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INVITED REVIEW

Prostate Cancer

Prostate cancer in East Asia: evolving trend over the last decade

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Prostate cancer is now becoming an emerging health priority in East Asia. Most of our current knowledge on Prostate cancer has been generated from studies conducted in Western population; however, there is considerable heterogeneity of Prostate cancer between East and West. In this article, we reviewed epidemiologic trends, risk factors, disease characteristics and management of Prostate cancer in East Asian population over the last decade. Growing evidence from East Asia suggests an important role of genetic and environmental risk factors interactions in the carcinogenesis of Prostate cancer. Exposure to westernized diet and life style and improvement in health care in combination contribute substantially to the increasing epidemic in this region. Diagnostic and treatment guidelines in East Asia are largely based on Western knowledge. Although there is a remarkable improvement in the outcome over the last decade, ample evidence suggests an inneglectable difference in diagnostic accuracy, treatment efficacy and adverse events between different populations. The knowledge from western countries should be calibrated in the Asian setting to provide a better race-based treatment approach. In this review, we intend to reveal the evolving trend of Prostate cancer in the last decade, in order to gain evidence to improve Prostate cancer prevention and control in East Asia.

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Keywords: Asians; diagnosis; epidemiology; genetics; prostate cancer; treatment outcome

INTRODUCTION

In the last decade, East Asia has undergone tremendous economic growth and culture globalization, which results in increasing life expectancy, changing in dietary pattern and westernized lifestyle. Once considered a disease commonly diagnosed in western countries, prostate cancer is now becoming an emerging health priority in East Asia. Because East Asia remains the world's most populous region, the number of individuals with Prostate cancer will increase substantially in the coming decades.

Most of our current knowledge on Prostate cancer has been generated from studies conducted in Western population. Since there is considerable heterogeneity of prostate cancer between East and West, new evidence is strongly needed to improve Prostate cancer prevention and control in East Asia. In this article, we reviewed epidemiologic trends, risk factors, disease characteristics, and management of Prostate cancer in East Asian population over the last decade.

EPIDEMIOLOGY

East Asia account for 23.6% of the male population worldwide and 8.2% of the male are aged 65 years or older.[1] In East Asia, Japan, Chinese Taiwan region, South Korea belong to high human development area, while China belong to medium human development area.[2]

Prostate cancer is the second most frequently diagnosed cancer in males worldwide, accounting for 14% of the total new cancer cases in 2008.[3] About 9% (82 691) were diagnosed within the East Asia (8.2/100 000).[4] Japan account for 47%, followed by China (41%) and Korean (8%). Incidence rates (IRs) varied by almost 10-fold across this region, ranging from estimates of 2.56/100 000 in rural China up to 31.2/100 000 in Japan.[5–10] Except for rural China, Prostate cancer incidence increased steadily over the last decade in other East Asia area (**Figure 1**). The changing trend was most significantly in Korea, with an annual percentage change of 12.8. Prostate cancer was ranked as the fifth most common cancer and also the most common genitourinary cancer in developed areas such as Korea, Japan, Taiwan region of China and Shanghai of China. The increase of incidence can't be simply attributed to more spread use of screen. The exposure rates of population based prostate specific antigen (PSA) screen have been still at around 10% in a recent Japanese report,[11] which was significantly lower than the data of United States (70%–80%).[12] Furthermore, the prostate biopsy rate of East Asian men was relatively low, only 54.2% and 64.3% for PSA in 4–10 and >10 ng ml^{-1} in a Korean nationwide survey study.[13]

In Japan, Chinese Hong Kong and Chinese Taiwan regions, a sharply increased incidence of Prostate cancer was observed after 60 years old. The distribution of age was different from patients in United States, where the increased incidence began with 50 years old (**Figure 2**).[14] The changing pattern of age distribution of Prostate cancer in Japan over the last decade was also examined. A general increase was observed without significant shift to the young age (**Figure 3**).

In 2008, 10% (26 751) of patients died of Prostate cancer were located in East Asia (2.5/100 000).[4] China account for 53%, followed by Japan (37%)

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and Korea (5%). There was less variation in the age-standardized mortality rate (MR) for Prostate cancer, with highest in Chinese Taiwan region and 4 times greater than in rural China (**Figure 4**).[5,7,8,10,15] Prostate cancer was ranked as the seventh most common cause of cancer-related deaths in a developed area as Korea, Japan and Chinese Taiwan region. For the trend of mortality, we found most of area shares a similar plateau pattern. Specifically, a significant decrease of mortality was observed in Japan.

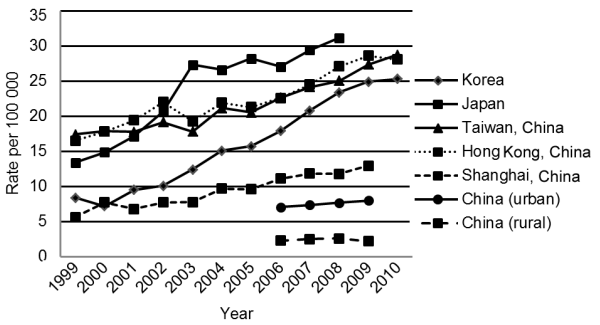
Regarding Prostate cancer survival, we evaluated the ratio of MR: IR. Over the last decade, a general decrease of the MR: IR value was observed in developed area. On the other hand, the value was approximately 0.6 in rural China, nearly 3 times over developed area (**Figure 5**). These data were consistent with reported 5-year survival rate from different areas. The latest survival rate was over 90% in Korea and Japan, comparable to the data in United States.[5,14,16] However, disease survival rate was only 36.1% in Shanghai between 1992 and 1995.[11] Stage migration may substantially account for improvement in disease outcome. In Japan, the proportion of localized disease improved dramatically from 30% to nearly 50% (**Figure 6**).[16] On the contrary, 68% of newly diagnosed Chinese patients had metastatic disease in a recent multicenter study.[17]

RISK FACTORS

The carcinogenesis of Prostate cancer is a complex interplay between genetics and environment exposure. Observed differences between race groups may be reflective of not only the differences in genetic structure or function, but also disparity in common environmental exposure, diet, lifestyle, and attitudes toward health care. One example is that Asian American had much higher of Prostate cancer incidence than their ancestry.[18] Although the improvement of health care including cancer screen account for some increase in Prostate cancer incidence, they can hardly interpret all increase according to the epidemiology data above mentioned. Therefore, we discuss possible risk factors, which fasten the increase of Prostate cancer in East Asia.

Diet plays a major role in Prostate cancer carcinogenesis and biology. In Western countries, diet tends to be high in animal products and fine processed, while in Eastern countries, the diet is relatively lower in calories and is more likely to contain greater amounts of certain essential nutrients.[19] Many epidemiological studies showed that increased fat and meat intake is associated with Prostate cancer risk,[20] most studies (including one study from China, of which the odds ratio was 3.3[21]) found positive associations (odds ratio [OR] ≥1.3) between total fat intake and the risk of Prostate cancer while slightly fewer failed to find this relation. The data on meat and Prostate cancer are more consistent than those on fat, 16 of the 22 studies reviewed showed a risk ratio of 1.3 or more,[20] of which included one study from Japan (OR = 2).[22]

Tea, a traditional drink in East Asia, is found to have a protective effect for Prostate cancer. Zheng *et al.*[23] indicated that green tea may have a protective effect on prostate through a meta-analysis, the summary odd ratio of Prostate cancer indicated a borderline significant association in Asian populations for highest green tea consumption versus non/



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	APC	Rank in male
Korea	8.4	7.2	9.5	10.1	12.4	15.1	15.7	17.9	20.8	23.4	24.9	25.3	12.8[a]	5
Japan	13.4	14.9	17.1	20.7	27.3	26.6	28.2	27.1	29.4	31.2	--	--	9.9[a]	5
Taiwan, China	17.42	17.87	17.78	19.17	17.83	21.16	20.52	22.63	24.16	25.06	27.38	28.77	4.9[a]	5
Hong Kong, China	16.5	17.8	19.4	22	19.3	21.9	21.3	22.6	24.5	27.1	28.6	28.1	4.8[a]	3
Shanghai, China	5.6	7.7	6.78	7.73	7.78	9.67	9.59	11.1	11.81	11.8	12.96	--	8[a]	5
China (urban)	--	--	--	--	--	--	--	7.04	7.34	7.66	8	--	--	6
China (rural)	--	--	--	--	--	--	--	2.29	2.5	2.56	2.17	--	--	>10

Figure 1: Prostate cancer standardized incidence in East Asian areas from 1999 to 2010. APC: annual percentage change. [a]indicates statistical significant results.

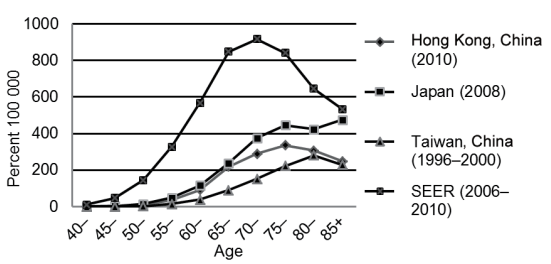


Figure 2: Age-specific incidence of prostate cancer in East Asian areas and United States. SEER: Surveillance, Epidemiology and End Results Program.

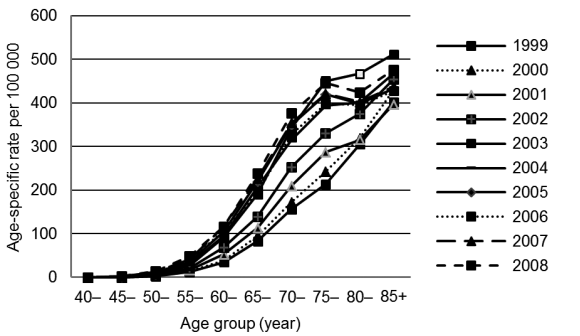
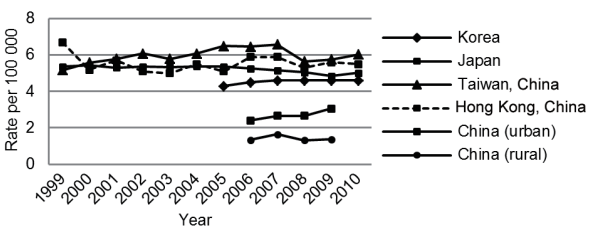
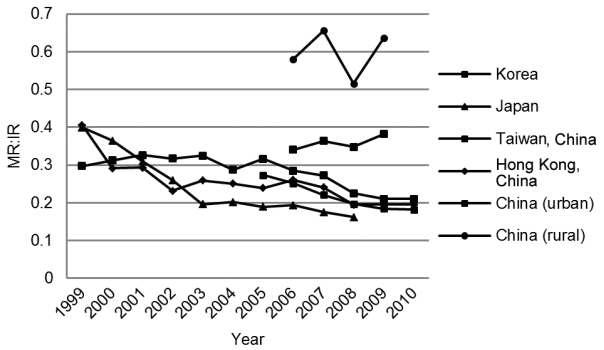


Figure 3: Changing trend of prostate cancer age-specific incidence in Japan from 1999 to 2008.



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	APC	Rank in male
Korea	--	--	--	--	--	--	4.3	4.5	4.6	4.6	4.6	4.6	1.16	7
Japan	5.4	5.4	5.3	5.4	5.3	5.4	5.4	5.3	5.2	5.1	4.9	5.0	-0.76	7
Taiwan, China	5.18	5.58	5.80	6.09	5.80	6.08	6.50	6.46	6.58	5.65	5.76	6.04	0.9	7
Hong Kong, China	6.7	5.2	5.7	5.1	5	5.5	5.1	5.9	5.9	5.3	5.6	5.5	-0.3	5
China (urban)	--	--	--	--	--	--	--	2.40	2.67	2.67	3.06	--	--	8
China (rural)	--	--	--	--	--	--	--	1.33	1.64	1.32	1.38	--	--	>10

Figure 4: Prostate cancer standardized mortality in East Asian areas from 1999 to 2010.



2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
--	--	--	--	--	0.27	0.25	0.22	0.20	0.18	0.18
0.36	0.31	0.26	0.20	0.20	0.19	0.19	0.18	0.16	--	--
0.31	0.33	0.32	0.33	0.29	0.32	0.29	0.27	0.23	0.21	0.21
0.29	0.29	0.23	0.26	0.25	0.24	0.26	0.24	0.20	0.20	0.20
--	--	--	--	--	--	0.34	0.36	0.35	0.38	--
--	--	--	--	--	--	0.58	0.66	0.52	0.64	--

Figure 5: Prostate cancer MR: IR (MR divide IR) in East Asian areas from 1999 to 2010. MR: mortality ratio; IR: incidence ratio.

lowest (OR = 0.62). The protective capacity of green tea is also confirmed by Japanese studies,[24] the multivariate relative risk was 0.52 for men drinking five or more cups/day compared with <1 cup per day. Soybean, as another traditional food in East Asia, also has anti Prostate cancer affect. A meta-analysis including eight epidemiological studies showed that soybean intake can reduce the prevalence of Prostate cancer for more than 30%.[25] It is said that soybeans are a rich source of isoflavones, a main type of plant estrogens, which have been suggested to modulate endogenous hormone homeostasis or hormone metabolism.[26,27]

There are less interethnic differences in risk of Prostate cancer if diet is similar between different ethnics. Whittemore *et al*.[28] conducted a multi-ethnic research in populations mainly from the US, and indicated that a positive statistically significant association of Prostate cancer risk and total fat intake was found for all ethnic groups combined (Blacks, Whites, Asian-Americans). Interestingly, for Asian-Americans, the author found that saturated fat intake was associated with higher risks for Asian-Americans than for Blacks and Whites.

Physical activity has shown to be linked to a significantly decreased risk of breast and colorectal cancer in numerous studies, in Prostate cancer the evidence was weaker but still probable in a Poland study.[29] A study from Malaysia indicated that the past history of not engaging in any physical activities at the age of 45–54 years old increased risk of Prostate cancer by approximately three folds (adjusted OR 2.9 [95% confidence interval = 0.8–10.8]) ($P < 0.05$).[30] However, a study for Asian-Americans didn't support the linkage.[28] Limitations of these results exists that the methods are various in the assessment of physical activity, including its frequency, duration and intensity.[31]

The change of diet and lifestyle inevitably resulted in obesity. The increased prevalence of obesity was evidenced in East Asia.[32] Using WHO criteria, the percentage of overweight men in Japan, Korea, and China are 30.1%, 34.3%, and 25.5% in 2008. Furthermore, raised cholesterol was found in 57%, 42.2%, and 31.8%, respectively. The rising trend of metabolism disorders may be responsible for increasing trend of Prostate cancer in East Asia.

GENETICS

Over the last decade, breakthrough improvement in sequencing techniques provides better understanding of the role of genetic alterations in the etiology of Prostate cancer. Therefore, the hypothesis whether Prostate cancer is different in East Asian population was tested by genetic evaluation. Better knowledge of genetic changes open the door of personalized medicine covering prevention, screening and management.

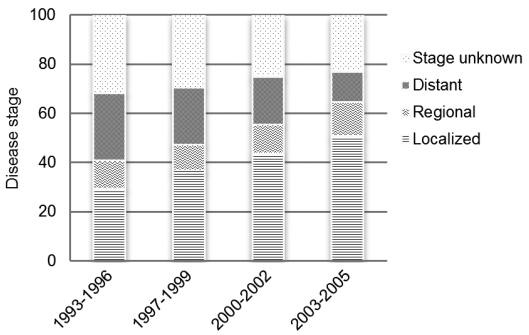


Figure 6: Distribution of disease stage of prostate cancer in Japan from 1993 to 2005.

Germline variations

Genetic factors play important roles in Prostate cancer etiology and that genetic research can help clarify Prostate cancer susceptibility. Until now, genome-wide association studies (GWAS) on several 1000 samples of several ethnic groups had identified more than 70 single nucleotide polymorphism (SNP) on various genes or chromosomal loci that are associated with Prostate cancer susceptibility. Most of the GWAS were performed in European populations, while three GWAS were performed in Asian descent with two from Japanese[33,34] and one from Chinese.[35] New SNPs were found by Asian GWAS suggesting that SNP genotype frequencies may vary by race and partially account for racial differences in Prostate cancer risk. In addition, multiple researchers have aimed to replicate GWAS results identified from European descent in populations of Asians and provided evidence of ethnic differences and similarity in genetic susceptibility to Prostate cancer.[36,37] As shown in **Table 1**, more than 20 SNPs were confirmed to have homogeneous characteristics in both ethnics.[33–35,37–50] Interestingly, some of those SNPs were proved to have genetic functions associated with carcinogenesis.

Metabolism

Nearly all SNPs identified from GWAS studies, which were known to be linked with metabolism related genes, were successfully replicated and showed Prostate cancer risk association in Asian populations. Those SNPs included rs1465618 from 2p21 (*THADA*),[35] rs339331 from 6q22 (*GPRC6A*),[33,47] rs10486567 from 7p15 (*JAZF*1),[35,49] rs7501939, rs4430796 and rs11649743 from 17q12 (*HNF*1*B*).[48]

Inflammatory

Rs1983891, a loci related with Prostate cancer risk identified by a Japanese GWAS was replicated by an American research.[47] Rs1983891 was located in intron 2 of *FOXP*4 (forkhead box P4), which is expressed in both thymocytes and peripheral CD4 (+) and CD8 (+) T-cells and is necessary for normal T-cell cytokine recall responses to antigen following pathogenic infection.[51]

Recently, GWAS on Chinese Prostate cancer patients identified a new susceptibility locus rs103294 at 19q13, which is linked with *LILRA*3. *LILRA*3 is a gene regulating inflammatory response, and was significantly associated with the messenger ribonucleic acid expression of *LILRA*3 in T-cells.[35] It remains unknown whether this loci is also associated with Prostate cancer susceptibility in European populations because no replication studies were published yet. However, Spanish

Table 1: SNPs which showed homogeneous characteristics in different ethnics

Characters	*SNP*	*Gene*	*Reported information*				*Replicated in other ethnics*	
			References	*Heterozygous OR*	*Homozygous OR*	*Per allele OR*	*References*	*OR*
2p21	rs1465618	*THADA*	(C)[41]	1.08	1.15	1.08	(A)[40]	1.16
2p15	rs721048	*EHBP*1	(C)[42]			1.15	(A)[40]	1.36
2p24	Rs13385191	*C2orf*43	(A)[36]			1.15	(C)[50]	1.07
2q31	rs12621278	*ITGA*6	(C)[41]	0.78	0.35	0.75	(A)[40]	1.16
3p12	rs2660753		(C)[43]	1.1	2.09	1.18	(A)[51]	1.42
3q23	rs6763931	*ZBTB*38	(C)[44]			1.11	(A)[38]	1.15
4Q24	rs7679673	*TET*2	(C)[41]	0.89	0.83	0.91	(A)[40]	1.2
5p15	rs12653946	*IRX*4	(A)[36]			1.26	(C)[50], (A)[38]	1.1
6p21	Rs1983891	*FOXP*4	(A)[36]			1.15	(C)[50]	1.09
6q22	rs339331	*RFX6/GPRC6A*	(A)[36]			0.82	(C)[50], (A)[38]	0.93
7p15	rs10486567	*JAZF*1	(C)[45]	0.74–0.89	0.71–0.84		(A)[38], (A)[52]	1.47
8p21	rs1512268	*NKX*3.1	(C)[41]	1.04	1.11	1.05	(A)[36], (A)[40]	1.23
8q24	Rs16901979		(C)[46]			1.79	(A)[40], (A)[51], (A)[52]	1.44
	Rs6983267		(C)[47]	1.26	1.58		(C)[53]	1.15
	Rs1447295		(C)[46], (C)[47]	1.43	2.23	1.6	(A)[40], (A)[51], (A)[52]	1.38
	rs13254738		(C)[48]			1.18	(A)[51], (A)[52]	1.59
	Rs6983561		(C)[48]			1.42	(A)[51], (A)[52]	1.81
	Rs10090154		(C)[48]			1.32	(A)[51]	1.41
10q11	rs10993994	*MSMB*	(C)[43]	1.15	1.61	1.25	(A)[40]	1.12
10q26	rs2252004		(A)[37]			1.16	(A)[38]	1.2
13q22	rs9600079		(A)[36]			1.18	(A)[38]	1.19
17q12	rs4430796	*HNF*1*B*	(C)[49]			1.22	(A)[51]	1.51
22q13	rs5759167		(C)[41]	0.84	0.74	0.86	(A)[40]	1.19

C: caucasian; A: Asian; OR: odds ratio; SNPs: single nucleotide polymorphism

and Polish studies indicated its association with multiple sclerosis,[52,53] indicating *LILRA*3 is responsible for immunity defects not only in Chinese patients.

Prostate specific single nucleotide polymorphisms

Prostate specific genes are usually associated with prostate carcinogenesis as well as prostate susceptibility. Most of their related SNPs were replicated both in European populations and Asian populations, showing homogeneous characteristics. Of which, three were successfully replicated in Asian populations and showed an association with Prostate cancer risk, including rs12653946 from 5p15 (*IRX*4),[33,54,55] rs1512268 from 8p21 (*NKX*3.1)[37,42] and rs10993994 from 10q11 (*MSMB*).[37,49]

8q24

The 8q24 region was the first to show its association with Prostate cancer risk,[56] subsequent GWAS studies have further identified the importance of 8q24 as a region of susceptibility to Prostate cancer.[42–45,57–59] SNPs of this region were also responsible for increased risk for other cancer types.[60,61] Despite that this region contains various independent Prostate cancer-susceptibility loci within a 1Mb segment; it appears to have little transcriptional activity.

Some other positively confirmed SNPs were associated with Prostate cancer risk in both Eastern and Western countries. Those included function unidentified SNPs such as rs2660753 from 3p12[48] and rs5759167 from 22q13,[37] as well as gene specific SNPs such as rs721048 from 2p15 (*EHBP*1),[37] rs13385191 from 2p24 (*C2orf*43),[47] rs12621278 from 2q31 (*ITGA*6),[62] rs6763931 from 3q23 (*ZBTB*38),[35] rs7679673 from 4q24 (*TET*2) etc.[37]

Somatic variations

In addition to the aforementioned SNPs associated with Prostate cancer susceptibility, a variety of genetic and epigenetic alterations have been found to be involved in Prostate cancer initiation, progression, metastasis and drug resistance (**Table 2**).

The most common known genetic alteration in Prostate cancer is a fusion of *TMPRSS*2: *ERG*. The fusion involve the 5' untranslated region of the androgen-regulated gene *TMPRSS*2 and members of the *ETS* transcription factor family, *ERG* or *ETV*.[63,64] The presence of these gene fusions is essentially 100% specific for Prostate cancer, and can be detected in as many as 50%–70% of Prostate cancer samples. The *TMPRSS*2: *ERG* gene fusion have been causally linked to cancer progression because it promotes invasion, and over expression of the fusion product in mice shows great enhanced Prostate cancer development.[65] The prevalence of the *TMPRSS*2: *ERG* fusion in Prostate cancer appears to vary in different ethnic groups. It was reported that in Caucasians the frequencies were 50%–70%,[66] while in Asian patients the frequencies were lower than 20%.[67,68]

Another common known gene of interest is *PTEN*. Deletions in *PTEN* are observed in over 60% of Prostate cancers, and in 20%–25% of *HGPIN* lesions. The loss of inhibition of pathway downstream of *PTEN* may be important in cancer, including *AKT* and mammalian target of rapamycin.[69] It was reported that loss or alteration of *PTEN* allele is correlated with disease progression to the metastatic stage.[70] Mao *et al*.[71] compared *PTEN* deletion/inactivation frequency among Chinese and UK patients. In this article, he revealed that low-level (– or +) expression of *PTEN* was detected in 69.8% (111/159) of UK samples, but only in 34% (31/91) of Chinese samples. In Japanese, loss of heterozygosity at the *PTEN* locus was observed in 11.1% of Prostate cancers.[72]

RAS-RAF-MAPK pathway mutants were much more frequently found in Asian patients than patients from western countries.[73,74] It is unknown if genetic factors or environmental factors cause the difference in *RAS* mutation rates among different ethnic groups,

Table 2: The prevalence of genetic events for prostate carcinogenesis among different ethnic groups

Genetic variation (%)	*Prevalence in East Asian patients (%)*	*Frequency in patients from Western countries (%)*
TMPRSS2:ERG	<20[70,71]	50–70[69]
PTEN deletion	10[75]–34[74]	69.80[74]
KRAS mutations	9.1–17[76,160]	≤3[160–162]
BRAF copy number gain	29[78]	9.2[78]

although the latter seems more likely. A similar difference in the frequency of *BRAF* mutation was also found in both ethnics.[75] These results indicate that the *RAS-RAF-MAPK* signaling pathway may be essential for prostate susceptibility for Asian men.

DIAGNOSIS

Early diagnosis is the key to successful treatment of cancer. The introduction of PSA screen in the mid-1980s increased Prostate cancer IR drastically in United States, at about 12%/year, and peaked in 1992. The rate subsequently declined, at about 10%/year for the following 3 years and then appeared to stabilize from 1995 to 2005.[76,77] Simultaneously, the incidence of distant disease decreased to 2.9%,[78] much lower than it is in China (68%).[17] Since a substantial part of men in East Asian are diagnosed at an advanced stage, massive screening such as PSA screen of Prostate cancer is suggested by physicians. Therefore, the diagnostic performance of PSA and other innovative markers should be evaluated before widely used.

The general cut-off for prostate biopsy was a total PSA of 4 ng ml^{-1}. In western countries this threshold is associated with risks of Prostate cancer ranging from 15% to 40%.[79] One research enrolling 16222 Chinese patients tried to find out the PSA levels of Chinese men. They discovered that the PSA level of Chinese men who are under 60 years is lower than that of Caucasians, while the PSA level of Chinese men who are above 60 years is higher than that of Caucasians, which means for patients above 60 the PSA cut-off should be higher than usual for Chinese men.[80] Na *et al*.[81] observed only 4.7% of men with a PSA level of 4 ng ml^{-1} were diagnosed with Prostate cancer, much lower than rates in western countries. In another study in ethnic Chinese, the PSA test sensitivity at the traditional cut-off (4.0ng ml^{-1}) was 96% (specificity = 14%) and if a cutoff of 6.0 ng ml^{-1} is used the sensitivity will be 90% together with a higher specificity (36%). Thus, the author suggests among the population with low incidence of Prostate cancer as Chinese, minimizing unnecessary biopsies might be more important issue than maximizing cancer detection rate.[82]

Various adjustments, such as the ratio of free-to-total (f/t) PSA, PSA density or PSA velocity were attempted to improve the diagnostic value of PSA. The most common PSA derivative is the ratio of free PSA to total PSA, and the recommend cut-off is 0.14–0.16 in some Asian countries.[83,84] However, the effects of PSA derivatives are affected by differences in prostate volume. Lam *et al*.[85] reported that at similar levels of total PSA, PSA density may be higher in Hispanic than in Caucasian. In Asia, patients may also have smaller prostate volumes compared to whites, resulting in a higher PSA level per unit volume. Results showed that PSA density in Asian was a significantly better predictor of Prostate cancer than f/tPSA.[86,87]

Diagnostic procedures apart from serum PSA-related testing are also of great interest, for this can greatly ignore the heterogeneity of cancer development. Cao *et al*.[88] established a multiplex model including urine *PCA*3, *TMPRSS2: ERG*, Annexin A3 and sarcosine to predict Prostate cancer in Chinese patients and got favorable results. He mentioned that further validation experiments and optimization for the strategy of constructing this model are warranted.

TREATMENT

Be aware of the rising threat of Prostate cancer, physicians in East Asia work together to establish the best treatment strategies for their patients. Over the last decade, regional guideline regarding management of Prostate cancer was published by medical associations.[89] Although standardized treatment remarkably improve the implementation of state-of-art knowledge in East Asia, most of evidence are gain from Western countries and are used under the hypothesis that a similar outcome will be replicated in Asians. Fortunately, more and more studies published form Asian physicians investigate the hypothesis and discussed whether we should adapt other than adopt the western approach. Hereby, we followed the nature history of Prostate cancer, discussed the treatment across early to advanced disease.

Active surveillance

Overdiagnosis and overtreatment are considered a common scene in screen detected Prostate cancer. To overcome the drawbacks, active surveillance has been evolving as a management strategy for indolent tumors. Unfortunately, the selection criteria of active surveillance, especially in Asian populations, still remain to be standardized.[90–93] One study from Korea suggested that 30.5% (40/131) of patients who meet all the conditions of the contemporary Epstein criteria for prediction of clinically insignificant Prostate cancer might actually harbor Prostate cancer with unfavorable pathological features (Gleason score ≥7 and/or extraprostatic extension) and such an underestimation rate of tumor grade by the Epstein criteria is relatively high compared with data from Western countries.[90,94,95] Other cohorts also concluded there was a difference in incidence of about 13%–16% between populations according to the results of Asian and Western studies using each of the same AS protocols.[90,93,96] Since similar observation was found in African American, these results indicated different carcinogenesis pathway may possible affect tumor characteristics. For example cancer in the anterior prostate is quite difficult to detect using current biopsy techniques. Thus a more accurate and balanced active surveillance protocol for Asian cohorts is needed. Recently, data derived from Asia demonstrated that the statistical model (nomogram) and the measurement of the diameter of suspicious tumor lesions on diffusion weighted magnetic resonance imaging could improve the prediction of insignificant Prostate cancer in candidates for active surveillance.[97,98] Therefore, these tools might be helpful in guiding urologists' selection of the proper active surveillance candidates.

Radiation therapy

External beam radiation therapy

In Japan, one of the most developed countries in Asia, the use of external beam radiation therapy (EBRT) is gaining acceptance as a first-line treatment for Prostate cancer. Moreover, patient characteristics and treatment characteristics are becoming more similar to patients in the United States.[99] In a multi-institutional study of EBRT for Prostate cancer in Japan, the 5-year overall, clinical progression-free, and biochemical relapse-free survival rate were 93.0%, 95.3%, and 71.9% for all patients. The 5-year progression-free, and biochemical relapse-free survival rates according to the risk group were 100%, 90.8% in the low-risk group, 98.3%, 75.7% in the intermediate-risk group and 93.6%, 67.6% in the high-risk group.[100] The author also mentioned that the survival result is comparable to T1-T2 patients who had a radical prostatectomy in Japan,[101] indicating that EBRT is a promising option in low and intermediate risk patients in Asia. However, consensus has

not been reached on the practice and management of postoperative RT for patients with Prostate cancer in Japan yet.[102] In a study of EBRT for intermediate and advanced Prostate cancer in China, the 5-year survival was 79.5%,[103] a bit higher than 71.4% from a Europe randomized trial.[104] Unfortunately, little solid data of EBRT for Prostate cancer from other Asian countries can be reached.

Brachytherapy

Permanent prostate brachytherapy using iodine-125 seeds has grown rapidly since the establishment of guidelines. In a Japanese study involving 663 patients with low-risk and low-tier intermediate-risk confined disease, The 7-year cause-specific survival and overall survival (OS) were 99.1% and 96.4% and there were no significant difference between different risk groups.[105] In addition, the result was excellent compared to data from other studies (5-year biochemical disease-free survival-rates = 81% from Austria,[106] 10-year biochemical disease-free survival rate was 83% for Caucasians[107]). On the other hand, brachytherapy for high-risk Asian patients also had favorable results.[108,109]

Radical prostatectomy

Radical prostatectomy is the major curative treatment for men with localized Prostate cancer and is the only one that has been proven to show a benefit for OS and cancer-specific survival compared with conservative management in a prospective randomized trial.[110] Recently, robot-assisted laparoscopic prostatectomy (RARP) has been developed and the shift toward RARP has reshaped the surgical approach for localized Prostate cancer. Several recent reports compared the outcomes of RARP with open RP or laparoscopic RP and suggested that RARP might be noninferior in terms of oncological outcomes and might be superior in functional outcomes with a lower or equal rate of complications.[111–114] Although the use of RARP in East Asia has been somewhat delayed and less widespread compared with Western counties due to the obstacles in financial reimbursement, patient volume and surgical skill development, the outlook for RARP in East Asia remains rosy.[115,116] Future robotic systems (da Vinci S models) with a smaller footprint, leaner instrument arms and lower costs would better serve many Asian patients.

We reviewed the current literatures[117–129] and compared perioperative parameters and the trifecta outcomes (cancer control, continence, and potency) following RP among Asians and Westerners (**Table 3**). As the improvement of the technical expertise and the migration toward low-risk disease in recent years, the perioperative complication rate and oncological outcomes has been comparable in the series from East Asia and Western countries. However, it is reported that the potency recovery following RP is inferior in Asian populations.[130–135] Namiki *et al.*[130] prospectively compare the recovery of sexual function and bother during the first 2 years after RP between American and Japanese men and found that Japanese men had a smaller improvement in sexual function and bother over time than did the American men postoperatively after adjusting for baseline score, age, baseline PSA and nerve-sparing. That is to say, American men were more likely to regain their baseline sexual function by 24 months after surgery (hazard ratio [HR] =1.60) and were less likely to return to baseline sexual bother (HR = 0.57) than Japanese men. The cultural differences may contribute to the different patterns of recovery of sexual function between Asian and Western patients after RP. Furthermore, the fact that in many parts of Asia the PSA screening is not common and the proportion of pT3-4 tumor is high, which result in less use of nerve-sparing techniques, may play a certain role in the discrepancy.

Androgen deprivation therapy

Currently, androgen deprivation therapy (ADT) is widely used as primary treatment for advanced Prostate cancer and as adjuvant treatment for locally advanced Prostate cancer. The influence of race on the effectiveness of ADT has aroused some scholar's interest due to the incidence of Prostate cancer vary widely in different races. Fukagai *et al.*[136] compared the outcomes of Caucasian men (CM) and Japanese-American men (JAM) treated with ADT and reported that JAM showed a much better outcome than CM in terms of overall and cause-specific survival rate (P = 0.001 and 0.036, respectively). Moreover, they found that race was one of the significant prognostic factors in the multivariate analysis (P = 0.03). Soon afterwards, Fukagai *et al.*[137] investigated the clinical outcome after ADT among Chinese, Filipino, JAM and CM and reported that Chinese men show almost the same prognosis as JAM and better prognosis than CM while Filipinos show a worse prognosis after ADT than JAM but a better prognosis than CM. These data indicated that ADT is more effective in Asians. Lately, Fujimoto *et al.*[138] reported that active androgen transport *SLCO2B*1 genotype (GG allele), which occurred more frequently in African and Caucasian populations than in Japanese and Han Chinese population, is associated with the shorter time to progression in patients who received ADT. Therefore, the germline genetic function alterations underlying ADT efficacy warrant further evaluation to answer the discrepancy in outcome.

It is likely that not only sensitivity of Prostate cancer to ADT but also side effects of ADT differ among racial groups. Studies from Japan[139,140] indicated the low prevalence of osteoporosis in both hormone-naïve and ADT-treated Japanese Prostate cancer patients, even in patients treated with ADT for more than 2 years, which are quite different from studies examining patients in Western counties.[141,142] In addition, data for the general population show that the incidence of ischemic heart disease is much lower in Japanese than in Westerners. For bone fractures, as well, the incidence is much lower in Japanese than in Westerners.[143] The fact that overall rates of cardiovascular disease and metabolic syndrome at baseline in Asian populations were lower might be associated with the less frequency of ADT-related side effects.[144–146] Therefore, it should be interesting to explore possible protect factors underlying race difference.

Chemotherapy

Although the effectiveness of ADT has been confirmed for advanced Prostate cancer, in virtually all patients, the disease inevitably advances to the androgen-independent stage within a median of 18–24 months after castration.[147] To such relapsed Prostate cancer after primary ADT failure, chemotherapy could be used as the standard treatment. Currently, docetaxel combined with prednisone is still used as the standard first-line chemotherapy for castration-resistant prostate cancer (CRPC) patients due to the survival benefit as well as palliative benefit in the TAX 327 and Southwest Oncology Group (SWOG) 99–16 studies.[148,149] However, the reports on the efficacy of docetaxel-based chemotherapy mainly included patients from Western countries and studies from Asia are relatively limited. A study in Korean men showed that the PSA response of 51% and median OS of 22.8 months are comparable to or even better than those from TAX 327 study, which revealed the PSA response rate of 45% and median OS of 19.2 months.[148,150,151] Also, in the Korean study,[150] the time to PSA progression (5.8 months) is comparable to time to progression reported in SWOG 99–16 study (6.3 months) and the clinicopathologic characteristics of Korean patients, with the exception of the fact that more Korean patients with a Gleason score ≥8, were quite similar to those of the TAX 327 and SWOG 99–16 studies.

Table 3: Comparison of perioperative parameters and the trifecta outcome following RP among Asians and Westerners

Author	*Country*	*Year*	*Approach*	*Number of cases*	*pT2 (%)*	*Gleason score≥7 (%)*	*Overall complication (%)*	*PSM (%)*	*Follow-up period (months)*	*Definition of BCR (PSA level)*	*BCR-free rate (%)*	*Definition of continence*	*Continence rate (%)*	*Definition of potency*	*Potency rate (%)*
Eastham *et al.*[117]	USA	2008	RRP	1577	71	59	-	11	48	>0.2	91	0 pad	94	ESI	67
Krambeck *et al.*[118]	USA	2009	RRP	564	88.6	33.5	8	17	12	>0.4	92.2	0 pad	93.7	ESI	62.8
			RARP	286	90.1	34.5	4.8	15.6	12	>0.4	92.4	0 pad	91.8	ESI	70
Ploussard *et al.*[119]	France	2011	LRP	911	59.8	76.1	-	28.6	24	>0.2	86.7	0–1 pad	97.4	ESI	64.6
Patel *et al.*[120]	USA	2011	RARP	332	93.0	54.2	6.6	9.3	12	>0.2	96.4	0 pad	96.4	ESI	89.8
Chan *et al.*[121]	China*	2008	LRP	85	79	-	9.4	22	12	>0.2	26	0 pad	92	-	-
Ko *et al.*[122]	Korea	2009	RARP	63	80.9	-	7.8	26.9	6	>0.2	100	0 pad	94.4	ESI	70.6
Lo *et al.*[123]	China*	2010	RRP	20	-	-	-	20	42	>0.2	80	0–1 pad	85	-	-
			RARP	20	-	-	-	25	6	>0.2	100	0–1 pad	95	-	-
Park *et al.*[124]	Korea	2011	LRP	62	59.6	45.2	11.3	21	12	-	-	0 pad	95	ESI	48
			RARP	44	68.2	43.2	11.4	20	12	-	-	0 pad	94	ESI	55
Imamoto *et al.*[125]	Japan	2011	LRP	100	72	88	18	32	6	>0.1	98	0–1 pad	85.9	ESI	83.3
Yip *et al.*[126]	China*	2012	RARP	235	74.9	38.7	6.8	20.7	12	>0.2	90.6	0 pad	72.5	ESI	37.3
Ou *et al.*[127]	China#	2013	RARP	300	35	-	8.7	37	12	>0.2	94.6	0 pad	97.8	ESI	87.2
Yao *et al.*[128]	China	2013	RRP	379	53.0	62.8	21.9	18.2	30	>0.2	89.5	0 pad	83.9	-	-
Choo *et al.*[129]	Korea	2013	RRP	176	58.5	62.5	-	40	24	>0.2	88	0–1 pad	98	ESI	51
			RARP	77	48.1	51.9	-	39	24	>0.2	94	0–1 pad	95	ESI	56

ESI: erection sufficient for intercourse; IIEF: International Index of Erectile Function; LRP: laparoscopic radical prostatectomy; RARP: robotic-assisted radical prostatectomy; RRP: retropubic radical prostatectomy; PSM: positive surgical margin; BCR: biochemical relapse; PSA: prostate specific antigen; RP: radical prostatectomy. *Hong Kong, China. #Taiwan region, China.

As cancer treatment goals shift from mere improvement in OS to maintaining better quality of life, attention should be paid to chemotherapy-related toxic effects. In TAX 327 and SWOG 99–16 studies, the most common Grade 3 or 4 adverse events associated with docetaxel or mitoxantrone chemotherapy were nausea/vomiting, neutropenia, alopecia, cardiovascular events, infection, pain, diarrhea, nail changes, sensory neuropathy, and anorexia.[148,149] Results from East Asia revealed that the docetaxel-based chemotherapy was clinically feasible for Asian patients with metastatic CRPC and the main adverse events were neutropenia, leukopenia, febrile neutropenia, asthenia, anorexia and neuropathy.[150,152–155] It is reported that febrile neutropenia occurred much more frequently (13%) in Korean patients with metastatic CRPC treated with docetaxel (75 mg m^{-2} every 3 weeks) than those of phase III studies or systemic review incorporating Western patients (3%–6%).[148–150,156] Previously, Naito *et al.*[153] have reported that the incidence of febrile neutropenia was as high as 16% in Japanese patients with CRPC treated with lower docetaxel (70 mg m^{-2} every 3 weeks). It is possible that the observed differences in clinical toxicity to docetaxel between Asian and Western patients may be related to the docetaxel pharmacokinetic differences and that the diversity of polymorphisms in CYP3A isoenzymes in patients from different racial backgrounds may contribute to these differences.[157,158] Moreover, the liver function impairment, which is common in East Asia, especially in China, is associated with the development of severe docetaxel-induced side-effects.[159] Therefore, caution should be exercised when treating Asian patients with docetaxel-based chemotherapy, especially with respect to the development of febrile neutropenia in patients of older age, or with poor performance status.

CONCLUSIONS

Prostate cancer epidemic in East Asia is characterized by rapid rates of increase over the last decade. Exposure to westernized diet and life style and improvement in health care in combination contribute substantially to the increasing epidemic in this region. Growing evidence from East Asia suggests an important role of genetic and environmental risk factors interactions in the carcinogenesis of Prostate cancer. Further research of secular trends and risk factors is strongly needed to prevent the disease in the area with a huge population.

Diagnostic and treatment guidelines in East Asia are largely based on Western knowledge. Although there is a remarkable improvement in the outcome over the last decade, ample evidence suggests an inneglectable difference in diagnostic accuracy, treatment efficacy and adverse events. The knowledge from western countries should be calibrated in the Asian setting to provide a better race-based treatment approach. For the next decades, translational research investigating underlying disparities in East Asia Prostate cancer subjects is felt with highest needs.

AUTHOR CONTRIBUTIONS

YZ carried out the epidemiology part of the study and helped to draft the manuscript. HKW worked on risk factors, genetics, diagnosis and part of treatment and outcome section. YYQ worked on treatment and outcome. DWY conceived of the study and participated in its design and coordination.

COMPETING INTERESTS

All authors declare no competing interests.

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