

REVIEW

An overview of prostate diseases and their characteristics specific to Asian men

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In this paper, we reviewed the features of common prostate diseases, such as benign prostatic hyperplasia (BPH), prostate cancer (PCa) and chronic prostatitis (CP) that are specific to Asian men. Compared to the Westerners, Asians exhibit particular characteristics of prostate diseases. Through summarizing the epidemiology, symptomatology, diagnostics and therapeutics of these diseases, we find that Asians have a lower incidence of PCa than whites, but the incidences of BPH and CP are similar. Asian men with CP often suffer from fewer disease sites, but have a higher frequency of pain during urination rather than after sexual climax. Prostate-specific antigen (PSA) is a widely used marker for the diagnosis of PCa in both Asian and Western countries. Although the PSA level may be lower in Asians, the threshold used is based on whites. After reviewing the treatments available for these diseases, we did not find a fundamental difference between Asians and whites. Furthermore, the selection for the most appropriate treatment based on the individual needs of patients remains a challenge to urologists in Asia. After considering the traits of prostate diseases that are specific to Asian men, we hope to pave the way for the development of specific diagnostic and therapeutic strategies targeted specifically to Asian men.

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INTRODUCTION

Prostate diseases are common diseases in urology. Benign prostatic hyperplasia (BPH), prostate cancer (PCa) and chronic prostatitis (CP) are the most frequent. Asians and whites exhibit differences in race, diet, lifestyle and environmental factors; thus, these three prostate diseases have features that are specific to Asian men. Therefore, we reviewed these features with respect to epidemiology, symptomatology, diagnostics and therapeutics. After considering the characteristics of prostate diseases that are specific to Asians, we hope to pave the way for the development of specific diagnostic and therapeutic strategies targeted specifically to Asian men.

BENIGN PROSTATIC HYPERPLASIA (BPH)

Ethnic features

BPH is a common disease among men attending urology clinics. Early clinical observations and studies have shown that Asians generally have a similar or higher International Prostate Symptom Score (IPSS) compared with whites (Table 1).^{1,2} However, the differences in the prostate tissue between Asians and whites may deserve special mention with regard to BPH. First, the cellular composition of the prostate may be different. The prostates of Chinese men contain significantly more glandular lumens and less smooth muscle and connective tissue than Caucasian-Americans.³ Second, Korean men have been shown to have a higher transition zone enlargement ratio relative to total prostate volume in comparison to Caucasians and Hispanics.²

Lower urinary tract symptoms (LUTS)

BPH patients in Asian countries typically have accompanying LUTS.⁴ Traditionally, LUTS are considered a consequence of BPH-related prostate enlargement. However, the theory that there is a simplistic causal relationship between them has been challenged. Recently, LUTS have been considered not only attributable to prostatic enlargement, but also to the aging of the bladder muscle, metabolic factors and prostatic inflammation, a dynamic component of the smooth muscle tone of the prostate, serum sex steroid hormones and other factors.^{5–8}

LUTS can be categorized as storage symptoms, voiding symptoms and postmicturition symptoms. The most common symptom in both Asians and whites is nocturia.^{4,9,10} In addition to the symptoms mentioned above, patients with LUTS also suffer sexual dysfunctions, which are correlated with the severity of LUTS.^{11–13} In a survey of five regions of Southeast Asia, 82% of men with LUTS experienced sexual dysfunction. The most common sexual problems were erectile dysfunction (ED) (71%), reduced ejaculation (66%) and pain with ejaculation (18%).⁴ The link between LUTS and ED has been attributed to the following factors: (i) the autonomic hyperactivity and metabolic syndrome hypothesis; (ii) a decrease in the release of nitric oxide in the penis and the prostate; (iii) the activation of Rho kinase and the endothelin pathway; (iv) pelvic arteriosclerosis; and (v) an altered composition of the myosin isoform.^{14,15}

BPH progression parameters

In Asian men, BPH usually begins in the fourth decade of life and is attributed to dynamic changes with age in the glandular tissue

Table 1 Age-specific prevalence of men with IPSS ≥ 8 in various areas¹

Area	Prevalence of men with IPSS ≥ 8 (%)			
	40–49 years	50–59 years	60–69 years	70–79 years
Asia ^a	18%	29%	40%	56%
Australia	—	36%	33%	37%
USA	12%	17%	23%	29%
Canada	—	15%	27%	31%
France	—	8%	14%	27%
The Netherlands	—	26%	30%	36%

Abbreviation: IPSS, International Prostate Symptom Scores.

^a Asian data were obtained from mainland China, Taiwan (China), Korea, the Philippines, Thailand, Singapore, Pakistan and India.

composition and cell proliferation activity.^{16–18} There are several useful parameters to identify the risk of BPH progression, including age, prostate volume and serum prostate-specific antigen (PSA) level.^{19,20} Intravesical prostatic protrusion level is also a useful parameter.¹⁹ Interestingly, there are some links between these parameters, including an age-dependent trend towards increased prostate volume with a greater intravesical prostatic protrusion level. Meanwhile, serum PSA level is significantly correlated with prostate volume in Asian communities.^{21–26}

Treatment: the current situation, trends and challenges

Generally speaking, drugs and surgery are two main treatment options for BPH. Some trends have been discovered in the last few decades. The utilisation of pharmaceutical therapy is increasingly the first choice for BPH treatment.²⁷ While the use of transurethral prostatectomy (TURP) has been challenged by minimally invasive surgical therapy (MIST),^{28,29} it remains the gold standard of ablative therapy.

α_1 -blockers and 5 α -reductase inhibitors are the two classes of medications that are recommended by the European Association of Urology guidelines for the medical management of LUTS/BPH.³⁰ In Asian countries, clinical evidence has demonstrated that this medical therapy relieves the symptoms of patients.^{18,31} In addition, the combination of these two classes of drugs has been proven to significantly reduce the relative risk of clinical progression of BPH, and the relief of LUTS is greater in combination than when either drug is used alone. However, the effect on reducing the relative risk of acute urinary retention or BPH-related surgery remains controversial.^{20,32–36} Furthermore, the combination of α_1 -blockers with antimuscarinic agents is useful for relieving symptoms of LUT/BPH without increasing urinary retention.^{33,37} A comparison of different α_1 -blockers in the same individuals demonstrated no statistically significant difference between terazosin (5 mg daily) and alfuzosin (10 mg daily) for 3 months in the IPSS and maximum flow rate.³⁸

As LUTS associated with BPH are generally accompanied by sexual dysfunction, many clinical trials have indicated that combination therapy is the optimal treatment. Randomized placebo-controlled trials have shown that PDE5 inhibitors, which are used for the treatment of patients with ED, improved voiding and storage in LUTS/BPH.^{39–41} A clinical study showed that combining tadalafil and alfuzosin resulted in greater improvements in ED, IPSS and International Index of Erectile Function scores than either drug used alone.⁴² Similarly, an *in vitro* experiment using this combination showed an additive relaxant effect on human prostate and detrusor tissue.⁴³ However, one survey reported that sildenafil and tamsulosin used in combination is not superior to monotherapy in treating LUTS and ED.⁴⁴ In Asian men, alfuzosin improved ejaculatory function, while tamsulosin had a slight negative impact on ejaculation.^{45–48} Rosen *et al.*⁴⁹ reported that alfuzosin, doxazosin and terazosin appeared to be associated with better ejaculatory function than tamsulosin.

Although the medical treatment of BPH is well established, the following questions remain:

1. How long and for whom should combination therapy of α_1 -blockers and 5 α -reductase inhibitors be utilized?³⁶
2. Does tamsulosin elicit an apoptotic response to reduce the prostate volume?⁵⁰
3. Which PDE5 inhibitors are the most effective, safe and cost-effective for treating LUTS/BPH?
4. What are the long-term outcomes of combination therapy with α_1 -blockers and PDE5 inhibitors in the treatment of LUTS/BPH.⁵¹

As the gold standard of surgical therapy, TURP is the most commonly used surgical option.²⁹ However, new minimally invasive surgical techniques, such as the bipolar modification of TURP (bipolar TURP or bipolar transurethral resection of prostate), various laser-assisted techniques (holmium laser enucleation/resection of the prostate, photo-selective vaporization of the prostate and thulium laser) and plasmakinetic enucleation has grown in popularity.⁵²

Many clinical studies have indicated that these MISTs are safe and effective compared to TURP. Recently, two meta-analyses have compared MIST and TURP.^{53,54} The efficacy of each is shown in **Table 2**, and the analyses found that bipolar TURP and bipolar transurethral electrovaporization of the prostate are comparable to TURP in short- and medium-term follow-up, while photo-selective vaporization of the prostate may be effective only in small to mid-sized prostates. They also concluded that holmium laser enucleation of the prostate (HoLEP) is at least as effective as TURP in long-term follow-up. Among surgical complications, catheter time following TURP was found to be the longest among all the techniques, and all adverse inter- and peri-operative events were significantly less frequent following MIST compared to TURP. Considering the limited long-term follow-up data after MIST and the low complication rate of TURP, the durability of TURP outcomes is still not surpassed.^{53,54}

Table 2 Comparisons of efficacy in different transurethral procedures and TURP⁵³

	IPSS		Qmax		PVR		QoL	
	Mean difference	P value	Mean difference	P value	Mean difference	P value	Mean difference	P value
Bipolar TURP vs. TURP	0.094	0.827	−0.539	0.070	3.677	0.416	−0.100	0.502
Bipolar TUVP vs. TURP	−0.060	0.900	−1.696	0.052	−12.866	0.584	−0.286	0.386
HoLEP vs. TURP	1.309	0.005	1.687	0.012	5.667	0.196	−0.003	0.978
PVP vs. TURP	−5.377	0.146	−1.826	0.414	−42.644	0.158	—	—

Abbreviations: HoLEP, holmium laser enucleation of the prostate; IPSS, international prostate symptom scores; PVP, photo-selective vaporization of the prostate; PVR, postvoid residual volume; Qmax, maximum flow rate; QoL, quality of life score in IPSS; TURP, transurethral resection of prostate; TUVP, transurethral electrovaporisation of prostate.

Additionally, a systematic review reported that the outcome of male sexual function after holmium laser surgery and TURP were similar. Some patients reported decreased erectile function (HoLEP: 7.5% vs. TURP: 7.7%), while some reported increased function (HoLEP: 7.1% vs. TURP: 6.2%). There were high incidences of ejaculatory dysfunction following both holmium laser surgery and TURP.⁵⁵

Currently, the choice of the most appropriate surgical treatment for individual patients with BPH remains challenging.

PROSTATE CANCER (PCA)

Epidemiological characteristics

It is well established that the incidence and mortality rates of PCA are significantly lower in Asia than in Western countries. Recently, important new epidemiological studies have been published showing several findings.^{56–58} First, the incidence of PCA has risen over the last two decades (Table 3). Second, the stage distributions of PCA are more unfavourable in Asians, with a higher occurrence of medium- or high-grade PCA than whites. Third, mortality rates of PCA may continue to rise in most Asian countries. For instance, in South Korea, PCA mortality increased 12.7-fold over a 20-year period.⁵⁹ This may be attributable to genetic factors, such as a gradual westernisation of lifestyle, increased dietary fat intake, environmental changes or a low rate of PSA screening in Asia.^{58–61}

Diagnosis: PSA and other tumour markers

Serum PSA is a tumour marker that is currently used for PCA screening and diagnosis in both Asian and Western countries. Currently, the generally accepted upper cut-off level of normal PSA is 4.0 ng ml⁻¹ in Asians and whites. However, this cut-off level has limited specificity and sensitivity for the clinical diagnosis of PCA. Regarding specificity, the PSA level can be affected by several factors, such as age, body surface area, body mass index, prostate volume, prostatitis and medical or surgical interventions.^{21,24,61–64} In terms of sensitivity, PSA levels less than 4.0 ng ml⁻¹ were found in 15.2% of PCA patients in the United States of America, 23% of PCA patients in Europe and 12.4% of PCA patients in Asia.^{61,65–67}

Because of the drawbacks of using the PSA level for the detection of PCA, many PSA derivatives have appeared. The most accurate 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.^{68,69} At the same time, PSA density, PSA velocity and PSA doubling time are also used occasionally.⁷⁰ A combination of these indices may reduce the number of repeat biopsies when the PSA level is between 4 and 10 ng ml⁻¹.⁷¹ Besides PSA and its derivatives, other new markers that have been used include early PCA antigen,⁷² and urinary PCA gene 3.^{70,73–75}

PSA levels may be lower and prostate volumes may be smaller in Asians compared to whites, but Asians may have a higher PSA level per unit volume. This evidence is shown in studies among Korean,

Japanese, Chinese, Malay, Indian and Arab men.^{21,26,76–81} However, Asians often use the PSA threshold that is based on whites. Therefore, additional and collaborative clinical studies should be conducted in order to establish separate PSA cut-off values or nomograms for Asian men.⁵⁸

Diagnosis: prostate biopsy

A prostate biopsy is strongly indicated for patients with a PSA level above 10 ng ml⁻¹.⁸² Sextant biopsy has been the gold standard for several years. However, some recent studies have demonstrated that 10–14 core-extended biopsy is optimal for first-time prostate biopsy.^{63,83–85} In order to predict a positive biopsy, some parameters and nomograms can be used, such as positive digital rectal examination results, prostate volume and hypo-echoic lesions on TRUS.^{65,86–93} For patients with clinically suspected PCA but a negative first biopsy, a saturation biopsy (minimum of 20 cores) with lateral and apical cores may be indicated, which is also efficacious for staging patients who are undergoing active surveillance protocols.^{63,85,94,95} Pepe *et al.*⁹⁶ suggested that in addition to the presence of LUTS, TURP should be a part of the diagnostic procedure in cases of a repeated negative saturation biopsy. Meanwhile, the sample from the prostatic transition zone by directed needle biopsies may be omitted due to a lower detection rate compared to TURP.^{97,98}

Initial therapy in primary localized PCA

Initial therapy in primary localized PCA includes radical prostatectomy (RP), hormone therapy (HT), brachytherapy and external-beam radiation therapy (RT).

RP can be performed either by retropubic radical prostatectomy (RRP) or laparoscopic radical prostatectomy (LRP). A study among Asians showed that LRP is comparable to RRP with no significant morbidity and a positive surgical margin rate. Meanwhile, LRP has been reported to have decreased blood loss and decreased need for blood transfusion, but also extends operative time.⁹⁹

Furthermore, robot-assisted LRP is a new option that has been widely used in America and many parts of Europe, though it is in its infancy in Asia. Until 2009, only eight regions had a robot system; in total there were 24 systems in Asian countries, namely in the mainland of China, South Korea, Japan, Taiwan (China), India, Thailand, Singapore and Malaysia. It is uncertain whether robotic surgery will result in superior oncologic and functional outcomes and decreased postoperative morbidity in Asians.¹⁰⁰ Yip *et al.*¹⁰¹ painted a rosy outlook of robotic prostatectomy in Asia after viewing the evolving trends in East Asia.

HT is known to be beneficial in high-risk and advanced PCA. Although its benefits in low- or intermediate-risk PCA remains controversial,¹⁰² it is widely used as the initial treatment in Asian countries such as Korea, Japan, China, Singapore, Indonesia and Vietnam.^{58,103}

Table 3 Incidence and mortality rates of prostate cancer in seven Asian countries (per 100 000 person-year, age-adjusted using the world standard)^{56,59,143–145}

	Incidence (%)			Mortality (%)		
	1978–1982	1993–1997	1998–2002	1978–1982	1993–1997	1998–2002
Philippines	11.1	16.6–19.3	21.9	—	—	—
Singapore	6.6	14.4	30.9	1.9	5.2	9.6
Japan	6.7	14.1	—	2.4	4.8	8.6
HongKong (China)	6.2	8.6	—	2.1	3.6	4
Thailand	4.0	4.2	—	0.2	0.3	—
South Korea	—	7.9–8.5	10.9	0.30–0.50	1.8	3.82

A marked racial difference in the clinical outcome after HT has been observed between Asians and Caucasians.^{104,105} Japanese men had a better overall and cause-specific survival rate compared with Caucasian men ($P=0.001$ and 0.036). Chinese men demonstrated a similar trend.⁵⁸

Unlike HT, brachytherapy and external-beam RT are not routinely used in most Asian areas.^{103,106,107} Therefore, few data can be found regarding the outcome of these two therapies in Asian men.

In intermediate-risk PCa, Vassil *et al.*¹⁰² recently demonstrated that choosing RRP, brachytherapy or RT appeared to improve 5-year biochemical relapse-free survival and delayed salvage therapy compared with LRP.

In high-risk PCa, RP is commonly used as the primary therapy. However, more than 50% of PCa patients in Asia are treated using HT. Furthermore, a combined androgen blockade (CAB), which consists of luteinizing hormone-releasing hormone agonists plus an anti-androgen, was more effective than hormone monotherapy in terms of disease-specific survival in high-risk PCa in Asia (Table 4) ($P=0.037$).¹⁰⁸ A survey in Japan showed that RT+HT resulted in significantly better survival rates compared with primary HT ($P=0.029$). There were, however, no statistically significant differences between RT+HT and RP+HT or between RP+HT and primary HT.¹⁰⁹ Mizokami *et al.*¹⁰⁸ suggested that in high-risk patients with an initial PSA level of ≤ 20 ng ml⁻¹, a Gleason score of ≤ 6 and a nadir in the PSA of ≤ 0.2 ng ml⁻¹ within 6 months of HT, monotherapy using RP, RT or HT is likely to be effective. Combined therapies with CAB and brachytherapy may be useful for higher grade and stage tumours. One study in Taiwan (China) showed that high-dose brachytherapy plus RT can achieve satisfactory biochemical control with acceptable complications for T1c to T3a PCa patients.¹¹⁰

In local advanced PCa, androgen deprivation therapy is the main treatment strategy. However, to prolong the period before PCa becomes refractory to HT, complementary treatments following androgen deprivation therapy should be considered with RT being a common choice.¹¹¹ Recently, Wu *et al.*¹¹² reported that in Chinese patients who had undergone androgen deprivation therapy, high-intensity focused ultrasound combined with low-dose RT resulted in a higher 5-year disease-specific survival rate than both conventional-dose RT and high-intensity focused ultrasound (75.29% vs. 64.47% and 46.35%, respectively) with lower incidences of radiation-related late gastrointestinal and genitourinary toxicity grades. Additionally, RP may be considered in selected cases of local advanced PCa, with 5-year PSA-free survival rates at from 45% to 62%. The European Association of Urology guidelines recommend that only

Table 4 Five- and ten-year survival rates after different treatments for high-risk prostate cancer

	5-year survival rate (%)	10-year survival rate (%)	P value
Mizokami <i>et al.</i> ¹⁰⁸			
CAB	92.8	92.8	
Hormone monotherapy	87.4	78.5	0.037
Saito <i>et al.</i> ¹⁰⁹			
RT+HT	96.6	93.6	
RP+HT	93.8	71.4	
Primary HT	88.6	62.3	0.029 ^a

Abbreviations: CAB, combined androgen blockade; HT, hormone therapy; RP, radical prostatectomy; RT, radiation therapy.

^a RT+HT vs. primary HT.

cT3a patients with a PSA level of <20 ng ml⁻¹ and a biopsy Gleason score of ≤ 8 are suitable for this strategy.¹¹³

PROSTATITIS

Currently, CP syndromes represent an important healthcare problem worldwide. In many Asian countries, the direct and indirect costs (e.g., work and productivity loss) associated with CP are large and pose significant financial burdens for men.^{114,115} In Iran, CP is one of the six greatest burdens of urologic diseases.¹¹⁶ In China, the treatment of one CP patient usually costs \$1151 per year.¹¹⁷

Symptomatology features

According to the recommended National Institutes of Health categorisation system,¹¹⁸ chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of prostatitis. The prevalence of prostatitis-like symptoms in China is 8.4% and the prevalence of CP was 4.5% in an investigation of 12 743 Chinese men.¹¹⁹ In a meta-analysis of five studies (three from America and two from Asia), Krieger *et al.*¹²⁰ reported that the prevalence of prostatitis symptoms ranged from 2.2% to 9.7%, with a median rate of 8.7%. There are also reports showing that 4.9%–10.5% of men from North American, Europe and Asia have prostatitis-like symptoms.^{121–124} To date, there is no direct evidence to demonstrate that regional or ethnic factors are related to the prevalence of CP. However, differences in the basic clinical characteristics of CP/CPPS between North Americans and Asians are truly interesting. Lee *et al.*¹²⁵ showed a lower quality of life, a shorter duration of CP/CPPS symptoms, and fewer disease sites, as well as a higher frequency of pain in Asian men than American men. In these men, the pain generally occurred during urination rather than after sexual climax. However, the National Institutes of Health Chronic Prostatitis Symptom Index total scores, the pain plus urinary subscores, and the average pain level were similar between Asian and North American men.¹²⁵

Besides discomfort or pain in the lower genitourinary tract or perineum, sexual dysfunction is also a threat to men with CP/CPPS. CP symptoms were significantly correlated with the indices of sexual function in the patients and their quality of sexual life. Premature ejaculation and ED are common complications of CP.^{118,126–131}

Treatment: confusion and multimodal therapy

From the data presented above, we consider CP/CPPS to be a significant problem for men with a spectrum of urological diseases. However, urologists generally experience much confusion and frustration in the management of CP because the treatment efficacy is unsatisfactory.^{117,132,133} In clinical practice, pharmacotherapy (antibiotics and α -blockers) is the most commonly used treatment and is primarily used to relieve patients' discomfort, even though urologists know that CP/CPPS is not a bacterial disease.^{117,132} However, some studies have confirmed that medical therapy is truly effective to some patients.¹³⁴ Antibiotics have been reported to be useful in the treatment of premature ejaculation in CP/CPPS.^{135,136} For those who failed this therapy, several additional methods have been tried, including anti-inflammatory drugs, pollen extract, sitz baths, prostate massage and pelvic floor physical therapy.^{117,132–134,137–139} Some evidence suggests that CP/CPPS may be neuropathic in origin, and treatment based on that theory might provide greater treatment options. One retrospective analysis in China showed that chlormezanone (a drug for anxiety) may relieve CP/CPPS symptoms.¹⁴⁰ However, no single attempt has shown efficiency for the cure of CP/CPPS. The current question is why so many therapies have failed to cure or control CP/

CPPS. Although the answer remains unknown, there are some studies and assumptions that can help answer the question. After finding a higher incidence of CPPS in females than in males, Marszalek *et al.*¹⁴¹ asked questions about the role of the prostate as the leading cause of CP/CPPS, and Zaak¹⁴² commented that a defect in urothelial permeability might play a role in CP/CPPS.

In general, multimodal therapy that includes pharmacotherapy, sitz baths, prostate massage and pelvic floor physical therapy may help patients to control the symptoms of CP/CPPS. Additional efforts should be made to more deeply understand the mechanism of CP/CPPS in order to find more effective therapy.

CONCLUSION

There is a high incidence of BPH in Asia. Age, prostate volume and PSA level may be useful parameters to identify the risk of BPH progression. LUTS are the most common symptom in BPH. However, LUTS are attributable not only to prostatic enlargement, but also to the aging of the bladder muscle, metabolic factors and prostatic inflammation, the dynamic component of the smooth muscle tone of the prostate, serum sex steroid hormones and other factors. The two main options to treat BPH are medical therapy and surgical treatment. A combination of α_1 -blockers and 5α -reductase inhibitors are recommended. While new surgical therapies are continuously emerging and being developed, TURP rightly remains the dominant mode of treatment. Identifying the most appropriate treatment option and long-term management plan of each individual patient remains a great challenge.

The incidence of PCa is rapidly increasing in Asia. Although PSA level is the most widely used marker for PCa, the cut-off level suitable for Asians should be ascertained through large multicentre clinical trials, as should the protocol for prostate biopsy. RP, HT, brachytherapy and external RT are options for the treatment of localized PCa. In intermediate-risk PCa, RRP, brachytherapy and RT have similar 5-year biochemical relapse-free survival rates. In high-risk and localized advanced PCa, combination therapy may show a higher survival rate.

CP/CPPS places a heavy burden on the health of Asian men. Conventional pharmaceutical therapy may fail in some patients. Multimodal therapy that combines pharmaceutical therapy, sitz baths, prostate massage and pelvic floor physical therapy may help patients better control the symptoms of CP/CPPS.

After reviewing BPH, PCa and CP/CPPS in Asian men, we conclude that Asians have distinct characteristics compared to the westerners regarding epidemiology, symptomatology and diagnostic methodology of prostate diseases, and urologists in Asian countries face bewildering complexities in their treatment. Additional efforts should be made to study these differences and treatment complexities in order to better manage prostate diseases and promote prostate health in Asian men.

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