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Review

Prostate cancer screening in Europe and Asia

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Received 30 June 2016; received in revised form 16 August 2016; accepted 16 August 2016

KEYWORDS

Prostate cancer; Early detection; Biomarkers; Imaging; Risk prediction; Europe; Asia Abstract Prostate cancer is the second most common cancer among men worldwide and even ranks first in Europe. Although Asia is known as the region with the lowest PCa incidence, it has been rising rapidly over the last 20 years mostly due to the introduction of prostate-specific antigen testing. Randomized PCa screening studies in Europe show a mortality reduction in favor of PSA-based screening but coincide with high proportions of unnecessary biopsies, overdiagnosis and subsequent overtreatment. Conclusive data on the value of PSA-based screening and hence the balance between harms and benefits in Asia is still lacking. Because of known racial variations, Asian countries should not directly apply the European screening models. Like in the western world also in Asia, new predictive markers, tools and risk stratification strategies hold great potential to improve the early detection of PCa and to reduce the worldwide existing negative aspects of PSA-based PCa screening.

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1. Incidence of prostate cancer in Europe and Asia

Prostate cancer (PCa) is the second most common malignancy and the fifth leading cause of cancer death in men worldwide [1]. However, the incidence differs by more than 25-fold among regions, with the highest in Australia/New Zealand and the lowest in South-Central Asia [1] (Fig. 1, adapted from Ref. [1]).

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Peer review under responsibility of Second Military Medical University.

This wide variation in incidence is strongly related to the use of the prostate-specific antigen (PSA) test as a screening tool [2]. In most European countries such as France, The Netherlands, and the Czech Republic, the PCa incidence increased significantly in the early 1990s, soon after the introduction of the PSA test, and is still increasing [3,4]. The incidence in Asian countries like China and Japan, began to increase after 1995. Although later than in Europe because of the delayed use of the PSA test as a screening tool, the increase of PCa incidence in Asian countries is more pronounced in a comparable period [3] (Fig. 2 adapted from Ref. [3]).

As said, the worldwide variation in the use of the PSA test is probably the most important reason for the variability in PCa incidence. It is interesting to note that in the early 1980s, when PSA was not yet used, a nearly 20-fold PCa incidence difference already existed (USA 91.43 vs

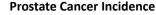
http://dx.doi.org/10.1016/j.ajur.2016.08.010

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Please cite this article in press as: Zhang K, et al., Prostate cancer screening in Europe and Asia, Asian Journal of Urology (2016), http://dx.doi.org/10.1016/j.ajur.2016.08.010

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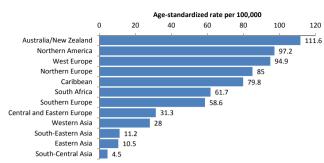


Figure 1 Prostate cancer incidence worldwide.

Average Annual Percent Change

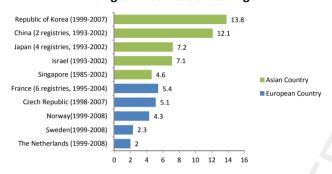


Figure 2 Prostate cancer incidence trend in Europe and Asia.

Japan 4.87, per 100,000) [5]. This could be explained by factors like dietary differences (e.g. a high-fat diet in the western world), the prevalence of obesity, and genetic factors [3]. A striking example is the significantly higher PCa incidence in Japanese-American men than in native Japanese men, suggesting that westernization through a high-fat diet is strongly related to the risk of having PCa [6]. Furthermore, the PCa incidence in African-American men is 2—3 times higher than in White and Asian-American men in the US, which indicates that gene and race also contribute to PCa risk [7].

2. Screening trials in Europe and Asia

The European Randomized study of Screening for Prostate Cancer (ERSPC) is the largest randomized trial for PCa screening and is still ongoing. It started in 1993 and includes 162,338 men, aged 55–69 yr at time of randomization. After 13 years of follow-up, the trial showed that PCa mortality was reduced by 21% in favor of the screening arm [8]. This finding is contrary to that of a large American randomized trial, the so-called prostate arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). This trial, also initiated in 1993 and in which 76,685 men were randomized showed no difference in PCa mortality between the screening and control arm with 13 years of follow-up [9]. A recent publication on the basis of the PLCO data showed a 90% PSA contamination rate in the control arm which seriously questions the value of the reported outcomes [10].

The Goteborg Randomized Prostate Cancer Screening Trial is a European prospective, randomized trial that started in 1995 and included 19,904 men, aged 50—64 yrs at time of randomization. After 14 years of follow-up, it showed that PCa mortality decreased by 44% in the screening group as compared to the control group [11].

It is important to note that all three PCa screening trials were based on Caucasian populations. Hence, their outcomes cannot be directly translated to an Asian population.

The Japanese Prospective Cohort Study of Screening for Prostate Cancer (JPSPC) is the only known prospective controlled PCa screening study in Asia (Table 1). It started in 2002 and ended in 2014. The aim of the study is to compare the PCa mortality between the screening and control cohort. This study comprises of 200,000 men in the age range between 50 and 79 from Hokkaido, Gunma, Hiroshima and Nagasaki prefectures. A PSA >3 ng/ml in men aged 50-64, a PSA \geq 3.5 ng/ml in men aged 65-69 and a PSA \geq 4.0 ng/ml in men aged 70-79 triggered biopsy [12]. The compliance rate of PSA testing in the Isesaki city screening cohort was about 75% over 5 years and the contamination (PCa screening) in the Kiryu city control cohort was low at 8% between 1992 and 2006 [13]. The contamination rate for the whole control cohort is expected to be considerably low, due to the absence of opportunistic PCa screening in Japan. The study outcome is eagerly awaited to show whether PSA-based screening has any potential in an Asian setting [14].

The Kanazawa population-based screening cohort study is another large PCa screening study in Japan. A total of 32,769 men aged 55-69 yr participated in the program from 2000 to 2006. Contrary to the JPSPC study, the indication of biopsy varied among the different urologists participating in this study. From 2000 to 2002, all men with a PSA > 2.1 ng/ml were recommended to undergo the secondary screening (consisting of a digital rectal examination (DRE) and transrectal ultrasonography (TRUS) examination) and to consult a urologist who would decide whether or not to perform a systematic biopsy taking into account the results of the DRE and TRUS [15]. From 2003 onwards, men with PSA values 2.1-10.0 ng/ml and a fPSA/tPSA ratio higher than 0.22, were not referred for further screening. 4766 men (14.9%) required secondary screening and 1041 men (3.2%) underwent prostate biopsy. A total of 249 men (0.76%) were diagnosed with PCa, of whom 231 (93.5%) were classified as clinically localized cancer. Comparing the outcomes of this screening study with those done among predominantly Caucasian men it again highlights the considerable difference in PCa incidence; 0.76% and 8.33% in this Japanese screening study and the ERSPC respectively) [8]. The percentage of localized tumors (T1,T2) in Japan was, however, remarkably higher than in the ERSPC (93.5% and 78.2% respectively) [16].

A South Korean screening study focused on the relation between the PSA value and PCa mortality. It included 118,665 men from 1994 to 2004, and followed these men up to 2011. The results showed a PCa death risk of 1.0, 1.57, 2.41, 4.32 and 65.0% for baseline PSA values of <1.0, 1–2, 2–4, 4–10 and \geq 10 ng/ml respectively after adjusting for age, body mass index (BMI) and smoking status [17]. By contrast, although having a longer follow-up, in a subgroup of The Malmo Preventive Project which included 1167 men

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