**Editorial**

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# Prostate-specific antigen screening for prostate cancer: An old but never-ending story

Prostate cancer (PC) has become the most important cancer in men worldwide in terms of incidence and mortality. Once considered primarily a western disease, PC is now the leading male cancer in terms of incidence on every continent except Asia, where it ranks fifth [1]. It is the most lethal cancer in Latin America and Africa, the second in North America and Oceania, and the third in Europe. Asia, once considered a relatively safe place when it comes to PC, is starting to betray this belief, with PC ranking first in Japan a few years ago and becoming the third leading cancer in South Korea in 2020.

The Korean National Cancer Screening Program, which started in 1999, provides free screening services for important cancers to low-income Medical Aid recipients and to beneficiaries of the National Health Insurance (NHI) Program within the lower income bracket (50%) and their dependents. Initially starting with stomach, breast, and uterine cervix, the program has since added sequentially liver, colorectum, and lung to now include six target cancer sites. PC has consistently ranked among the top 5 most diagnosed cancers over the past 20 years and is the fastest growing cancer among Korean men. Most urologists consider it the potential number one cancer in Korean men—an inevitable consequence of national economic prosperity and an aging population. Controversy arose when the Ministry of Health and Welfare refused to integrate prostate-specific antigen (PSA) screening into the National Cancer Screening Program on the grounds that PC has a lower incidence rate and a better prognosis than the other six cancers. Furthermore, randomized PC screening trials showing little or no benefit on cancer-specific mortality have been used as a counterpoint to argue that PSA screening does nothing more than increase the diagnosis of clinically insignificant cancers, an argument that further rationalized the defensive stance [2,3].

Since the US Preventive Services Task Force (USPSTF) recommended against screening for PC in 2012 on the basis of negative results of PSA screening trials, worrisome changes began to emerge. The PC incidence rate rose by 3% per year from 2014 to 2019 [4]. Also, regional-stage and distant-stage diagnoses increased annually by 4.5%. This lead the USPSTF to upgrade in 2018 to informed decision-making in men aged 55 to 69 years [5]. Furthermore, the most recent analysis of the European Randomized Prostate Cancer Screening Study (ERSPC) found an increased benefit of PSA screening over time in reducing PC-specific mortality and metastasis at an extended follow-up of 21 years, with a concomitant decline in the number needed to invite and the number needed to diagnose, which are key indicators of overdiagnosis [6].

In Korea, PC mortality was 4.0 per 100,000 in 2019, far lower than the 18.8 per 100,000 in the United States between 2015 and 2020 [4]. However, this illusion of safety is unlikely to last in a country with much higher rates of moderate to high-risk cancer despite low incidence. In fact, there are consistent reports that Asian men harbor higher Gleason score cancers than non-Asian men [7,8]. This will inevitably lead to a poorer prognosis compared with Westerners in the Asian male population with PC.

According to statistics in 2020, the top 10 cancers in Korean men and women with the exception of thyroid cancer were lung (n=29,180), colorectal (n=27,877), stomach (n=26,662), breast (n=24,923), prostate (n=16,815), liver (n=15,152), pancreas (n=8,414), biliary tract (n=7,452), and kidney (n=5,946), in descending order. Among the top 10, prostate, pancreas, biliary tract, and kidney are excluded from the National Cancer Screening Program. With only 2,998 new cases in 2020, is there still a reason to maintain uterine cervix in the program when it is not on the top 10 list? Could there be a better new candidate to replace uterine cervix than PC, which has twice the incidence of pancreas, which is immediately next on the list? Concerns about overdiagnosis of clinically insignificant diseases are becoming obsolete as prebiopsy magnetic resonance imaging is gaining ground and the decision to perform a biopsy based solely on PSA is

becoming history as more and more physicians turn to use of the Prostate Imaging Reporting and Data System, better known as PI-RADS, in their decision-making. Now we need to provide evidence to convince the authorities that if we do not adopt a screening program for PC, ominous things could happen in the future in terms of PC survival.

In the article entitled "Trends of stratified prostate cancer risk in a single Korean province from 2003 to 2021: A multicenter study conducted using regional training hospital data," Ko et al. [9] have reilluminated the controversy over the need for PSA screening in Korea. They systematically collected clinical information for patients with PC diagnosed over the last 20 years by prostate biopsy performed in the region of Daegu Metropolitan City and the surrounding Gyeongsangbuk Province, which account for about 12% of the Korean population. The purpose of this study was to investigate changes in the risk stratification of PC in Korea over the past 20 years, during which time the social awareness of PC was initially limited owing to the relatively low incidence rate but expanded with growing awareness of prostate disease in the general population. Probably to highlight the temporal difference, the authors set target years every 4 years starting from 2003 to 2019 (i.e., 2003, 2007, 2011, 2015, and 2019) in addition to 2021. Risk stratification was performed according to contemporary guidelines, with prebiopsy PSA, biopsy Gleason score, and clinical stage forming the basis of the criteria. A total of 3,393 patients were diagnosed during the study period, of which 64.1%, 23.0%, and 12.9% were stratified as high, intermediate, and low risk, respectively. As the authors pointed out, PSA testing has been subject to medical reimbursement since 2007, which coincided with a sharp increase in the proportion of low- and intermediate-risk patients from 2011, the year closest to 2007 in this study. However, from 2011 to 2021, the curve remained static. It is also noteworthy that only 232 patients were diagnosed with PC in 2003 and 2007, or 7% of the study population. In brief, lack of any movement to promote PSA screening in this country since 2007 has led to an overwhelming majority of patients still being diagnosed with high-risk PC. The only indication that patients showed up earlier for prostate biopsy over time was that from 2011 to 2021 the proportion of patients with prebiopsy PSA ≥20 ng/mL continued to decline. During the same period, however, the Gleason score remained the same and the stage shifted for the worse for unexplained reasons. A Gleason score of 8 or higher still accounted for 49% of cases in 2021. This is still 10% higher than the most recently reported opportunistic PSA-driven biopsy results from a single prefecture in Japan in 2012 and 2017 [10]. PSA screening in the United States has resulted in the well-known risk migration from higher to lower risk during a relatively short period of 13 years as shown in the CaPSURE study [11]. Here again, presentation of patients with lower PSA resulted in a parallel decrease in local stage, whereas changes in Gleason score were more inconsistent with time and seen as multifactorial.

Taking all this in consideration, it seems too simplistic to assume that PSA screening will lead to the detection of an excess of clinically insignificant PC in a population that has consistently demonstrated generally more aggressive clinical features. This article has several limitations. As the authors pointed out, the number is too small to represent the entire country. It also appears that there were problems with the collection process, such as the 5% rate of metastatic disease being too low. Clinical stage T3 and higher, a common criterion for high-risk disease, was not presented.

A similar nationwide study, initiated by the same investigator, is underway with the goal of collecting prostate biopsy data from all provinces of South Korea from 2010 to 2020. It is hoped that the results of this latest study will provide more solid arguments for the need for PSA screening.

## CONFLICTS OF INTEREST

The author has nothing to disclose.

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