Asian Journal of Andrology (2015) 17, 475–480

www.asiaandro.com; www.ajandrology.com

Open Access

REVIEW

Prostate Cancer

Prostate-specific antigen-based population screening for prostate cancer: current status in Japan and future perspective in Asia

Yasuhide Kitagawa, Mikio Namiki

In Western countries, clinical trials on prostate cancer screening demonstrated a limited benefit for patient survival. In the Asia-Pacific region, including Japan, the rate of prostate-specific antigen (PSA) testing remains very low compared with Western countries, and the benefits of population-based screening remain unclear. This review describes the current status of population screening and diagnosis for prostate cancer in Japan and discusses the efficacy of population screening for the Asian population. Since the 1990s, screening systems have been administered by each municipal government in Japan, and decreases in the prostate cancer mortality rate are expected in some regions where the exposure rate to PSA screening has increased markedly. A population-based screening cohort revealed that the proportion of metastatic disease in cancer detected by screening gradually decreased according to the increased exposure rate, and a decreasing trend in the proportion of cancer with high serum PSA levels after population screening was started. The prognosis of the prostate cancer detected by population screening was demonstrated to be more favorable than those diagnosed outside of the population screening. Recent results in screening cohorts demonstrated the efficacy of PSA. These recent evidences regarding population-based screening in Japan may contribute to establishing the optimal prostate cancer screening system in Asian individuals.

Asian Journal of Andrology (2015) **17**, 475–480; doi: 10.4103/1008-682X.143756; published online: 26 December 2014

Keywords: free prostate-specific antigen; pro-prostate-specific antigen; prostate cancer; prostate cancer gene 3; prostate-specific antigen-based population screening; serum prostate-specific antigen distribution

INTRODUCTION

Prostate cancer is the most common cancer among males in Western countries with a high mortality in the 1990s.[1] However, recent trends show a continuous decrease in the prostate cancer mortality rates in the Western countries.[2,3] This could be the result of new treatments for prostate cancer that have emerged in the past two decades; however, the high rate of prostate-specific antigen (PSA) testing among middle-aged males may have partially contributed to the decrease in the prostate cancer mortality rate in these countries.[3] In Asian countries, including Japan, the incidence rate of prostate cancer has increased in Asia, and the trend is expected to continue in the near future.[4–6] Nonetheless, PSA testing for prostate cancer remains low compared with the USA and Western Europe,[7–9] despite the rapid westernization of lifestyle and diet.[10]

Widespread PSA-based population screening was proposed as an efficient approach to detecting early-stage prostate cancer. However, a meta-analysis of five randomized control trials (RCTs) indicated that PSA testing did not significantly decrease prostate cancer-specific mortality.[11] Only one RCT, the European Randomized Study of Screening for Prostate Cancer (ERSPC), reported a significant reduction (21%) in prostate cancer-specific mortality among men 55-69 years old.[12] Based on this finding, the American Urological Association (AUA) states that well-informed men aged 55-69 years old cannot be denied PSA testing.[13] Furthermore, the European Association of Urology (EAU) states that an individual risk-adapted strategy should be offered to well-informed men age > 50 years with a life expectancy of at least 10-15 years.[14]

Whether these statements apply to the Asian population remains unclear. Racial differences in clinical characteristics of prostate cancer have been reported,[15] and the risks factors of prostate cancer may vary from population to population. The Japanese Urological Association (JUA) recommends PSA-based population screening in Japan and challenges the clinical evidence of screening and diagnosis of prostate cancer.[6] In this review, we describe the current status of the screening and diagnosis of prostate cancer in Japan, discuss the efficacy of population screening for the Asian population, and provide guidance to establish optimal screening systems in the Asian region on the basis of recent evidence regarding the PSA-based population screening.

SCREENING SYSTEMS FOR PROSTATE CANCER IN JAPAN

Since the 1990s, screening systems have been employed by each municipal government in Japan, and decreases in the prostate cancer mortality rate are expected in some regions where the exposure rate to PSA screening has increased markedly.[6] Population screening systems implemented by municipal governments are reasonable ways

Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa 920-8640, Japan.
Correspondence: Dr. Y Kitagawa (yasukita@med.kanazawa-u.ac.jp)
Received: 02 June 2014; Revised: 01 September 2014; Accepted: 29 October 2014

of increasing the exposure rate to PSA testing, and several studies have suggested that these systems may be effective for the early detection of prostate cancer.[16–19] However, there have been several issues in PSA-based population screening systems in Japan.

First, the screening program implemented by municipal governments does not provide coverage of all of the city population, and the proportion of the participants is not so high. In Japan, self-employed males and those working for small companies or retirement homes are covered with municipal government screening programs. In contrast, salaried workers are screened by their company's health check-up program or human dry dock (**Figure 1**). For example, the government prostate cancer screening applies to approximately 60% of the population of Kanazawa city, but only 20% of the candidates participate in the program (e.g., 5502 participants (12.2%) among 45 116 males aged 55–69 years in Kanazawa city in 2011).[19] Such low participation is apparently typical for Japanese cities.

Second, it is difficult to obtain the information regarding population screening results, including the clinical outcomes of screening to detect patients, because detailed examinations and subsequent treatment for males with abnormal findings in population screening are performed in several urology departments in the region, especially in cities with large populations. There have been a few reports regarding the clinical outcomes of prostate cancer patients detected by population screening.[19]

PROSTATE CANCER DETECTION AND CANCER CHARACTERISTICS IN PROSTATE-SPECIFIC ANTIGEN-BASED POPULATION SCREENING

It has recently been reported that the annual cancer detection rates in the Japanese population screening cohort were 0.54%–1.13%.[16–19] This range is lower than for other screening programs like clinical trials (e.g., 9.6% in ERSPC[11]). The relatively low cancer detection rate may be due to repeated data on the same individuals who participate in the screening every year, which is a characteristic of Japanese screening programs.[17,20] Considering the effectiveness of population screening, the decrease in annual cancer detection rate due to the increase in the number of repeat examinees may not be beneficial; however, favorable shifts in cancer characteristics were observed in repeated screenings.[20] This finding was similar to that of a European screening cohort study, in which population screening was carried out with 2 years or 4 years intervals.[21–23] One of the most important aims of PSA-based population screening for prostate cancer was to detect cancer at an early stage, when it is curable by optimal treatment; thus, repeat screening may play an important role in the early detection of cancer during regular annual screening.

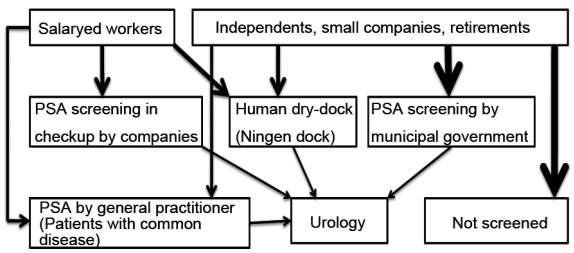

Figure 1: Screening systems for prostate cancer in Japan.

In terms of the clinical characteristics of prostate cancer patients detected by screening, there was an inverse correlation between the exposure rate to population screening and the proportion of advanced cancer in an assessment of the Japanese regional cancer registry.[24] In Gunma prefecture in Japan, population screenings for prostate cancer have been carried out in 50 (74.6%) of all 67 municipalities, and it was demonstrated that the proportion of metastatic disease in prostate cancer detected by screening gradually decreased according to the increased exposure rate in each municipality (**Table 1**).[24] Furthermore, with regard to longitudinal studies, a large nationwide survey was carried out by JUA; it demonstrated that the proportion of metastatic disease among all recorded cases decreased from 21.3% in 2000[25] to 11.6% in 2004.[26] These findings suggested that PSA-based population screening contributed to detect prostate cancer in early stages and has improved in the past decade.[9] Although, there have been a few studies regarding clinical stage distribution of prostate cancer in Asian countries, the proportions of metastatic disease were reported to be 26.1% and 26.9% in a Chinese[27] screening cohort and Saudi Arabian[28] screening cohort, respectively.[9] The high proportion of metastatic disease indicated that the favorable stage shift followed by the widespread of PSA screening had not occurred in these countries. Together, the promotion of PSA-based population screening in countries in which PSA screening has not been widely adopted will contribute to the earlier detection and prevention of prostate cancer.

Interestingly, a decreasing trend in the proportion of prostate cancer with high serum PSA levels was demonstrated among the first screening participants after starting population screening, especially in the few initial years.[29] A previous epidemiological cohort study using data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) demonstrated that in the PSA era, prostate cancer was increasingly diagnosed in younger males with lower risk and at an early disease stage.[30,31] The database did not show the exposure rate to PSA screening among the subjects, but it was certain that the widespread use of PSA screening has led to these trends. Several rounds of PSA screening in middle-aged males after instigation of PSA screening may identify those males with high serum PSA levels. Moreover, it is possible that the widespread adoption of PSA-based population screening promotes awareness of PSA screening among general practitioners; the resultant increase in PSA screening by general practitioners may lead to an increase in number of patients with high serum PSA levels detected outside of the population screening.

The overdiagnosis and overtreatment problem for prostate cancer may result from a favorable stage shift after the instigation of population screening. In the Kanazawa population-based screening cohort, 297 (70.4%) of the 422 cancer patients detected by PSA screening were diagnosed with clinically significant cancer,[19] which was inconsistent with the criteria of the Japanese prospective active surveillance cohort.[32] The relatively high rate of clinically significant cancer patients requiring optimal treatment supports the clinical importance of

Table 1: Correlation between exposure rate of population screening and prostate cancer detection in Gunma prefecture

Exposure rate	*Municipalities (n)*	*Prostate cancer, (n)*	*Metastatic disease, n (%)*
No screening	17	449	123 (29.2)
≤10%	9	1504	344 (23.9)
10.1%–20%	5	269	52 (20.9)
20.1%–30%	15	578	101 (18.5)
≥30.1%	21	469	63 (13.9)

PSA-based population screening. On the other hand, the treatment of approximately 20% of the patients with very low risk of prostate cancer should be carefully discussed. However, no consensus currently exists on the treatment modalities for prostate cancer, including active surveillance. The clinical trial on active surveillance currently underway in Japan[32] will provide critical information that can avoid and reduce the overtreatment for prostate cancer. Physicians involved with population screening should follow the treatment guidelines for cases of very low risk prostate cancer.

CLINICAL OUTCOMES IN PROSTATE CANCER PATIENTS DETECTED BY POPULATION SCREENING

Using the Kanazawa population-based screening cohort, we examined the clinical outcomes of prostate cancer patients detected by PSA-based population screening.[19] A total of 249 cancer patients were diagnosed at 15 urology departments in Kanazawa city or the surrounding areas, and 231 patients (93.5%) were diagnosed as having clinically localized cancer. Only four patients (1.65%) died of prostate cancer during the study period, and this result led to a high probability (93.3% at 8 years) of cause-specific survival (**Figure 2**).[19] Although longer follow-up is needed to evaluate the impact of population screening on prostate cancer mortality, this high probability may have been because cancer patients detected by screening were followed-up appropriately not only for prostate cancer but also for ordinary health care at each hospital.

In another hospital-based cohort study performed during the same period, it was demonstrated that 73.5% patients aged 55-69 years in our institution were identified by PSA screening, and these patients had a better prognosis than those diagnosed with local and/or systemic symptoms.[33] A similar result was obtained from another Japanese population screening cohort study, in which the prognosis of prostate cancer patients detected by population screening was demonstrated to be more favorable than that for those diagnosed outside of population screening.[16] Although various types of bias need to be taken into account when comparing cancer patients and people who undergo cancer screening,[34,35] this study demonstrated the favorable prognosis of the patients with stage-III prostate cancer and prognosis improvement after the introduction of PSA screening in the population groups; it also defined the effectiveness of population screening even if lead-time and length biases were considered.[16]

The ultimate aim of population screening for cancer is decreasing cancer mortality, and the controversy regarding this matter was raised in 2009 by the large-scale population-based prostate cancer screening cohort study in USA (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)[36] and in Europe (ERSPC).[12,37] The subsequent results of these screening cohorts demonstrated that a benefit regarding prostate cancer mortality was limited among middle-aged males, and led to the statement that well-informed men aged 55–69 years cannot be denied PSA testing, as stated in the AUA guidelines.[13] However, this is the situation in Western countries, and there has been no clear evidence regarding the effect of prostate cancer screening on cancer mortality on the basis of a large-scale prospective screening cohort in Asian countries. The ongoing Japanese Prospective Cohort Study of Screening for Prostate Cancer (JPSPC) is a cluster prospective cohort study that was initiated in 2002 to assess the effectiveness of prostate cancer screening using mortality rate as the primary end point.[38] Various municipalities within the Hokkaido, Gunma, Hiroshima, and Nagasaki Prefectures participated in the screening and control cohort studies, and these cohort studies has been conducted successfully, with high compliance for PSA screening protocols in the screening cohorts and relatively low compliance in the control cohorts.[38] As the low screening rates of prostate cancer in Asia are expected to minimize the contamination of the control cohort, the JPSPC ending in 2014 should clarify the efficacy of prostate cancer screening for the reduction of cancer-related mortality.[9]

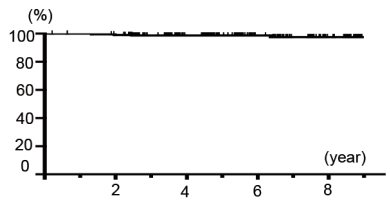

Figure 2: Kaplan–Meier plots of the cause-specific survival rates of prostate cancer patients detected by prostate-specific antigen-based population screening in Kanazawa city (modified from Reference[19]).

FUTURE PERSPECTIVE OF SCREENING FOR PROSTATE CANCER IN ASIA

An optimal and ideal population screening system for prostate cancer is one that maximizes mortality reduction and cost-effectiveness while minimizing the drawbacks of screening, such as overdetection, subsequent overtreatment, and adverse effects on quality of life. From this point of view, setting individualized screening, including screening interval, cut-offs for biopsy indication, and upper limit of age for screening, may lower the costs of screening in the community and decrease the likelihood of overdetection and false-positive PSA test results, while maintaining the benefit of mortality reduction. Future population screening should be established on the basis of these concepts, and indeed, the limited and conditional recommendations of screening for prostate cancer are in the AUA and EAU guidelines.[13,14] No official guidelines on screening for prostate cancer in Asian countries are available, except in Japan;[8,9] thus, the development of general guidelines for prostate cancer screening for Asian individuals is urgently needed. The characteristics and nature of middle-aged Asian males regarding serum PSA levels should be revealed to establish an optimal screening program, develop the general guidelines for prostate cancer screening, and subsequently widespread PSA screening in Asian countries. As stated above, population screening in Japan may become a good example of such personalized screening due to the lack of spontaneous PSA practice.

With regard to PSA-based population screening, the standard cut-off serum PSA level has been 4.0 ng ml^{-1}, which had predictive value for the diagnosis of prostate cancer.[39,40] However, several recent studies demonstrated that prostate cancer, including high-grade cancer, is not rare among males with serum PSA levels below 4.0 ng ml^{-1}.[41–43] Moreover, it is well-known that serum PSA levels gradually increase with age. The age-specific reference range of PSA is a reasonable concept for PSA-based screening, and may decrease the costs of screening and decrease the likelihood of overdetection and false-positive PSA test results, while maintaining the benefit of mortality reduction. In the JUA guidelines for prostate cancer, alternative cut-offs for biopsy indications are set at PSA levels of 3.0, 3.5, and 4.0 ng ml^{-1} for the age ranges of 50–64, 65–69, and ≥ 70 years, respectively, on the basis of clinical evidence in a Japanese population screening cohort study conducted in the 1990s.[6,44] Recently, we reported that the age-specific PSA cut-offs determined from the receiver operating characteristic curves ranged from 2.3 to 2.6 ng ml^{-1} in the Kanazawa population-based screening cohort, which were lower than those in the JUA guidelines.[45] Moreover, more than half of the patients with

serum PSA levels below the age-specific PSA cut-offs stated in the JUA guidelines had unfavorable features of cancer.[45] Several studies, including the Kanazawa population-based screening cohort study, indicated interracial differences in the age-specific PSA reference range, that is, serum PSA levels may be higher in European and Middle-Eastern males than in Japanese males.[28,45–49] On the other hand, the 95th percentiles in the participants excluding prostate cancer aged 60–69 years were 4.10 ng ml^{-1}, which was similar to recent studies in Korea (3.90 ng ml^{-1}) and China (4.10 ng ml^{-1}).[48,49] Further screening studies conducted in Asian countries are needed to define the optimal age-specific PSA cut-off for Asian individuals, which should lead to a modification of the standard cut-off serum PSA level of 4.0 ng ml^{-1} currently used to diagnose prostate cancer in biopsies. An optimal screening interval should be defined for the participant with baseline serum PSA below the cut-offs. Several studies have demonstrated the cumulative probabilities of increased PSA above the cut-offs and prostate cancer detection in subsequent screenings in those males.[50–54] On the basis of the Japanese study results in the 2000's, the JUA guidelines for PSA-based screening proposed a baseline PSA-adjusted screening interval, which was set every 3 years and annually in males with baseline PSA of 0.0–1.0 ng ml^{-1} and 1.1–2.0 ng ml^{-1}, respectively.[6] In the Kanazawa population screening cohort, the cumulative probabilities of developing prostate cancer at 4 years in males with baseline PSA of 0.0–1.0 and 1.1–2.0 ng ml^{-1} were 0.05% and 1.10%, respectively (**Figure 3**).[54] All cancer cases with unfavorable clinicopathological features were diagnosed at least 3 years after the initial screening visit in males with baseline PSA levels of 0.0–1.0 ng ml^{-1}.[54] On the other hand, there was a risk of developing cancer with unfavorable features within 1 year after the initial screening visit in males with baseline PSA levels of 1.1–2.0 ng ml^{-1}. Furthermore, prostate cancer cases with unfavorable clinicopathological features were detected every year, including one case with metastatic lesions diagnosed 5 years after the initial screening visit in this range of baseline PSA levels.[54] The cohort study well validated and supported the recommendation of the screening interval proposed by the JUA guidelines.[6]

Prostate-specific antigen screening has been recognized as a reasonable and convenient way to screen for prostate cancer widely as part of the health check-up of the participants who are healthy and undergo these check-ups to prevent illness; however, the specificity of serum PSA screening has been regarded as poor in those with serum PSA levels below 10 ng ml^{-1}. Approximately 20%–35% males with serum PSA levels of 4–10 ng ml^{-1} will be diagnosed with prostate cancer,[55,56] and the rates of prostate cancer detection of males with serum PSA levels of 2–4 ng ml^{-1} were reported to be approximately 25%.[42,57] These results suggested that unnecessary closer examinations, including prostate biopsy, will be performed at a considerable rate in males with serum PSA levels of 2–10 ng ml^{-1}. Many previous studies suggested that, in males with total PSA (tPSA) levels of 2–10 ng ml^{-1}, measurement of the free to tPSA (f/t PSA) ratio can distinguish better between malignant and benign prostate disease than tPSA alone,[58] and the usefulness of f/t PSA ratio in population screening was recognized in several studies.[58–61] Recent longitudinal studies of population screening cohorts demonstrated the effectiveness of f/t PSA ratio regarding the predictive values of f/t PSA ratio for future prostate cancer detection (**Figure 4**).[62–65]

In the same fashion, f/t PSA ratio, pro-PSA, and prostate cancer gene 3 (PCA3) were revealed as useful biomarkers for the prediction of a positive biopsy result for prostate cancer in Japanese males with "gray zone" of serum PSA levels.[66,67] Pro-PSA is formed by pro-leader peptide sequences comprising seven, five, four, and two amino acids and its more often associated with peripheral zone cancer than transition zone hyperplasia in prostate tissue and with cancer patients rather than noncancer patients when measured in the serum.[66,68–71] In a Japanese cohort, the prostate dimension-adjusted [-2]pro-PSA-related indices could distinguish patients with cancer from those without more accurately than classical PSA-related indices, such as f/t PSA ratio, PSA density, and PSA transition density.[66] It has been reported that PCA3 encodes a prostate-specific messenger RNA, which is highly overexpressed in prostate cancer tissue compared with its level in normal or benign tissue,[72] and this laboratory findings made PCA3 a prostate cancer diagnostic tool of great promise. Indeed, PCA3 urine assay has been superior to serum PSA or classical PSA-related indices for predicting prostate cancer in American and European populations, and it could be used as a diagnostic tool to select biopsy candidates.[73–75] The recent results in a large Japanese cohort[67] might indicate that racial differences do not affect PCA3 expression in prostate cancer patients and the possibility of PCA urine test as a screening tool for prostate cancer in Asian region. Future population-based screening program for detecting prostate cancer should be addressed by these novel biomarkers to select the indication of prostate biopsy, and Asian countries, in which conventional PSA-based screening program has not been widespread, may have a chance to establish novel efficiently population screening systems using these novel biomarkers in future.

CONCLUSION

In this review, we presented several results mainly in Japanese PSA-based population screening cohort studies conducted during the past two decades of the PSA era. These findings led us to the

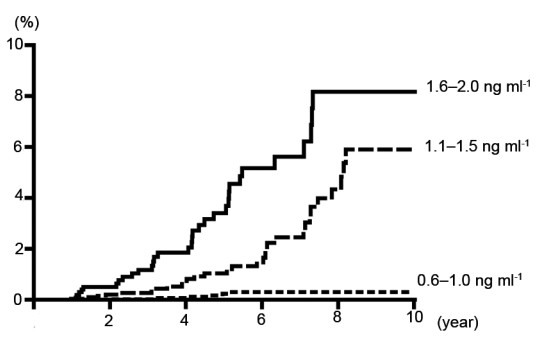

Figure 3: Cumulative probabilities of developing prostate cancer during follow-up in the participants with baseline prostate-specific antigen levels of 2.0 ng ml^{-1} or lower (modified from Reference[54]).

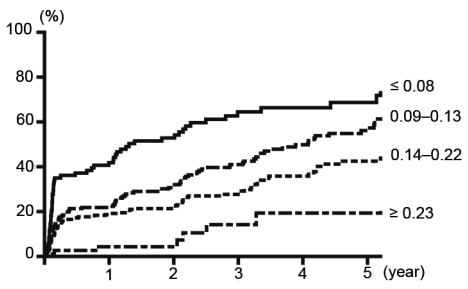

Figure 4: Cumulative probabilities of prostate cancer detection according to free to total prostate-specific antigen (PSA) ratio during follow-up in participants with baseline PSA levels of 2.1–10.0 ng ml^{-1} (modified from Reference[65]).

conclusion that PSA-based screening sufficiently contributed to detecting prostate cancer at an early stage, in which the decreased mortality rate following optimal treatments was expected. At present, the conventional PSA-based population screening is not carried out and PSA screening is not widespread in many Asian countries; however, recent evidence regarding serum PSA kinetics in middle-aged males, PSA-related indices, and novel biomarkers for prostate cancer screening may contribute to establish an optimal and natural history-adjusted screening system in Asian individuals.

AUTHOR CONTRIBUTIONS

YK contributed to the study design and drafted the manuscript. NM supervised the study and assisted in drafting the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ACKNOWLEDGMENTS

We thank Dr. Kazuto Ito of Gunma University, Maebashi, and Dr. Koji Okihara of Kyoto Prefectural University of Medicine, Kyoto, for providing data and valuable advice.

REFERENCES

1 Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999; 49: 33–64, 1.
2 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; 63: 11–30.
3 Bouchardy C, Fioretta G, Rapiti E, Verkooijen HM, Rapin CH, *et al.* Recent trends in prostate cancer mortality show a continuous decrease in several countries. *Int J Cancer* 2008; 123: 421–9.
4 Ohno Y, Nakamura T, Murata K. Prediction of the future incidence of cancer in Japan. In: Oshima A, Kuroishi T, Tajima K, editors. White Paper on Cancer and Statistics-Incidence/Mortality/Prognosis-2004 (in Japanese). Tokyo: Shinohara Shuppan; 2004. p. 201–17.
5 Ito K. Prostate-specific antigen-based screening for prostate cancer: evidence, controversies and future perspectives. *Int J Urol* 2009; 16: 458–64.
6 Committee for Establishment of the Guidelines on Screening for Prostate Cancer, Japanese Urological Association. Updated Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010. *Int J Urol* 2010; 17: 830–8.
7 Sothilingam S, Sundram M, Malek R, Sahabuddin RM. Prostate cancer screening perspective, Malaysia. *Urol Oncol* 2010; 28: 670–2.
8 Namiki M, Akaza H, Lee SE, Song JM, Umbas R, *et al.* Prostate cancer working group report. *Jpn J Clin Oncol* 2010; 40 Suppl 1: i70–5.
9 Ito K. Prostate cancer in Asian men. *Nat Rev Urol* 2014; 11: 197–212.
10 Zhang J, Dhakal IB, Zhao Z, Li L. Trends in mortality from cancers of the breast, colon, prostate, esophagus, and stomach in East Asia: role of nutrition transition. *Eur J Cancer Prev* 2012; 21: 480–9.
11 Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. *Cochrane Database Syst Rev* 2013; 1: CD004720.
12 Schröder 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.
13 Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, *et al.* Early detection of prostate cancer: AUA guideline. *J Urol* 2013; 190: 419–26.
14 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, *et al.* EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014; 65: 124–37.
15 Fukagai T, Namiki T, Carlile RG, Namiki M. Racial differences in clinical outcome after prostate cancer treatment. *Methods Mol Biol* 2009; 472: 455–66.
16 Kubota Y, Ito K, Imai K, Yamanaka H. Effectiveness of mass screening for the prognosis of prostate cancer patients in Japanese communities. *Prostate* 2002; 50: 262–9.
17 Kato T, Habuchi T, Tsuchiya N, Sato K, Kitajima S, *et al.* Mass screening of prostate cancer and its impact on inhabitants in Akita Prefecture, Japan. *Aktuelle Urol* 2010; 41 Suppl 1: S53–6.
18 Okihara K, Kitamura K, Okada K, Mikami K, Ukimura O, *et al.* Ten year trend in prostate cancer screening with high prostate-specific antigen exposure rate in Japan. *Int J Urol* 2008; 15: 156–60.
19 Kitagawa Y, Mizokami A, Nakashima K, Koshida K, Shimamura M, *et al.* Clinical outcomes of prostate cancer patients detected by prostate-specific antigen-based population screening in Kanazawa City, Japan. *Int J Urol* 2011; 18: 592–6.
20 Kitagawa Y, Sawada K, Mizokami A, Nakashima K, Koshida K, *et al.* Clinical characteristics and prostate-specific antigen kinetics of prostate cancer detected in repeat annual population screening in Japan. *Int J Urol* 2014; 21: 461–5.
21 Mäkinen T, Tammela TL, Stenman UH, Määttänen L, Aro J, *et al.* Second round results of the Finnish population-based prostate cancer screening trial. *Clin Cancer Res* 2004; 10: 2231–6.
22 Hugosson J, Aus G, Lilja H, Lodding P, Pihl CG. Results of a randomized, population-based study of biennial screening using serum prostate-specific antigen measurement to detect prostate carcinoma. *Cancer* 2004; 100: 1397–405.
23 Postma R, Schröder FH, van Leenders GJ, Hoedemaeker RF, Vis AN, *et al.* Cancer detection and cancer characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC) – Section Rotterdam. A comparison of two rounds of screening. *Eur Urol* 2007; 52: 89–97.
24 Takechi H, Ito K, Yamamoto T, Ohi M, Kubota H, *et al.* Correlation between exposure rates of screening for prostate cancer and clinical features of the patients diagnosed with prostate cancer in Gunma prefecture, Japan (Japanese). *Jpn J Urol Surg* 2005; 18: 997–9.
25 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.
26 Fujimoto H, Nakanishi H, Miki T, Kubota Y, Takahashi S, *et al.* Oncological outcomes of the prostate cancer patients registered in 2004: report from the Cancer Registration Committee of the JUA. *Int J Urol* 2011; 18: 876–81.
27 Zhang HF, Wang HL, Xu N, Li SW, Ji GY, *et al.* Mass screening of 12,027 elderly men for prostate carcinoma by measuring serum prostate specific antigen. *Chin Med J (Engl)* 2004; 117: 67–70.
28 Rabah DM, Arafa MA. Prostate cancer screening in a Saudi population: an explanatory trial study. *Prostate Cancer Prostatic Dis* 2010; 13: 191–4.
29 Kitagawa Y, Machioka K, Yaegashi H, Nakashima K, Ofude M, *et al.* Decreasing trend in prostate cancer with high serum prostate-specific antigen levels detected at first prostate-specific antigen-based population screening in Japan. *Asian J Androl* 2014.
30 Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol* 2007; 178: S14–9.
31 Glass AS, Cowan JE, Fuldeore MJ, Cooperberg MR, Carroll PR, *et al.* Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. *Urology* 2013; 82: 60–5.
32 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.
33 Kitagawa Y, Mizokami A, Namiki M. Trends of clinical symptoms and prognosis of middle-aged prostate cancer patients after instigation of prostate specific antigen-based population screening. *Prostate Int* 2013; 1: 65–8.
34 Miller AB, editor. Principles of screening and of the evaluation of screening programs. Screening for Cancer. Orlando: Academic Press; 1985. p. 3–24.
35 Miller AB, editor. Screening for cancer of the breast. Screening for Cancer. Orlando: Academic Press; 1985. p. 325–46.
36 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.
37 Schröder 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.
38 Ito K, Kakehi Y, Naito S, Okuyama A. Japanese Urological Association. Japanese Urological Association guidelines on prostate-specific antigen-based screening for prostate cancer and the ongoing cluster cohort study in Japan. *Int J Urol* 2008; 15: 763–8.
39 Cooner WH, Mosley BR, Rutherford CL Jr, Beard JH, Pond HS, *et al.* Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol* 1990; 143: 1146–52.
40 Brawley OW, Knopf K, Merrill R. The epidemiology of prostate cancer part I: descriptive epidemiology. *Semin Urol Oncol* 1998; 16: 187–92.
41 Krumholtz JS, Carvalhal GF, Ramos CG, Smith DS, Thorson P, *et al.* Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. *Urology* 2002; 60: 469–73.
42 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, *et al.* Prevalence of prostate cancer among men with a prostate-specific antigen level<or=4.0 ng per milliliter. *N Engl J Med* 2004; 350: 2239–46.
43 Park HK, Hong SK, Byun SS, Lee SE. T1c prostate cancer detection rate and pathologic characteristics: comparison between patients with serum prostate-specific antigen range of 3.0–4.0 ng/mL and 4.1–10.0 ng/mL in Korean population. *Urology* 2006; 68: 85–8.
44 Ito K, Yamamoto T, Kubota Y, Suzuki K, Fukabori Y, *et al.* Usefulness of age-specific reference range of prostate-specific antigen for Japanese men older than 60 years in mass screening for prostate cancer. *Urology* 2000; 56: 278–82.
45 Kitagawa Y, Izumi K, Sawada K, Mizokami A, Nakashima K, *et al.* Age-specific reference range of prostate-specific antigen and prostate cancer detection in population-based screening cohort in Japan: verification of Japanese Urological Association Guideline for prostate cancer. *Int J Urol* 2014; 21: 1120–5.
46 Battikhi MN. Age-specific reference ranges for prostate-specific antigen (PSA) in

Jordanian patients. *Prostate Cancer Prostatic Dis* 2003; 6: 256–60.
47 Casey RG, Hegarty PK, Conroy R, Rea D, Butler MR, *et al*. The distribution of PSA age-specific profiles in healthy Irish men between 20 and 70. *ISRN Oncol* 2012; 2012: 832109.
48 Lee SE, Kwak C, Park MS, Lee CH, Kang W, *et al*. Ethnic differences in the age-related distribution of serum prostate-specific antigen values: a study in a healthy Korean male population. *Urology* 2000; 56: 1007–10.
49 Liu ZY, Sun YH, Xu CL, Gao X, Zhang LM, *et al*. Age-specific PSA reference ranges in Chinese men without prostate cancer. *Asian J Androl* 2009; 11: 100–3.
50 Ito K, Yamamoto T, Ohi M, Takechi H, Kurokawa K, *et al*. Possibility of re-screening intervals of more than one year in men with PSA levels of 4.0 ng/ml or less. *Prostate* 2003; 57: 8–13.
51 Ito K, Yamamoto T, Ohi M, Takechi H, Kurokawa K, *et al*. Cumulative probability of PSA increase above 4.0 NG/ML in population-based screening for prostate cancer. *Int J Cancer* 2004; 109: 455–60.
52 Ito K, Raaijmakers R, Roobol M, Wildhagen M, Yamanaka H, *et al*. Prostate carcinoma detection and increased prostate-specific antigen levels after 4 years in Dutch and Japanese males who had no evidence of disease at initial screening. *Cancer* 2005; 103: 242–50.
53 Candas B, Labrie F, Gomez JL, Cusan L, Chevrette E, *et al*. Relationship among initial serum prostate specific antigen, prostate specific antigen progression and prostate cancer detection at repeat screening visits. *J Urol* 2006; 175: 510–6.
54 Sawada K, Kitagawa Y, Ito K, Takeda Y, Mizokami A, *et al*. Cumulative risk of developing prostate cancer in men with low (=2.0 ng/mL) prostate-specific antigen levels: a population-based screening cohort study in Japan. *Int J Urol* 2014; 21: 560–5.
55 Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, *et al*. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; 324: 1156–61.
56 Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, *et al*. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. *J Natl Cancer Inst* 2005; 97: 433–8.
57 Schröder FH. Diagnosis, characterization and potential clinical relevance of prostate cancer detected at low PSA ranges. *Eur Urol* 2001; 39 Suppl 4: 49–53.
58 Roddam AW, Duffy MJ, Hamdy FC, Ward AM, Patnick J, *et al*. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis. *Eur Urol* 2005; 48: 386–99.
59 Pelzer AE, Volgger H, Bektic J, Berger AP, Rehder P, *et al*. The effect of percentage free prostate-specific antigen (PSA) level on the prostate cancer detection rate in a screening population with low PSA levels. *BJU Int* 2005; 96: 995–8.
60 Kobori Y, Kitagawa Y, Mizokami A, Komatsu K, Namiki M. Free-to-total prostate-specific antigen (PSA) ratio contributes to an increased rate of prostate cancer detection in a Japanese population screened using a PSA level of 2.1-10.0 ng/ml as a criterion. *Int J Clin Oncol* 2008; 13: 229–32.
61 Ishidoya S, Ito A, Orikasa K, Kawamura S, Tochigi T, *et al*. The outcome of prostate cancer screening in a normal Japanese population with PSA of 2-4 ng/ml and the free/total PSA under 12%. *Jpn J Clin Oncol* 2008; 38: 844–8.
62 Ito K, Yamamoto T, Ohi M, Kurokawa K, Suzuki K, *et al*. Free/total PSA ratio is a powerful predictor of future prostate cancer morbidity in men with initial PSA levels of 4.1 to 10.0 ng/mL. *Urology* 2003; 61: 760–4.
63 Aus G, Becker C, Franzén S, Lilja H, Lodding P, *et al*. Cumulative prostate cancer risk assessment with the aid of the free-to-total prostate specific antigen ratio. *Eur Urol* 2004; 45: 160–5.
64 Finne P, Auvinen A, Määttänen L, Tammela TL, Ruutu M, *et al*. Diagnostic value of free prostate-specific antigen among men with a prostate-specific antigen level of <3.0 microg per liter. *Eur Urol* 2008; 54: 362–70.
65 Kitagawa Y, Ueno S, Izumi K, Kadono Y, Konaka H, *et al*. Cumulative probability of prostate cancer detection in biopsy according to free/total PSA ratio in men with total PSA levels of 2.1-10.0 ng/ml at population screening. *J Cancer Res Clin Oncol* 2014; 140: 53–9.
66 Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, *et al*. Diagnostic significance of [-2] pro-PSA and prostate dimension-adjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/mL range. *World J Urol* 2013; 31: 305–11.
67 Ochiai A, Okihara K, Kamoi K, Oikawa T, Shimazui T, *et al*. Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. *BJU Int* 2013; 111: 928–33.
68 Kumar A, Mikolajczyk SD, Goel AS, Millar LS, Saedi MS. Expression of pro form of prostate-specific antigen by mammalian cells and its conversion to mature, active form by human kallikrein 2. *Cancer Res* 1997; 57: 3111–4.
69 Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, *et al*. A prospective, multicenter, national cancer institute early detection research network study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1193–200.
70 Le BV, Griffin CR, Loeb S, Carvalhal GF, Kan D, *et al*. [-2]Proenzyme prostate specific antigen is more accurate than total and free prostate specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study. *J Urol* 2010; 183: 1355–9.
71 Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, *et al*. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol* 2011; 185: 1650–5.
72 Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, *et al*. DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res* 1999; 59: 5975–9.
73 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.
74 Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, *et al*. PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. *Urology* 2007; 69: 532–5.
75 Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, *et al*. Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. *Eur Urol* 2008; 54: 1081–8.