test. However, because of the distinctive epidemiology and rapidly increasing incidence of PCa in many Asian countries, it is evident that the prohibitive screening policies based on western-based RCTs largely performed between the late 1990s to 2000s are out-of-date, which means that the merits and demerits of PSA testing should be re-evaluated using data derived from Asian populations. At pres-

ent, though little data is available on the effectiveness of PSA-based public screening for the PCa, positive evidence for the Asia population looks acculturating recently. A Japanese trial that used a biopsy PSA cut-off value of  $3$  ng/mL conducted from 2001 to 2015 revealed PSA screening increased overall and cancer-specific survival [28], and an analysis of Korean PCa registry data of around 73,000 PCa patients demonstrated a 2-fold increase in overall survival in a PSA tested population [20]. Focusing on the efficacy of PSA screening in men aged over 75 years who is a major PCa population in Japan as well as in Korea, a recent Japanese study reported that the screened group had significantly longer overall survival and cancer-specific survival than the control group, even though the screening was not an independent factor associated with prolonged survival outcomes on multivariate analysis [29].

#### **5. The 'minimal' change of PSA testing in practice manifested in recent US data**

Despite the decline in the incidence of PCa in the US observed after it peaked in the early 2000s, the incidence of PSA testing in the general population appears to have been maintained, except among the elderly. Based on the National Health Interview Survey during the period 2005 to 2015 [30], the proportion of men in the US aged  $\geq 55$  years that received a PSA screening test was slightly lower than the maximum estimate of  $43.1\%$  in 2008 but was maintained at  $>30\%$  since then ( $32.8\%$  in 2013 and  $33.8\%$  in 2015). A clear diminishing trend was observed solely among the elderly ( $\geq 70$  years old) from  $51.1\%$  in 2008 to  $36.4\%$  in 2015, following the first negative recommendations for PSA screening by the USPSTF in 2008 for aged men  $\geq 75$  years [31]. From another report utilizing the SEER data registry that represents cancer incidence rates in approximately  $48\%$  of the US population, PSA screening rates between 2010 and 2018 for men aged 55 to 69 years only had a slight decrease from  $46\%$  to  $39\%$ . However, between 2013 and 2018, the screening rate remains stable with an annual average percentage change of  $0.40$  [32].

Rather, the most recent study has shown that when evaluating PSA screening in insured men between 2016 and 2019, there was a  $12.5\%$  relative increase in rates of PSA testing for men aged 40 to 89 years (from  $32.5$  to  $36.5$  tests per 100 person-years). Among men aged 55 to 69 years, the mean rate of PSA testing has been increased (from  $49.8$  to  $55.8$  tests per 100 person-years),

and this increasing trend was also observed among men 40 to 54 years and 70 to 89 years, outside of the USPSTF recommended screening age group [33]. Similarly, in a cross-sectional study of PSA screening trends conducted by the US Veterans Health Administration between 2009 and 2018 [34], the incidence of PSA testing in men aged 55 to 69 years was rather increased from 41% (2009) to 43.5% (2018). In 2018, US behavioral risk factor surveillance system data demonstrated that the screening prevalence was 43% in veterans and 40% in nonveterans, among then aged between 55 and 69 [35].

In 2021, PCa remained the most common cancer in the US among men; 248,530 new cases were registered [36], which looks similar to 239,567 new PCa cases registered in 2009 (the highest recorded since 2000) given that 181,295 new cases were registered in 2014 (the lowest recorded since 2000) [37]. Although a significant decline in overall PCa mortality was observed from 1993 to 2013 in the US, this trend appeared to stabilize since then [38]. Altogether, these figures indicate that implementation of PSA testing in daily practice in the US may not substantially decrease within the era of AS and guideline statements of shared decision-making on performing PSA tests. Then, why should Asians with recently rising incidence of PCa with distinctive epidemiologic backgrounds need to follow contemporary prohibitive screening policy based on western RCTs that were performed two decades ago, even without persuasive negative evidence on PSA testing based on their own population?

## CONCLUSIONS

Because the incidence of PCa is projected to increase significantly in parallel with societal aging, PSA screening has become an increasingly important health care issue for Asian men. PSA testing plays a pivotal role in the detection of PCa because, in the majority of cases, the disease does not manifest any specific symptoms, only ambiguous male lower urinary tract symptoms that originate more frequently from concomitant prostate enlargement. Unfortunately, prohibitive western guidelines based on studies performed in the early 2000s are negatively impacting the establishment of screening policies for Asian men likely to benefit in the 2020s. Concerns regarding over-diagnosis and over-treatment of insignificant diseases and their

impacts on adopted PSA testing policies are imperative. However, it should be emphasized when it comes to the establishment of screening policy, the distinctive epidemiologic characteristics of PCa in Asia areas, such as low exposure to PSA testing, the recent increase in its incidence driven by the elderly, and super-elderly, and racial differences should be considered.

## Conflict of Interest

The authors have nothing to disclose.

## Funding

None.

## Author Contribution

Conceptualization: YHK. Data curation: YHK. Formal analysis: YHK, BHK. Funding acquisition: none. Investigation: BHK. Methodology: YHK. Project administration: YHK. Resources: BHK. Software: BHK. Supervision: BHK. Validation: YHK. Visualization: YHK. Writing – original draft: YHK. Writing – review & editing: BHK.

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