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OPINION

Updated results from the European Randomized Study of Prostate-Specific Antigen (PSA) Screening for Prostate Cancer: are Asian countries encouraged to promote PSA screening?

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An updated result of European Randomized Screening Trial for Prostate Cancer encourages Asian countries to proceed prostate-specific antigen (PSA) screening for early detection. On the other hand, the issue of overtreatment is emerging as a serious problem. Active surveillance (AS) should be more prevalent than now to avoid overtreatment for patients with favourable-risk prostate cancer (PCa) detected by PSA test.

In 2011, the US Preventive Service Task Force (USPSTF) recommended not using PSA-based screening for the early detection of PCa (http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/draftrecprostate.htm). This recommendation was based primarily on the results from five screening trials thus far conducted, including the two most current studies carried out in the United States and Europe. The first of these studies was a randomized trial, the Prostate, Lung, Colorectal and Ovary study, which showed no reduction in PCa mortality in the screening arm. However, the results were criticized by the investigators because of the substantial percentage (52%) of contamination in the non-screening arm and violation (10%) in the screening arm.[1] In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated a 20% reduction in PCa mortality in the screening arm after a median observation period of 9 years with a low contamination rate (6%).[2] The quality of the ERSPC study may be higher than that of the Prostate, Lung, Colorectal and Ovary study. Furthermore, a recent article that reports on 2 additional years of observation in the ERSPC study has confirmed a positive effect of PSA screening by noting that screening reduced the PCa death rate (21% reduction).[3] After adjustments for non-compliance and selection bias, the risk reduction rate reached 29%. Despite these results, the USPSTF maintains their recommendation grade as 'D', which means that there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Thus, the overall recommendation is to 'discourage the use of this service'. The USPSTF considers the benefit (the reduction of cancer-specific mortality) of PSA-based screening to be ambiguous and emphasizes the harm associated with subsequent screening and treatments, namely, the issues of overdiagnosis and overtreatment.

On the contrary, the American Urological Association strongly opposes this position and stated that the 'PSA test provides important information in the diagnosis, pretreatment staging or risk assessment and monitoring of PCa patients. However, not all PCas are life-threatening. The decision to proceed to active treatment or use surveillance for a patient's PCa is one that men should discuss in detail with their urologists' (http://www.auanet.org/content/health-policy/government-relations-and-advocacy/in-the-news/uspstf-psa-recommendations.cfm?WT.mc_id=EML6621MKT). Moreover, the Japanese Urological Association immediately released an official statement that the USPSTF underestimates the PSA screening benefits. The recommendation cannot be applied to Japan because of the differences in the social background of PSA screening between the Unites States and Japan.

Previously, the incidence and mortality of PCa were relatively low in Asian countries. Today, however, just as in Western countries and North America, the number of PCa patients in Asian countries is increasing dramatically[4] as a result of lifestyle changes, i.e., dietary habits and/or the prevalence of PSA testing. PSA screening was claimed to be effective and useful in PCa mortality reduction in some prospective cohort studies, including the Tyrol study in Austria[5] and the Göteborg randomized population-based PCa screening trial in Sweden.[6] In Japan, however, only 10%–15% of men aged 50–75 years have undergone a PSA test at least once in their lives, which is a significantly lower rate compared to the United States where 70%–80% of men have undergone a PSA test.[7] Both the incidence and mortality rates of PCa in Japan are increasing (30 000 new cases and 10 000 or more men died from PCa in recent years). Moreover, approximately 20% of patients present with distant metastasis at diagnosis.[8]

Compared to patients included in the US PCa database, the Cancer of the Prostate Strategic Urologic Research Endeavor registry, Japanese patients are more likely to be diagnosed with high-risk features: 43% of Japanese patients *vs.* 5% of US patients.[9] One of the major reasons for this phenomenon is the low PSA testing rate in Japan compared to the United States, and therefore, early detection by PSA screening to reduce

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PCa deaths would be beneficial for Japan. Recent data from the International Agency for Research on Cancer showed that the estimated PCa incidence rates continue to increase in countries with abundant resources, including North America, Oceania and Europe.[4] Mortality rates tend to be higher in South America, the Caribbean and some Asian countries, such as the Republic of Korea. However, these regional differences in incidence depend on the prevalence of PSA screening and diagnostic practices, such as imaging modalities or biopsy techniques. It is suggested that PCa mortality reduction depends on the number of resources allotted to PSA screening as a national health service. Low PCa mortality rates may be related to high income or abundant resources.

A newly published study was conducted as a randomized, multicentre trial screening for PCa in several European countries. The primary end point was the rate of death from PCa. There were 162 388 men in the core age group (55–69 years) who were enrolled and randomized to the screening and control groups. The PSA cutoff value of 3.0 ng ml^{-1} as a biopsy indication was used in almost all centres. The screening interval at six of seven centres was 4 years. The PCa treatments were carried out according to each centre's policies and guidelines. The causes of death were evaluated and classified by independent committees as PCa or other causes.

The results of this clinical trial are quite important. The mean and median durations of follow-up for the core age group were 10.5 and 11.0 years, respectively. The incidence of PCa during the entire follow-up was 9.66 cases per 1000 person-year in the screening group (72 891) and 5.95 cases per 1000 person-year in the control group (89 352). The incidence of advanced cancers (stage T3 or T4) and aggressive cancers (Gleason score 8–10) was lower in the screening group than in the control group. There were 299 PCa deaths in the screening group and 462 deaths in the control group, with death rates of 0.39 and 0.50 per 1000 person-year, respectively. As described above, they found a relative PCa death risk reduction of 21% in favour of screening.

However, the issue of overdiagnosis and overtreatment has emerged with the increased early detection of PCa as a result of the increased prevalence of PSA screening. Overdiagnosis due to PSA screening is thought to be approximately 50%.[10] Unfortunately, this issue has not yet been resolved. In the 2009 ERSPC report, the number needed to screen and the number needed to treat to prevent one death from PCa were 1410 and 48, respectively. However, in this new study, which analysed 2 additional years of follow-up, the number needed to screen and the number needed to treat were decreased to 1055 and 37, respectively. These results indicate that a longer follow-up duration will confer greater PSA screening efficacy. These statistics are one of the most prominent findings in the European multicentre study.

Early diagnosis may lead to better outcomes. In fact, not all PCa patients undergo radical treatment. Because early and indolent cancers that are not life-threatening have increasing incidence, AS seems to be a reasonable strategy for patients with more favourable PCa risk profiles. AS has emerged as an optional selection that postpones definitive or radical treatment without forfeiting the curative chance so that the harm related to radical treatments can be reduced or the quality of life will not be impaired. Unfortunately, AS has not been fully utilized as an initial treatment option by physicians or patients. In order to popularize AS, it should be elucidated that favourable-risk PCa patients will not suffer an avoidable PCa death as a result of delayed intervention, and that the patients' selection criteria and the follow-up policy should be confirmed.[11] Results from international prospective AS studies, such as the Prostate Cancer International: Active Surveillance (PRIAS) Study,[12] which has been active since 2006 as an international web-based study, have yet to be released. In Japan, two prospective, multicentre AS studies are now under investigation. The first is the Japanese AS study that was carried out in favourable-risk PCa patients, starting in 2002.[13,14] The second is the PRIAS-JAPAN study (Japan has been participating in the PRIAS study as PRIAS-JAPAN since 2010). As of April 2012, 32 institutions had participated and approximately 250 patients were enrolled in the PRIAS-JAPAN study. We are anxious for the results from these studies of Japanese patients, because they will be helpful in understanding Asian PCa features.

Furthermore, the development of new biomarkers that can evaluate tumour aggressiveness with high specificity for PCa is warranted. If the aggressive features of a tumour can be correctly identified using a negligibly invasive examination, these characteristics can then be used to screen candidates for AS. They can then safely start the definitive treatment during the AS programme within the curative window. The *TEMPRESS:ERG* fusion gene[15,16] as a genomic marker or PCA3[17,18] as a urine marker are promising candidates for the near future. Moreover, imaging technology, especially magnetic resonance imaging, is considered to be a reliable diagnostic and staging tool. T2-weighted imaging combined with diffusion-weighted imaging and dynamic contrast enhancement or magnetic resonance spectroscopy have a high negative predictive value[19] and substantial potential to detect the unfavourable features of cancer foci in the prostate.[20] To eliminate the aggressive cancer foci or to select an appropriate candidate for AS, magnetic resonance imaging-guided prostate biopsy combined with ultrasonography will provide the necessary precise information.

There are some limitations in interpreting the results of the ERSPC screening trial. First, the inclusion and follow-up policies between the participating countries are not standardized. For instance, the PSA cutoff value used as an indication for biopsy is 3.0 ng ml^{-1} at most centres, but in Finland, a value of 4.0 ng ml^{-1} was used. With respect to the screening interval, Sweden used a 2-year interval; other centres used a 4-year interval. Moreover, there were different upper limits of the participant age among the centres. The second limitation relates to the issue of the pathological findings. A local pathologist performed the pathological evaluations for each centre, and central review was not carried out in this study. Quality control for pathological findings is needed. The third limitation is that there may be differences in the treatment quality between centres, and this issue will affect the PCa mortality.

The *Los Angeles Times* (26 April 2012) 'Booster Shots' blog (http://www.latimes.com/health/boostershots/la-heb-prostate-screening-guidelines-20120424,0,1588958.story) reported that the guidelines limiting PSA screening for PCa detection in men aged 75 years and older are widely ignored despite the USPSTF recommendation. It was also reported that physicians seem likely to continue to ignore them. Only 1.8% of the physicians stated that they would no longer carry out PSA tests, approximately 40% replied that they may not change their screening practices and the rest stated that they had not yet decided. There are data showing that PCa screening was conducted in 57% of men aged 75–79 years and 42% of men aged 80 years and older. Interestingly, college-educated men were the most likely to undergo screening; in contrast, those without a high school diploma were the least likely to be screened.[21] These results indicate that

the USPSTF recommendations are not likely to be easily adopted, even in the United States. In Asian countries, it seems that there has been little influence from the recommendations on PSA testing on daily clinical practice, at least in Japan, for both physicians and patients.

In conclusion, in Asian countries, including Japan, PCa is increasing annually, mainly as a result of changes in dietary habits. The prevalence of unfavourable-risk PCa or advanced cancers is still large compared to the US or European countries. Despite these facts, the public awareness of the PSA test is relatively low. These updated results from the ERSPC screening trial, which are based on a longer observation period, may encourage Asian countries to conduct PSA screening for the early detection of PCa. Moreover, AS should become a more popular treatment option to avoid the overtreatment of patients with low-risk PCa that is detected by the PSA test.

The diagnostic power of new biomarkers should be validated in Asian men. Moreover, because the population study of PSA screening and the survey of PSA test in both physicians and patients are still lacking, it might not be said that the emerging disease in Asian countries is fully understood. It is imperative to accumulate data as to natural history of PCa, changes in prostate volume and PSA kinetics with age, the efficacy of new biomarker and responsiveness to various treatment modalities in Asian men. Although there are substantial socioeconomic differences between Asian countries, based on the accumulated data, well-designed prospective randomized studies for PCa screening, diagnosis and treatment in Asia as one union are needed. This is a matter of great urgency.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1 Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D *et al*. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; **360**: 1310–9.
2 Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S *et al*. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; **360**: 1320–8.
3 Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S *et al*. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012; **366**: 981–90.
4 Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J *et al*. International variation in prostate cancer incidence and mortality rates. *Eur Urol* 2012; **61**: 1079–92.
5 Schroder FH, Zappa M. Prostate-specific antigen testing in Tyrol, Austria: prostate cancer mortality reduction was supported by an update with mortality data up to 2008. *Int J Public Health* 2012; **57**: 45–7.
6 Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A *et al*. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010; **11**: 725–32.
7 Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *JAMA* 2003; **289**: 1414–20.
8 Cancer Registration Committee of the Japanese Urological Association. Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association. *Int J Urol* 2005; **12**: 46–61.
9 Cooperberg MR, Hinotsu S, Namiki M, Ito K, Broering J *et al*. Risk assessment among prostate cancer patients receiving primary androgen deprivation therapy. *J Clin Oncol* 2009; **27**: 4306–13.
10 Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA *et al*. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003; **95**: 868–78.
11 Kakehi Y. Active surveillance as a practical strategy to differentiate lethal and non-lethal prostate cancer subtypes. *Asian J Androl* 2012; **14**: 361–4.
12 van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schroder FH *et al*. Prospective validation of active surveillance in prostate cancer: the PRIAS study. *Eur Urol* 2007; **52**: 1560–3.
13 Kakehi Y, Kamoto T, Shiraishi T, Ogawa O, Suzukamo Y *et al*. Prospective evaluation of selection criteria for active surveillance in Japanese patients with stage T1cN0M0 prostate cancer. *Jpn J Clin Oncol* 2008; **38**: 122–8.
14 Sugimoto M, Shiraishi T, Tsunemori H, Demura T, Saito Y *et al*. Pathological findings at radical prostatectomy in Japanese prospective active surveillance cohort. *Jpn J Clin Oncol* 2010; **40**: 973–9.
15 Mosquera JM, Perner S, Demichelis F, Kim R, Hofer MD *et al*. Morphological features of TMPRSS2-ERG gene fusion prostate cancer. *J Pathol* 2007; **212**: 91–101.
16 Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R *et al*. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* 2005; **310**: 644–8.
17 Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S *et al*. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem* 2006; **52**: 1089–95.
18 Aubin SM, Reid J, Sarno MJ, Blase A, Aussie J *et al*. Prostate cancer gene 3 score predicts prostate biopsy outcome in men receiving dutasteride for prevention of prostate cancer: results from the REDUCE trial. *Urology* 2011; **78**: 380–5.
19 Villers A, Puech P, Mouton D, Leroy X, Ballereau C *et al*. Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. *J Urol* 2006; **176**: 2432–7.
20 Choi S. The role of magnetic resonance imaging in the detection of prostate cancer. *J Urol* 2011; **186**: 1181–2.
21 Bellizzi KM, Breslau ES, Burness A, Waldron W. Prevalence of cancer screening in older, racially diverse adults: still screening after all these years. *Arch Intern Med* 2011; **171**: 2031–7.