Prostate cancer incidence has been rising in the last decade in Hong Kong. In 2008, prostate cancer was the third most common cancer with 1,369 new cases and the fifth major cause of death which killed 282 patients. As the community becomes more aware of the disease, more patients are screened for prostate cancer. Serum prostate specific antigen (PSA) and digital rectal examination (DRE) are the 2 commonest methods employed for the purpose. With the advances in prostate cancer diagnostics and state-of-the-art treatment options of early prostate cancers, it is hoped that prostate cancer mortality will decline in the next decade. In this article, the author would like to focus on the update of PSA test in prostate cancer diagnostics and the controversial issue of prostate cancer screening.

PSA was first discovered in 1960s as a gamma semenoprotein in seminal fluid, developed for forensic use in rape cases. It is a weak protease, which is present in large amounts in semen, with the physiological function of liquefying the semen and improving sperm motility. Before the PSA era, prostate acid phosphatase had been used as the historical male “PAP” test. It was not until the discovery of association between serum prostate antigen and prostate cancer by Wang et al at in 1979 that PSA was widely adopted worldwide as the screening test of prostate cancer. Unfortunately PSA has never been the ideal screening tool. Catalona et al had suggested 4ng per ml as the optimal cut-off for early detection of prostate cancer. Recent studies had shown that there was no single cut-off value which could attain the likelihood ratio required of a screening test. The sensitivity and specificity of PSA at cut-offs of 3, 4 and 5ng per ml was 59 and 87%, 44 and 92%, 33 and 95% respectively. The exception was PSA cut-off at 1ng per ml, which had a negative likelihood ratio of 0.08 and virtually ruled out prostate cancer diagnosis.

There had been multiple attempts to enhance the accuracy of PSA test and reduce unnecessary prostate biopsies. Free to total PSA ratio less than 10% was associated with increased risks of malignant disease while ratio more than 25% was suggestive of benign pathology. However, many patients lied in the gray zone between 10 and 25%. Age-specific PSA was associated with decreased specificity for young patients and decreased sensitivity for old ones. PSA density was an attempt to balance out the influence of large prostate volume. However, there were both inter- and intra-observer variations in prostate volume assessment. PSA velocity higher than 0.75ng per ml every year was predictive of prostate cancer, but it required multiple PSA tests and its subsequent calculation was not welcomed in routine clinical practice. Urine markers were promoted over the last few years as supplementary tests to PSA. PCA3 is now commercially available. PCA3 is a gene identified by Bussemakers et al at the University of Nijmegen, the Netherlands and Johns Hopkins Hospital. This gene is 60 to 100-fold overexpressed in 95% of prostate cancers. The test measures the expression of PCA3 gene in cells isolated from the urine of men after receiving a meticulous digital rectal examination, as a function of the expression of PCA3 gene controls for the total number of prostate cells in the sample. PCA3 has sensitivity of 50 to 75% and specificity of 80 to 90%. Its potential use includes the difficult scenario when patients have persistently elevated PSA and negative previous biopsies.

Prostate cancer screening is commonly practised in the United States. It is controversial in deciding whether its routine practice reduces prostate cancer mortality. In 2009, two independent large-scale randomised controlled trials had been published in Europe (ERSPC trial) and the United States (PLCO trial). The ERSPC trial included seven European countries with a total of 162,387 participants. With PSA cut-off at 3 to 4ng per ml and follow-up of nine years, the screening group was shown to reduce prostate cancer mortality by 20% in the age group of 55 to 69 years. The PLCO trial included ten US study centres with a total of 76,693 participants. With PSA cut-off at 4ng per ml and follow-up of ten years, there was no difference in prostate cancer mortality between the screening and control groups, at the age group of 55 to 74 years. However, the control group was found to be contaminated with prior PSA screening in up to 50% of participants. In 2010, Cochrane review reported meta-analyses of five randomised controlled trials since 2006, with a total of 341,351 patients. There was no reduction in all-cause or prostate-cancer specific mortality. Only ERSPC showed a reduction in prostate cancer-specific mortality in the age group of 55 to 69 years (RR 0.80, 95% C.I. 0.65-0.98). However, it needed to screen 1,410 participants, treat 48 prostate cancer patients in order to prevent one prostate cancer death at ten years later. It was commented that men with life expectancy less than 10 to 15 years should think twice before PSA screening. PSA screening was associated with a high false positive rate of PSA tests e.g. with PSA cut-off at 3ng per ml, the false positive rate was 75.9% in ERSPC trial. Screening was associated with over-diagnosis of clinically insignificant disease, with up to 50% in PLCO trial. Patients also need to consider the adverse effects of prostate biopsy e.g. pain, sepsis, haematuria and haemospermia, etc.
In conclusion, PSA remains the commonest screening test of prostate cancer. Various tests, including PCA3 urine markers, have been developed to enhance the accuracy of PSA test, in order to reduce unnecessary prostate biopsies. Population-based prostate cancer screening has not been shown to reduce disease-specific nor all-cause mortality. Individual patients need to be counselled about the pros and cons of PSA test, associated morbidities of prostate biopsies and prostate cancer treatments, especially in those elderly patients with a life expectancy of less than 10 years.

References
1. Hong Kong Cancer Registry, Hospital Authority.