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ASIAN FOCUS

Prostate cancer in Asia: A collaborative report



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Abstract The incidence of prostate cancer (PCa) within Asian population used to be much lower than in the Western population; however, in recent years the incidence and mortality rate of PCa in some Asian countries have grown rapidly. This collaborative report summarized the latest epidemiology information, risk factors, and racial differences in PCa diagnosis, current status and new trends in surgery management and novel agents for castration-resistant prostate cancer. We believe such information would be helpful in clinical decision making for urologists and oncologists, health-care ministries and medical researchers.

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1. Introduction

Approximately 238,590 new cases of prostate cancer (PCa) were diagnosed in the United States in 2013, causing 29,720 deaths in the same year [1]. During the past few decades, PCa incidence was reported to be much lower in Asian countries [2]; however, with dramatic economic growth and socio-cultural changes leading to an increased life expectancy and westernized lifestyle, the incidence and mortality

rates of PCa in some Asian countries have shown a rapidly growing trend [2]. Currently PCa has already ranked the sixth of the most frequent cancers in 2012 among Asian countries [3]. As the aging process of the Asian population is still going on and the benefits of economic development will continue to accelerate lifestyle changes towards Westerners, PCa was predicted to gradually become a more serious healthcare and socio-economic issue. Meanwhile, the average spending on healthcare in most Asian countries was still much lower

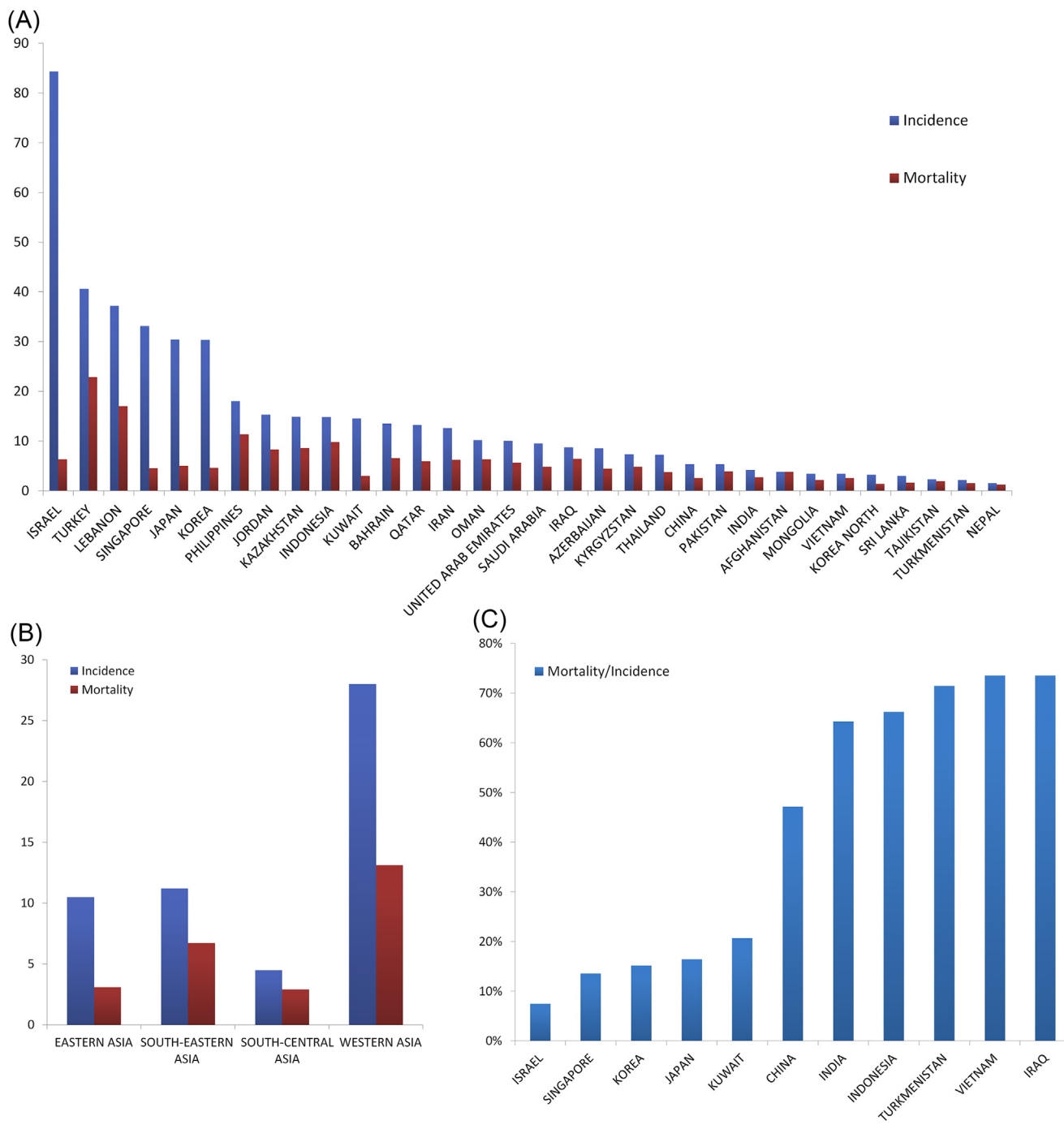


Figure 1 (A) Incidence and mortality rates (per 100,000) in Asian countries and regions in 2012. (B) Incidence and mortality rates (per 100,000) in different Asian regions in 2012. (C) Mortality/incidence ratios in Asian countries and regions in 2012 (Age specific rate, ASR). Data sources: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet].

than that of Western countries [4]. Dealing with such a trend of rapid growth of PCa with a limited budget in most Asian countries is extremely challenging. Here in this report, we not only systematically summarized currently available data, but also collected the first-hand clinical statistics on current diagnostic strategy and emerging treatment options both in surgery management and castration-resistant prostate cancer (CRPC) from Chinese Prostate Cancer Consortium (CPCC) and leading urologists in Asian countries and regions. These data are based on national registry data or from representative/leading hospitals in situations where the former is not available. Thus, cautions should be taken in interpreting these data. Hopefully, we believe such information would be helpful in decision making for urologists and oncologists, healthcare ministries and medical researchers from a clinical prospective.

2. PCa epidemiology in Asia

2.1. Incidence

Globally, PCa is the second most common cancer in men and the incidence varies more than 25-fold worldwide; the rates are highest in Australia/New Zealand and Northern America (age standardized rate (ASR) 111.6 and 97.2 per 100,000, respectively), and in Western and Northern Europe [3]. However, after reaching its peak in mid-1900s which is commonly attributed to the widespread use of prostate-specific antigen (PSA) tests, the incidence of PCa in several developed countries (Canada, the United States, United Kingdom, Italy, etc.) has witnessed a decrement in the past few years [5], but still remains higher than that in Asian populations. According to the WHO report in 2012, the incidence rates were estimated at 10.5% and 4.5% in East and South-Central Asia, respectively [3] (Fig. 1A, B). However, PCa incidence in Asian countries has been on a steady increase during the past few decades. Currently, PCa has already become the sixth most frequent cancer in Asian men, with the highest in Western Asia ranking second in all cancers and the lowest in South-Central Asia ranking eighth.

2.2. Mortality

With an estimated 307,000 deaths in 2012, PCa is the fifth leading cause of death from cancer in men globally (6.6% of the total deaths in men). It is still controversy if PSA testing had a significant influence on mortality rates. Less variation in mortality rates was seen worldwide (10-fold from approximately 3 to 30 per 100,000) than is observed for incidence, with the number of deaths from PCa larger in less developed than in more developed regions (165,000 and 142,000, respectively). The average mortality rate of PCa in Asian countries is 3.8 per 100,000. In economically developed regions such as Japan, Singapore, and Korea, these rates are 5, 4.5, and 4.6 per 100,000, respectively [3]. The trends of mortality rates were more variable; with increasing trends observed in China (Hong Kong), Kazakhstan, and Korea, decreasing trends seen in Israel, Japan, Kyrgyzstan, and Uzbekistan, and rather stable trends reported in Singapore and Tajikistan [3].

2.3. Changing trend in epidemiology

As illustrated in a previous review [6], the PCa incidence in developing East Asia countries has been on a rapid rise since the 1990s. For instance, the incidence rate has grown at a rate of 7.2% per year from 2004 to 2009. As the national cancer registry report shows, the incidence was 9.92 per 100,000 in 2009 [7]. The incidence in Korea has also been on a rapid rise from 8.4 per 100,000 in 1999 to 24.4 per 100,000 in 2011 [8]. Considering the similar genetic background between Korea and China, it is predicted that the incidence in China will increase to a level comparable to Korea if China adopts a similar healthcare policy to Korea in PCa detection. However, it is relatively difficult to predict if the incidence will continue to surge in Korea and Japan where this rate has already experienced rapid growth.

2.4. Mortality/incidence ratios

The MR/IR (mortality-to-incidence rate ratio) was as high as 40% in Asia compared to 18% in Europe, 10% in Northern America and 25% worldwide. The lowest MR/IR rate was witnessed in Israel, whereas it is typically much higher in countries with unfavorable economic situations, like Vietnam and Iraq (Fig. 1C). In several developed countries like Japan, Korea and Singapore, although the incidence is higher than other countries, the MR/IR is relatively lower than in that of several Southeast and West Asian countries [3].

3. Risk factors for PCa in Asian men

3.1. Genetic differences in prostate cancer in Asian men

Asians differ significantly with regards to race. East and Southeast Asians share a similar genetic background and are generally known as Mongolians; Northwest and Central Asians are of Turkic, Iranian or Caucasian ethnicity. The South Asians consist of mainly the Indian population which has been considered as a mixed population of Caucasians and Mongolians. As for the West Asian population, some of them are Caucasians and others are Arabians.

There are two types of genetic variations that are important in prostate carcinogenesis; one is somatic alteration in prostate tumors, and the other is germline common polymorphic conferring moderate-to-low risk for developing the disease. For the first type of genetic variation, substantial racial differences have been reported. For instance, the most prevalent gene fusion in Caucasians is the *TMPRSS2-ERG* fusion, with a prevalence of about 50%. However, much lower frequencies are reported in Asian populations (8%–21%) [9,10]. Another prominent variation is the *PTEN* inactivation in PCa patients. *PTEN* inactivation was reported in 70% of Caucasians but only 34% in Chinese patients [9,11]. Currently, there is evidence that *PTEN* loss and *TMPRSS2-ERG* fusion are related [12]. This may offer a potential explanation for the low incidence of *PTEN* loss and low expression of *TMPRSS2-ERG* fusion in the East Asian population. Other mutations, such as *KRAS* mutations and *BRAF* copy number gain, are seen more frequently in Asian

Table 1 SNPs identified in genome-wide association studies in Asian populations.

Locus	SNP	Nearby genes	Reference allele	Effect allele	Effect OR (95%CI)	Ethnic of identification	Reference
2p24	rs13385191	<i>C2orf43</i>	A	G	1.15 (1.10–1.21)	Japanese	[16]
5p15	rs12653946	<i>IRX4</i>	C	T	1.26 (1.20–1.33)	Japanese	[16]
6p21	rs1983891	<i>FOXP4</i>	C	T	1.15 (1.09–1.21)	Japanese	[16]
6q22	rs339331	<i>RFX6</i>	C	T	1.22 (1.15–1.28)	Japanese	[16]
13q22	rs9600079	<i>Unknown</i>	G	T	1.18 (1.12–1.24)	Japanese	[16]
3p11	rs2055109	<i>Unknown</i>	T	C	1.20 (1.13–1.29)	Japanese	[17]
10q26	rs2252004	<i>Unknown</i>	T	G	1.16 (1.10–1.22)	Japanese	[17]
11q12	rs1938781	<i>FAM111A</i>	T	C	1.16 (1.11–1.21)	Japanese	[17]
9q31	rs817826	<i>RAD23B–KLF4</i>	T	C	1.41 (1.29–1.54)	Chinese	[18]
19q13	rs103294	<i>LILRA3</i>	T	C	1.28 (1.21–1.36)	Chinese	[18]
9p24	rs7045455	<i>SMARCA2</i>	T	C	3.98 (1.97–8.05)	Tunisians	[19]
9p24	rs12686439	<i>SMARCA2</i>	G	A	3.32 (1.80–6.15)	Tunisians	[19]
9p24	rs10810919	<i>SMARCA2</i>	T	C	5.03 (2.22–11.4)	Tunisians	[19]
9p24	rs10963533	<i>SMARCA2</i>	T	C	4.19 (2.01–8.75)	Tunisians	[19]
9p24	rs10963540	<i>SMARCA2</i>	G	A	4.81 (2.23–10.4)	Tunisians	[19]
17q21	rs12601982	<i>STAT5A</i>	A	G	2.61 (1.67–4.07)	Tunisians	[19]
17q21	rs8078731	<i>STAT3</i>	A	T	2.47 (1.55–3.93)	Tunisians	[19]
22q13	rs5750627	<i>LOC646851</i>	C	T	2.40 (1.60–3.60)	Tunisians	[19]
22q13	rs6001173	<i>LOC646851</i>	C	T	2.32 (1.54–3.49)	Tunisians	[19]
22q13	rs138702	<i>SUN2</i>	T	A	2.44 (1.60–3.71)	Tunisians	[19]
22q13	rs138712	<i>SUN2</i>	A	G	2.47 (1.63–3.76)	Tunisians	[19]

SNPs, single nucleotide polymorphisms; OR, odds ratio, CI, confidential interval.

patients than in the Western population [13,14]. With the help of the next generation of sequencing technologies, more variations among races will be identified.

Single nucleotide polymorphisms (SNPs) are also different between Asian and Western populations. Genome-wide association studies (GWAS) have identified 76 susceptibility loci associated with PCa risk [15]. Of these, some loci have been validated in Asian population in GWAS and validation studies. To date, three GWAS in Asians were reported [16–18]. Ten SNPs were identified to be associated with PCa in Japanese and Chinese and 11 SNPs in Tunisians (Table 1). Findings of GWAS in East Asians identified a large portion of SNPs that are identical with Westerners, with some unique SNPs identified. However, reports from GWAS in Arabian populations indicated a relatively large number of SNPs that are different from previous findings [19].

Such differences in PCa risk-associated SNPs may suggest distinct mechanisms in the development of PCa against different ethnic groups. More importantly and from a clinical relevant point of view, these discrepancies will eventually influence the onset, diagnosis, prognosis and treatment of PCa in the Asian populations.

3.2. Lifestyle changes and PCa in Asian populations

Genetic variations aside, environmental differences may act as an important factor for PCa as well. Asian populations vary greatly on diet and lifestyles. Generally, East and Southeast Asians consume more vegetables, with a lower proportion of animal protein and high-fat food in their daily intake than Western populations [20]. However, the situation has been changing during these past few decades due to economic development.

Firstly, Asian men who immigrate to foreign countries may display a different epidemiologic pattern. For instance, the PCa incidence of Indians who immigrate to Singapore, UK and US were higher compared to Indians in India (9.9, 33.7, 47.4 and 4.6 per 100,000, respectively) [21]. Although the low rate in India may be partially due to under-diagnosis, they may also be due to lifestyle and environmental factors. Secondly, per capita consumption of animal fat in Asian countries has been on an increasing trend since more than 40 years ago. From the 1960s to the 2000s, consumption of animal fat increased by 591.7%, 578.6%, and 128.6%, respectively in Chinese, Korean and Japanese populations [22]. In these countries, nutrition transition played a role in the increasing incidence of colon cancer and PCa during the past few decades. Thirdly, environmental factors, particularly in countries with a Western diet, will keep a relatively high speed of increase in incidence. Other factors are mainly clinical, for example, the variation in access to PSA screening and physicians. All of these might be major contributing factors. In this aspect, incidence in China and India will probably increase substantially owing to the economic development and rapid lifestyle changes [22]. Meanwhile, countries like Japan, Korea and Israel that have a developed economy and a relatively stable lifestyle may present a more stable trend in incidence.

4. Diagnosis of prostate cancer in Asian countries

4.1. PSA-based screening in Asian countries

National PSA screening programs were not carried out in Asian countries, partially due to the lower incidence rate

Table 2 Reported age-specific PSA cut-off values for Asian population.

Study	Country or region	Ref.	Cases	PSA 95%CI (ng/mL)					
				<40	40–49	50–59	60–69	70–79	>80
Oesterling et al., 1993	United States	[28]	471	–	2.5	3.5	4.5	6.5	–
Liu et al., 2008	Mainland, China	[25]	8422	–	2.15	3.2	4.1	5.37	–
Lin et al., 2004	Taiwan, China	[27]	1008	1.85	2.59	3.31	5.03	5.73	–
Wu and Huang, 2004	Taiwan, China	[29]	1236	–	–	4.0	6.0	6.0	–
Choi et al., 2007	Korea	[30]	286	1.85	1.92	2.37	3.56	5.19	–
Oesterling et al., 1995	Japan	[31]	335	–	2	3	4	5	–
Imai et al., 1995	Japan	[32]	3526	–	2.1	2.9	4.0	5.2	5.9
Malati and Kumari, 2004	India	[33]	583	0.9	1.3	1.48	1.6	2	2.47
Abdrabo, 2011	Sudanese	[34]	1051	–	3	3.02	3.8	8.7 (70–90)	–
Kamal et al., 2003	Saudi Arabia	[35]	567	1.03	1.62	2.09	2.86	3.17	–
Saw and Aw, 2000	Singapore	[36]	513	1.4	1.7	2.3	4	6.3	6.6
Lim et al., 2014	Malay	[26]	378	–	0.6	1	1.2	1.4	–
Kehinde et al., 2005	Kuwait and Oman	[37]	396	–	0.9	1.6	2.9	5.5	–
Khezri et al., 2009	Iran	[38]	930	–	–	2.61	3.59	4.83	–

PSA, prostate-specific antigen; Ref., reference; CI, confidential interval.

and/or the inadequate financial resources for healthcare in some Asian countries. On a global scale, PCa screening remains controversial. The updated results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) did not illustrate a mortality benefit for PSA screening [23]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated a 21% reduction in PCa-specific mortality in favor of screening [24]. In most Asian countries, financial consideration has always been a key

factor. Based on current governmental spending on healthcare, PSA-based screening would probably not be launched in the near future for the majority of Asian countries.

4.2. Age-specific PSA cut-off value for Asian countries

As it has been shown, the PSA level in Asian populations is reported to be lower than that of Western populations [25].

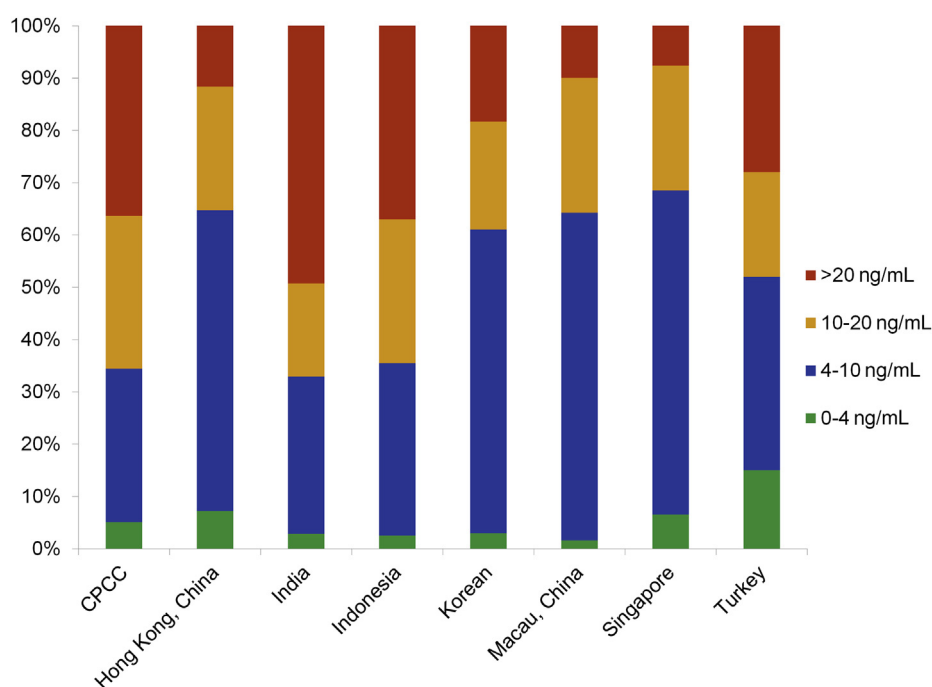


Figure 2 PSA distributions of patients who underwent biopsies in selected Asian countries and regions. Data sources: Mainland, China: Chinese Prostate Cancer Consortium (CPCC) statistics; Hong Kong, China: from HKU (Hong Kong University) and CUHK (The Chinese University of Hong Kong) university hospitals; Singapore: Robotic Transperineal Biopsy of Prostate Database of Singapore General Hospital; Indonesia: Database of Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia. Macau, China: PMID 18304459; Korea: PMID 18158028; India: PMID 25109719.

Age-specific cut-offs have been established for Japanese, Chinese, Indians, Koreans, and Malays [26]. Reported age-specific cut-off values have been summarized in Table 2 [25–38]. In general, these cut-off values are higher than that of the Western population, but there are some differences within these countries. For instance, the cut-off values of Malays and Arabians seem to be lower compared with Eastern Asians. In a clinical scenario such consideration should be noted and more importantly, healthcare policy-makers should acknowledge such differences.

4.3. Distribution of men who underwent prostate biopsies in different PSA categories

As screening programs in the Western population have led to an increase in the PCa incidence rate starting from the 1990s, PCa patients were diagnosed at a much earlier stage, with most of the patients having a PSA level under 20 ng/mL. In a clinical setting, patients diagnosed in Asian countries such as China and Japan are of an older age with a higher PSA level [39,40]. In fact, with the joint efforts of participating urology centers, we confirmed the pattern of PSA distribution of patients who underwent biopsies in different Asian countries and further illustrated the characteristics of specific countries (Fig. 2).

4.4. PCa detection rate in different PSA categories in different countries

The relationship between detection rate of PCa and PSA levels has been reported to vary distinctively in different countries [41]. In the Asian population, the detection rate of PCa has been shown to be much lower in the diagnostic gray zone of PSA 4–10 ng/mL. Here, we illustrated the detection rate of PCa in this PSA range in different populations of Asia (Fig. 3).

As is shown, although the data sources vary in different countries, a distinct difference lies in the detection rate of PCa between Asians and the Western population [42]. The detection rate is below 25% in most reports except for Macau, China due to the limited number of cases and Turkey mostly Caucasian, which is why they are an exception. The differences in the detection rates indicated strong racial differences and provided further evidence against the universal pattern of using PSA as a screening tool in these populations.

Recently, it has been reported that genetic factors may play in role in the differences of PSA levels between Asians and Western populations. A GWAS in the Japanese population [43] illustrated that SNP rs16856139 is significantly associated with the levels of PSA in the Japanese population, yet the genetic differences in PSA levels between different populations are yet to be unveiled.

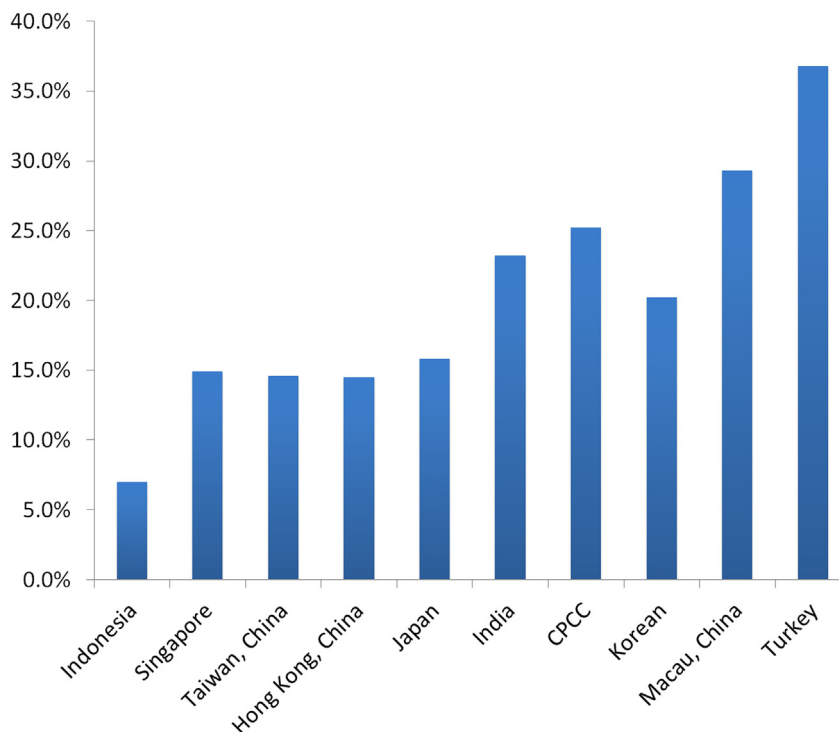


Figure 3 Prostate cancer detection rate of patients with different PSA levels in Asian countries and regions. Data sources: Indonesia: Hospital data, Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia. (2011–2013); Singapore: Robotic Transperineal Biopsy of Prostate Database of Singapore General Hospital; Taiwan, China: PMID 9610567; Hong Kong, China: from HKU (Hong Kong University) and CUHK (The Chinese University of Hong Kong) university hospitals; Japan: PMID 9861233; India: PMID 25109719; Korea: PMID 18158028; Macau, China: PMID 18304459; Turkey: Ferruh Zorlu et al., Prostate Cancer Incidence in Turkey: An Epidemiological Study, Accepted for publication in the Asian Pacific Journal of Cancer Prevention, Vol 15 (August 19, 2014).

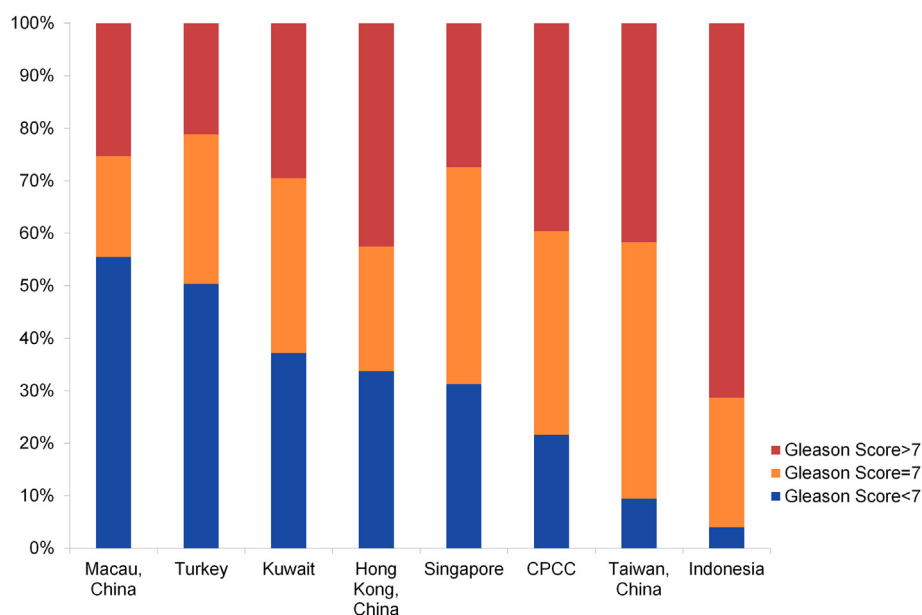


Figure 4 Gleason score of prostate cancer patients at diagnosis in Asian countries and regions. Data sources: Macau, China: PMID 18304459; Turkey: Ferruh Zorlu et al., Prostate Cancer Incidence in Turkey: An Epidemiological Study, Accepted for publication in the Asian Pacific Journal of Cancer Prevention, Vol 15 (August 19, 2014); Kuwait: Database of Mubarak Al-Kabeer Teaching Hospital, Kuwait; Hong Kong, China: from HKU (Hong Kong University) and CUHK (The Chinese University of Hong Kong) university hospitals; Singapore: Cancer Registry Singapore General Hospital; Taiwan, China: PMID 17482934; Indonesia: Hospital data, Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia (2011–2013).

4.5. Tumor grade and stage at diagnosis

With the application of the PSA tests and PSA-based screening in Western countries, there has been a significant trend of stage migration and a lower Gleason Score in patients at the time of diagnosis. In Asian countries/regions with more developed economic and healthcare situations, there are more patients with early stages and favorable Gleason Scores (Japan, Korea, Singapore, etc.) (Figs. 4, 5A). However, the majority of patients in China are still diagnosed with high-grade PCa (Gleason Score > 7). PCa of Asian populations generally display a high likelihood of advanced clinical stages compared to Western populations. Similar to that of Western countries, in developing countries of Asia such as China, there is also an emerging trend towards early stages at diagnosis (Fig. 5B). In regions with developed economic environment, such as Hong Kong, Turkey, and Singapore, the rate of localized PCa accounts for more than half of the diagnosed patients (Fig. 5A). However, there are more than 20% of patients diagnosed with metastatic disease in China and only about 40% patients were diagnosed with localized PCa who are favorable to undergo surgical treatments. However, this situation seems to change in recent years as more patients are diagnosed with localized disease in CPCC hospitals than before (Fig. 5B).

4.6. Emerging novel biomarkers

Currently, a couple of novel biomarkers for PCa have been approved by the United States Food and Drug Administration (FDA). PCa antigen 3 (PCA3) is a long non-coding RNA

that is highly expressed specifically in PCa tissue. It has been approved to help decision-making in repeat biopsies [44]. PSA isoform [-2]proPSA (p2psa) is an isoform of serum PSA with the ability to discriminate positive and negative biopsies. P2psa and its derivatives %p2psa and Prostate Health Index (PHI) have proven to be effective in discriminating PCa patients from negative biopsies [45]. Although both biomarkers have been validated in Caucasians, their effectiveness must be validated in Asian population before they can be put to clinical use.

The validation studies have been carried out in the Asian populations [44,46–53]. Although PCA3 and p2psa have achieved a comparable diagnostic accuracy with Western reports, their diagnostic accuracy is still limited in patients with PSA of 4–10 ng/mL. On the other hand, as the *TMPSSEGR* fusion varies significantly among different races, the lesson it has taught us is that all these biomarkers may vary among ethnicities and there may be better biomarkers for Asian populations as well. In this regard, Asian urologists also performed some pilot studies (Table 3). Biomarkers including metastasis associated in lung adenocarcinoma transcript 1 (MALT-1) [54], genetic score based on SNPs [55], polypeptide neurotransmitter polypeptide neuropeptide-Y (NPY) [56] and serum zinc [57] have been tested as diagnostic and risk stratification biomarkers.

A fragment of MALAT-1, named MD-miniRNA, has proved to be stable in plasma. This fragment has been validated to differentiate PCa and non-PCa patient at a cut-off of 867.8 MD-miniRNA copies per microliter of plasma with the sensitivity of 56.6% and specificity of 84.8% in discriminating PCa patients from non-PCa patients. This is the first time anyone has been able to test fragments of long non-

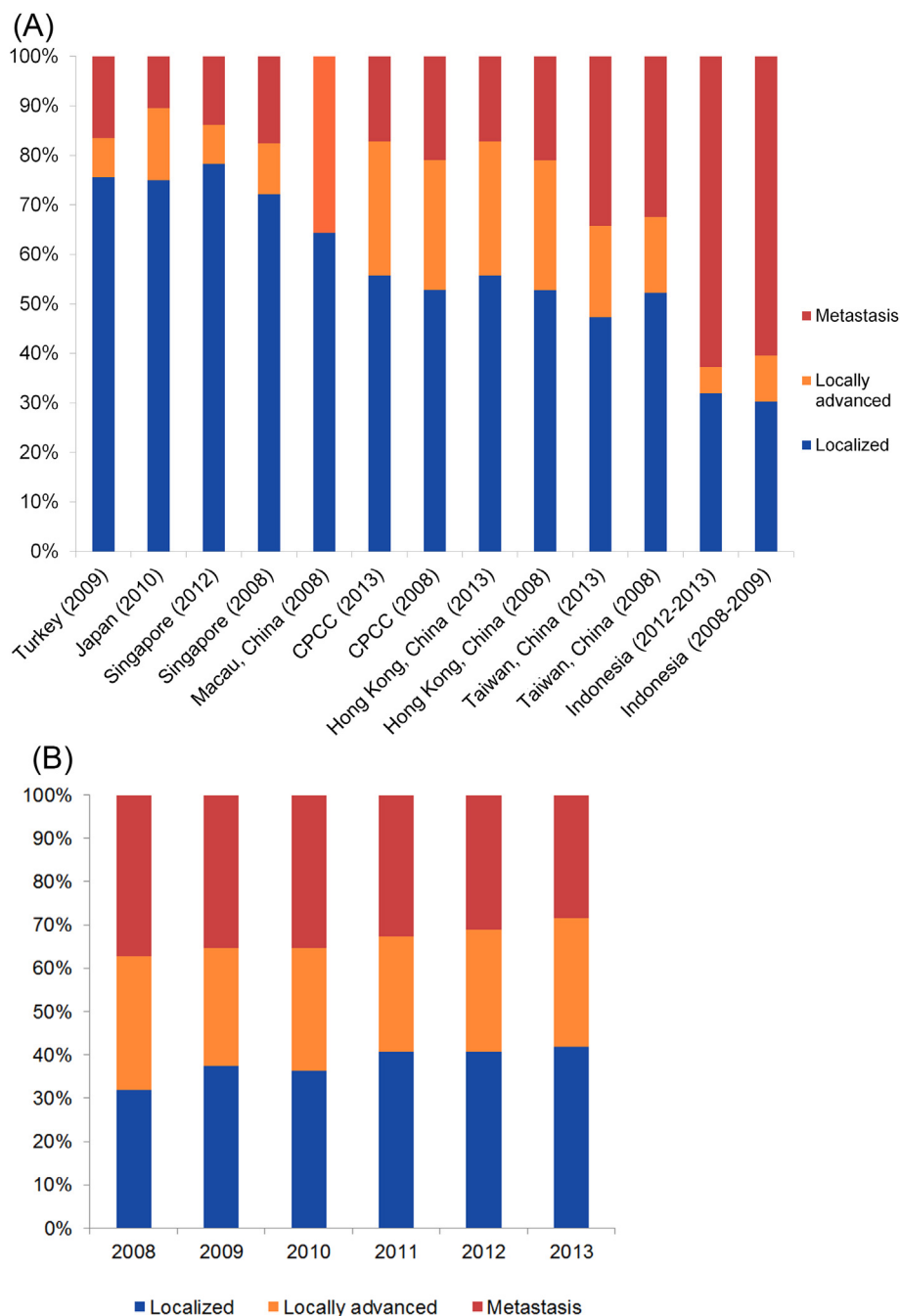


Figure 5 Stages of diagnosed prostate cancer in (A) Asian countries and regions; (B) Chinese Prostate Cancer Consortium hospitals in past 6 years. Data sources: Turkey: Ferruh Zorlu et al., Prostate Cancer Incidence in Turkey: An Epidemiological Study, Accepted for publication in the Asian Pacific Journal of Cancer Prevention, Vol 15 (August 19, 2014); Japan: Jpn J Clin Oncol 2014 Aug 6. pii: hyu104. (Epub ahead of print); Singapore: Cancer Registry Singapore General Hospital; Macau, China: 55.1% for localized PCa, 30.5% for non-localized PCa and 14.4% not available. PMID 18304459; CPCC: CPCC member hospitals statistics; Hong Kong, China: from HKU (Hong Kong University) and CUHK (The Chinese University of Hong Kong) university hospitals; Taiwan, China: PMID 17482934; Indonesia: Hospital data, Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia. (2011–2013); Kuwait: Database of Mubarak Al-Kabeer Teaching Hospital, Kuwait.

coding RNA in plasma to diagnose diseases. Recently, this approach to diagnose disease has also been validated in patients of gastric cancer [58], illustrating the viability of this approach. Other approaches in identifying novel biomarkers for Asian PCa detection included SNPs, polypeptide and other molecules with promising results [55–57].

However, research on biomarkers in Asian countries is still behind in both the number of studies and the quality of research compared with Western countries. Because of the heterogenous nature of PCa, it is predictable that biomarker research will be on a rising trend in Asian population.

Table 3 Validation of biomarkers found in the Western population and biomarker research in Asian countries and regions.

Biomarker	Property	Indication	Ethnic	Study	Ref.	Cases	AUC	Cut-off	Sen.	Spe.
PCA3	Urine long non-coding RNA	Repeat biopsy	Multicentric European	Haese et al., 2008	[44]	463	0.658	35.0	47.0	72.0
		Initial biopsy	Italian	Lazzeri et al., 2013	[47]	1026	0.733	1.7	70.4	70.1
		All biopsy	Japanese	Ochiai et al., 2011	[48]	105	NA	35.0	74.3	74.6
		Initial biopsy	Japanese	Ochiai et al., 2013	[49]	633	0.742	35.0	66.5	71.6
		Initial biopsy	Chinese (Hong Kong)	Ng et al., 2012	[50]	149	NA	35.0	92.0	71.0
		Initial biopsy	Chinese	Shen et al., 2010	[51]	102	0.786	0.107 (Real-Time PCR)	62.9	90.6
PHI	p2PSA/free PSA $\pm\sqrt{tPSA}$	Initial biopsy PSA 2.0–10.0 ng/mL	Italian	Guazzoni et al., 2011	[45]	268	0.76	48.5	90.0	42.9
		Initial biopsy PSA 2.0–10.0 ng/mL	Chinese	Na et al., 2013	[52]	636	0.73			
		Initial biopsy PSA 4–10 ng/mL	Chinese (Hong Kong)	Ng et al., 2014	[53]	230	0.781	26.5	90.0	45.2
		Initial biopsy PSA 2.0–10.0 ng/mL	Japanese	Ito et al., 2013	[54]	239	NA	23.9	90.0	28.0
		Initial biopsy PSA 4–10 ng/mL	Chinese	Ren et al., 2013	[55]	192	0.767	867.8	43.5	81.6
MALAT-1	Plasma long non-coding RNA	Initial biopsy PSA 4–10 ng/mL	Chinese	Ren et al., 2013	[55]	192	0.767	867.8	43.5	81.6
Genetic score	13 PCa associated SNPs	Initial biopsy (All PSA range)	Chinese	Jiang et al., 2013	[56]	667	0.63	1.5	52.0	52.0
NPY	Neurotransmitter polypeptide neuropeptide-Y	Pilot study (All PSA range)	Japanese	Ueda et al., 2013	[57]	110	0.717	5189.0	41.5	97.8
Serum zinc	Metal ion	Pilot study (PSA 4–10 ng/mL)	Chinese	Li et al., 2005	[58]	85	0.73	100.0	90.5	32.7

PCA3, prostate cancer antigen 3; PHI, prostate health index; Real-Time PCR, real-time polymerase chain reaction; PSA, prostate-specific antigen; MALAT-1, metastasis associated in lung adenocarcinoma transcript; SNPs, single nucleotide polymorphisms; p2PSA: [-2]proPSA; Ref., reference; AUC, area under the curve; Sen., sensitivity; Spe., specificity. NA: not available.

5. Surgery management of prostate cancer

5.1. Changes in approach of prostatectomy in Asia

Radical prostatectomy (RP) is a standard treatment option for patients with localized PCa. RP can be performed by either retropubic radical prostatectomy (RRP) or laparoscopic radical prostatectomy (LRP). Anatomic RRP was first performed by Professor Walsh in 1979 [59]. However at that time, few institutes in Asian countries focused their research on PCa. Even the first review of PCa in Japan was only published in 1983. In China, the first anatomic prostatectomy surgeries were performed around the middle of the 1990s.

LRP was first performed in 1992 and received more attention until reported by Schuessler et al. [60]. This time, Asian urologists caught up with this trend relatively faster. A search in the PubMed and CNKI (China National Knowledge Infrastructure) database indicated the first reported LRP from Japan and China was in 2001 and 2002, respectively [61,62].

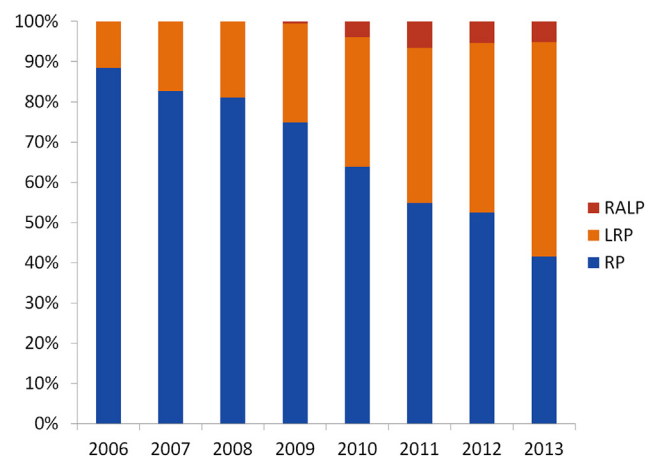


Figure 6 Changes of prostatectomy type in Prostate Cancer Consortium hospitals from 2006 to 2013. Data sources: CCCC member hospitals data. RALP, robotic-assisted radical prostatectomy; LRP, laparoscopic radical prostatectomy; RRP, retropubic radical prostatectomy.

The first robotic-assisted radical prostatectomy (RALP) was performed in 2000 by Binder et al. from Frankfurt [63]. RALP was performed in Asian countries from as early as 2003 in Singapore and 2004 in Taiwan, China. In Mainland China, the first RALP was performed in 2007 by Gao et al. [64]. The time span between the application of RALP between Western and Asian urologists has been shortened to only a couple of years. From anatomic RRP to LRP and from LRP to RALP, it is clear that Asian urologists are catching up in surgery methods and the time span between the first cases has shortened.

Once again with the collaboration of CPCC members, the current status of the percentage of each surgery approach has been summarized (Fig. 6). One other thing to note is that the data came from both a national level and the representative hospital (in case of failure to obtain a national figure). As is illustrated, the proportion of RRP is reduced whereas LRP takes the largest proportion in the 20 hospitals in CPCC. Although there is a substantial increase in the number of RALP, the proportion of RALP is still fairly low as only three out of 20 hospitals are equipped with da Vinci systems.

5.2. Current status of the effectiveness of prostatectomy in Asia

Although RP was adopted late in Asia and the number of cases is much smaller compared with Western countries, Asian surgeons have quickly adapted RP techniques. Asian reports of RP results indicated a comparable outcome in terms of preservation of both continence and sexual function to Western reports [65,66]. In recent years, an increasing number of urologists are not satisfied with just completing the surgery itself but also aimed to achieve the trifecta of RP (cancer free, potency and continence). More approaches have been developed and validated to be viable. For instance, Single-port LRP was preferred by Wen et al. [67] and has been shown to achieve better results in selected patients. Extraperitoneal LRP was preferred by Zheng et al. [66] for its advantages in preventing intra-abdominal complications and combined the advantages of minimally invasive laparoscopy and retropubic open prostatectomy.

There are now several high-volume centers for RP with a well-designed follow-up system that makes the long-term assessment of the surgery result possible in developed countries such as Japan, Korea, Israel and developing countries such as China and India. For instance, Namiki et al. [68] reported the long-term follow-up data for 91 patients in a median follow-up of 102 months. Mishra et al. [69] reported the oncological outcome of LRP in a median follow-up of 6 years. Koo et al. [70] reported a comparison study of RALP and open radical prostatectomy in 1172 patients with a mean follow-up time of 58.4 months. Their result indicated that RALP is as good as open RP in terms of oncological outcomes. Considering the relatively large population in Asia, the number of RP cases is expected to increase fast and there would be more opportunities for urologists to investigate the unique characteristics of RP in Asian men with its own anatomical characteristics.

Furthermore, urologists in Asia also developed some innovative work in RP. Gao et al. [71] performed the first

series of single-port transvesical LRP with promising functional outcomes regarding continence and potency. Another innovative approach in RALP is that Korean urologists reported the comparison of Retzius-sparing RALP with conventional RALP [72]. Retzius-sparing RALP was considered as not practical in the past, however, Lim et al. [72] confirmed it would reduce operating time and help to achieve a faster recovery of early continence.

However, it must be recognized that the advances in RP are still limited in Asia when compared with developed Western countries, regardless of the number of cases and techniques. In 2013, the 10th European Conference in Laparoscopic Robotic Surgery in Urology was held in Beijing, China. Well-organized academic meetings would facilitate the communication between urologists in Asia and other countries.

5.3. Trend of robotic-assisted radical prostatectomy in Asia

In recent years, RALP has gained popularity globally with advantages to both patients and urologists. The benefit for patients includes less blood loss, less pain and shorter hospital stay. The benefits for urologists are improved ergonomics, with accurate three-dimensional display, and the ease of use of maneuverable robotic instruments [73].

The literature has shown that RALP had a short learning curve and promising postoperative results, especially with regard to continence recovery [73]. RP is the most common robotically assisted surgical procedure performed in the United States. Reported 5-year biochemical failure-free survival for RALP ranges from 83.3% to 87%, which is better than open RP [73].

The major downside of RALP is the cost. In an ideal scenario, most urologists would be inclined to use this novel technique, but the reality is that the high cost of RALP is often hard to accept by patients in developing countries in Asia, especially when the governmental insurance covers a small or no proportion of the costs of surgery. As is illustrated, the number of da Vinci systems is surging in developed countries such as Japan and Korea but are

Table 4 Cumulative number of da Vinci Systems in Asian countries and regions.

Country	2010	2011	2012	2013
Japan	32	40	80	159
Korea	28	36	38	44
Mainland, China	10	13	15	18
Taiwan, China	4	10	15	20
India	6	17	19	20
Hong Kong, China	7	7	8	8
Singapore	3	6	7	7
Malaysia	1	3	3	3
Thailand	0	1	4	6
Philippines	0	1	1	2
Indonesia	0	0	1	1
Total	108	134	191	288

Data sources: Intuitive Surgical Inc., Shanghai, China.

Table 5 Newly FDA-approved agents for CRPC in Asia.

Agent	Mechanism	FDA approval	Clinical trials in Asia	Clinical trials in USA	Availability on market
Enzalutamide	Androgen receptor inhibitor	2012	11	48	Korea, Hong Kong, Japan
Abiraterone	Androgen biosynthesis inhibitor	2011	20	74	Singapore, Hong Kong, India, Indonesia, Israel, Japan, Jordan, Korea, Kuwait, Malaysia, Saudi Arabia, Taiwan, Turkey
Cabazitaxel	Novel taxane chemotherapy	2010	12	20	Singapore, Japan, Turkey, Taiwan, Indonesia
Sipuleucel-T	Autologous immunotherapeutic agent	2010	0	26	NA
Radium 223	Alpha particle-emitting radiopharmaceutical	2013	11	13	Korea, Singapore

Data sources: www.clinicaltrials.gov, searched on Aug 31, 2014.

difficult to find in most other Asian countries at the moment (Table 4). RALP is starting to take its momentum in Mainland China, Turkey and Taiwan (China) in recent years, while Japan has already out-weighted the total number of other Asian countries (Data source: Intuitive Surgical Inc., Shanghai, China). It is predicted that the number of RALP will likely keep this momentum with increases in number of cases in existing centers and the establishment of new da Vinci centers.

6. Novel agents for CRPC

The prognosis of CRPC patients is rather unfavorable with an overall survival time of 24–36 months [74]. Prior to 2010, the treatment options for CRPC were limited. In the

past 3 years, US FDA approved five new agents for CRPC (Table 5). These agents not only expanded the arsenal against CRPC but also enlightened the hope for patients with advanced prostate cancer. Currently, all of these agents are recommended by the AUA guidelines for PCa in different conditions. In Asian countries, with the joint efforts of manufacturers and clinical oncologists, clinical trials have been started in recent years (Fig. 7). Hopefully, with these new agents, patients will have a longer progression-free survival as well as an improved overall rate of survival. However, as there are two sides to every sword, the emergence of these new drugs are beneficial to patients with proper indications but may not always be helpful to the developing Asian countries that already have limited budget for cancer control. In this aspect, both the manufacture and the healthcare ministry of these countries

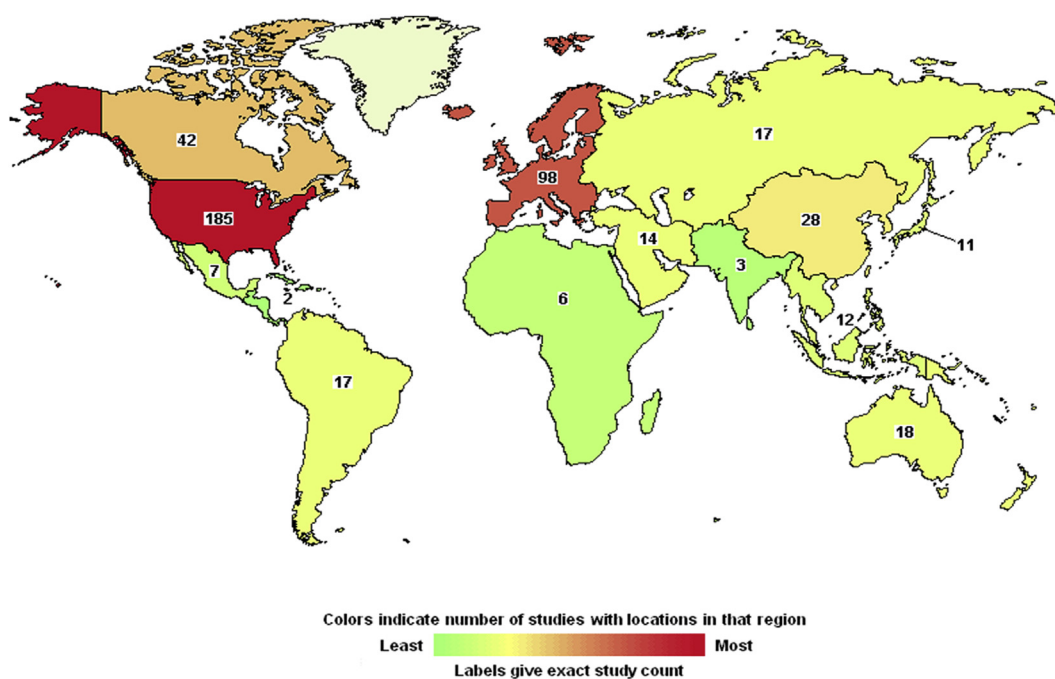


Figure 7 Number of completed and on-going clinical trials of five novel agents for CRPC worldwide. Data sources: <http://www.clinicaltrials.gov/>, searched on Aug 31, 2014.

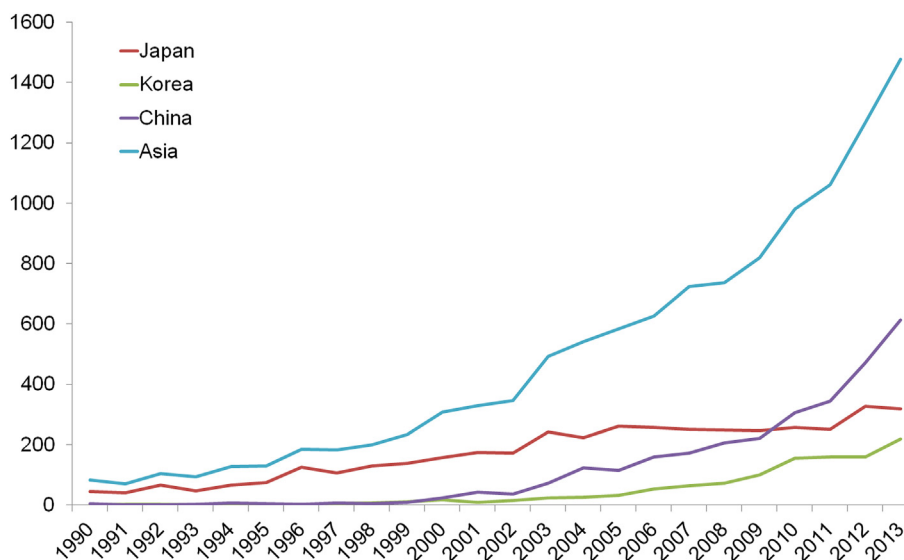


Figure 8 Prostate-cancer-related research papers by countries. Data sources: <http://www.ncbi.nlm.nih.gov/pubmed>, searched on Aug 31, 2014.

should make individualized policies for each country in order to achieve a win–win situation for all. Currently, there is no leading innovative pharmaceutical research group in Asian countries that could pave the way forward for novel CRPC agents.

7. Prospective

As incidence and mortality rates have continued to increase during the past decades and a trend towards an older population as well as a more Western lifestyle, PCa has now become one of the most prevalent malignancies in Asian countries. A recent autopsy study revealed that incidence of PCa is rather similar in Japanese and Russians [75]. Thus, if the Western strategy of management of PCa is introduced in Asia, it is possible that many more patients will be diagnosed with PCa in Asia. With joint efforts from urologists and researchers across Asia, research of PCa has been surging with more clinical and research articles being published (Fig. 8). With such scientific developments, the management of PCa in diagnosis and treatment has also been improving greatly. It is expected that Asian researchers and urologists will gain a better understanding of prostate cancer in their own countries and find better ways to combat this disease uniquely.

Conflicts of interest

The authors declare no conflict of interest.

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