Prostate cancer in Asian men

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Abstract | Prostate cancer incidence and mortality in most native Asian populations have gradually increased, but are around one-third lower than in corresponding Asian–American cohorts, which are themselves lower than the rates observed in other American cohorts. Although genetic and environmental factors, particularly a Western diet, could partially explain these differences, lower exposure to PSA screening in Asian individuals might be a major contributing factor. Genetic features and diet are, however, unlikely to differ substantially within the same region of Asia, and age-stratified PSA levels in men from various Asian countries are almost identical; therefore, variation in the epidemiology of prostate cancer among native Asian populations might be attributable to differences in access to PSA testing, urology clinics, and available therapies. Conversely, the proportion of patients with metastatic prostate cancer is substantially higher even in the more developed Asian countries than in migratory Asian populations residing in Western countries and in Westerners. Consequently, the most appropriate approaches to the management of prostate cancer in Asian countries probably also differ, and therefore individualized prostate cancer screening and treatment strategies based on the epidemiological features and socioeconomic status of each country are needed.

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Introduction

Prostate cancer is one of the most common cancers in men, particularly in developed Western countries. Indeed, the global incidence and mortality of prostate cancer in 2008 were estimated to be ~899,000 and 258,000 cases, respectively.[1] Almost all prostate cancers are detected in men aged >50 years, usually asymptomatic patients identified through screening programmes or symptomatic individuals who present to outpatient clinics, and about 70% of deaths due to prostate cancer are observed in the patients ≥75 years old in the USA[2] and Japan.[3] Patients with terminal prostate cancer show considerably decreased quality of life (QoL) for many years before death, owing to the adverse effects of long-term systemic treatments as well as physiological and psychological impairment resulting from progression of local disease and distant metastases. Furthermore, the number of new prostate cancer cases diagnosed annually is predicted to increase to 1,700,000 worldwide by 2030, possibly leading to around 500,000 deaths due to this disease.[1] Thus, effective screening, diagnostic, and treatment strategies are urgently needed to enable early identification of patients with prostate cancer, to prevent progression to advanced metastatic disease and, eventually, death, to maintain the QoL of patients, and to reduce the socioeconomic damage caused by this disease.

These requirements are particularly pertinent to Asian populations, which generally have higher proportions of men with advanced stage prostate cancer compared with Western populations, despite overall reports of prostate cancer incidence being substantially lower in the former. This epidemiological pattern suggest that prostate cancer often goes unnoticed, at least until later stages of the disease, possibly owing to restricted access to screening programmes and urology clinics in Asian countries. Interestingly, the incidence of prostate cancer is typically markedly increased among Asian–American individuals compared with native Asian people; however, the proportion of patients diagnosed with prostate cancer who die as a result of the disease tends to be considerably lower in Western populations than in native Asian populations. These observations again suggest that diagnosis and management of prostate cancer is suboptimal in Asian countries, although genetic and particularly environmental influences might also at least partially underlie these differences.

An overview of the often limited data that have been reported for Asian countries is shown in Figure 1. Importantly, direct evidence that clarifies the correlation between the aforementioned epidemiological features of prostate cancer in Asian populations and genetic variation, lifestyle differences, screening rates, or accessibility to internationally acceptable cancer registries is lacking from the available data. This Review focuses on the epidemiological observations relating to the incidence and mortality of prostate cancer in Asia, and the theoretical considerations that might explain the patterns that are emerging, in particular, those relating to the effects of screening programmes. In this context, the future perspectives for the management of this disease are also discussed.

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Prostate cancer incidence in Asia

The prevalence of different cancer types in Asian men differs among countries and the most common cancers

Key points

- The reported incidence of prostate cancer in native Asians is one-third lower than in Asian–American populations, probably primarily due to lower exposure to PSA screening in Asian countries
- Prostate cancer incidence also differs among native Asians, possibly reflecting variable accessibility to PSA testing and urology clinics as age-stratified median PSA levels are almost identical across several Asian countries
- A trend toward increasing incidence of prostate cancer demonstrated by epidemiological research in Asian countries might be due to gradual implementation of PSA screening and improved biopsy techniques in these regions
- Although the incidence of prostate cancer worldwide varies, the risk of developing prostate cancer might be almost equivalent among populations that have the same baseline levels of PSA
- Appropriate screening strategies and therapies for prostate cancer in Asian countries probably differ from those in Western countries: in Asia, prostate cancers generally demonstrate high likelihood of advanced clinical stage
- Thus, the prostate cancer screening and treatment protocols recommended for use in Asia should be individualized based on the epidemiological features and socioeconomic status of each country

affecting such individuals is mostly unique to each country, or even to regions within the same country (Supplementary Table 1).[4–18] Trends relating to cancer prevalence can be identified within regions of Asia: stomach cancer is most frequent in North-West Asian males (except those in Turkey) and men in Japan and Korea in North-East Asia; lung cancer is most predominant in the majority of southern Asia. Israel, and specifically the Jewish Israeli population, is the only Asian country in which the most frequent cancer in men seems to be that of the prostate. Among the 42 Asian countries or regions within Asian countries for which data are available, prostate cancer was ranked in the top three most frequent cancers, affecting men in 16 (38%). Interestingly, however, prostate cancer was one of the three most common cancers in Asian men immigrated to Hawaii or other regions of the USA, with the exception of Laotians (nine out of 10 populations assessed; 90%). In fact, prostate cancer was the most prevalent form of malignancy in seven of the 10 Asian–American groups analysed. These data, as well as the age-standardized incidence rates (AIRs) observed in these populations (Supplementary Table 1), suggest that prostate cancer incidence in native Asian men is relatively low compared with other cancer types, but is substantially increased in Asians living in Westernized countries.

The annual AIRs of the disease in Asian countries and in Asian immigrant populations in Hawaii, as well as African–American and non-Hispanic white individuals in the USA, based on cases reported over various periods between 1998 and 2009, are shown in Table 1.[4–7,19–29] These data reveal a high incidence of prostate cancer in African–American and non-Hispanic white populations in the USA compared with all populations comprising individuals of Asian descent. Among Asian natives, the incidence rates of prostate cancer were highest in Israel, followed by Cyprus, Singapore, Japan, and the Philippines, which might be considered the most developed and/or Westernized Asian countries. Genetic and/or environmental differences might be major contributors to these disparities in the incidence of prostate cancer between Western populations, Westernized Asian groups, and native Asians. Indeed, a limited number of studies have investigated the impact of a Westernized diet, in particular, on the trend towards the increasing incidence of prostate cancer in Asians. Nevertheless, genetic features and environmental exposures, such as diet, might not differ substantially within the same region in Asia. Of note, therefore, the incidence of prostate cancer in Iraq in 2005 was more than 40-fold lower than the rate observed in Cyprus between 1998–2002, despite the fact that these countries are both located in North-Western Asia. Furthermore, the AIRs of prostate cancer in the North-East Asian countries of Mongolia and Japan differed by over 50-fold in 2004. However, the effect of genetic and environmental factors is complex, and these influences probably vary considerably even between populations that are in close geographical proximity owing to variation in origins and histories, and continued cultural differences; thus, genetic and environmental factors might remain key factors in the huge discrepancies in AIRs of prostate cancer among these countries. In fact, countries that might share greater similarity in cultures and origins (such as Japan and Korea, or Iraq and Iran) generally had similar AIRs of prostate cancer.

Another possible reason for the marked intraregional discrepancies in the incidence of prostate cancer, a disease that predominantly affects individuals aged >50 years, is variation in life expectancy. Indeed, in 2000, the life expectancy at birth among Asian countries was longest in Japan and shortest in Mongolia (78 years versus 60 years; Table 1), potentially explaining the greater prevalence of this disease in the former. Age-standardization can adjust for differences in the life expectancy between countries; however, underlying fundamental health-care policies could be strongly influenced by life expectancies. The priority for prostate cancer screening and subsequent biopsy within the overall national health-care policy might, therefore, be lower in Mongolia than Japan, which could potentially underlie the large difference in the AIRs of prostate cancer in Japan and Mongolia after adjustment according to the age structure of a World Standard Population. The influence of factors other than life expectancy is supported by data from Israel and Qatar, which are also both located in South-West Asia, where life expectancy at birth during the same year was almost identical in at 77 and 78 years, respectively; although the discrepancy in the AIRs of prostate cancer in these two countries was smaller than the difference observed between Japan and Mongolia, the AIRs still differed by about 18-fold (Table 1). Thus, variation in access to PSA screening, physicians, and urology clinics also presents an explanation for the differences in prostate cancer incidence observed between Asian countries.

With regard to the incidence of prostate cancer in Asian–American populations, the prevalence of this disease in Asian immigrants in Hawaii was two-thirds the rate observed in non-Hispanic white individuals

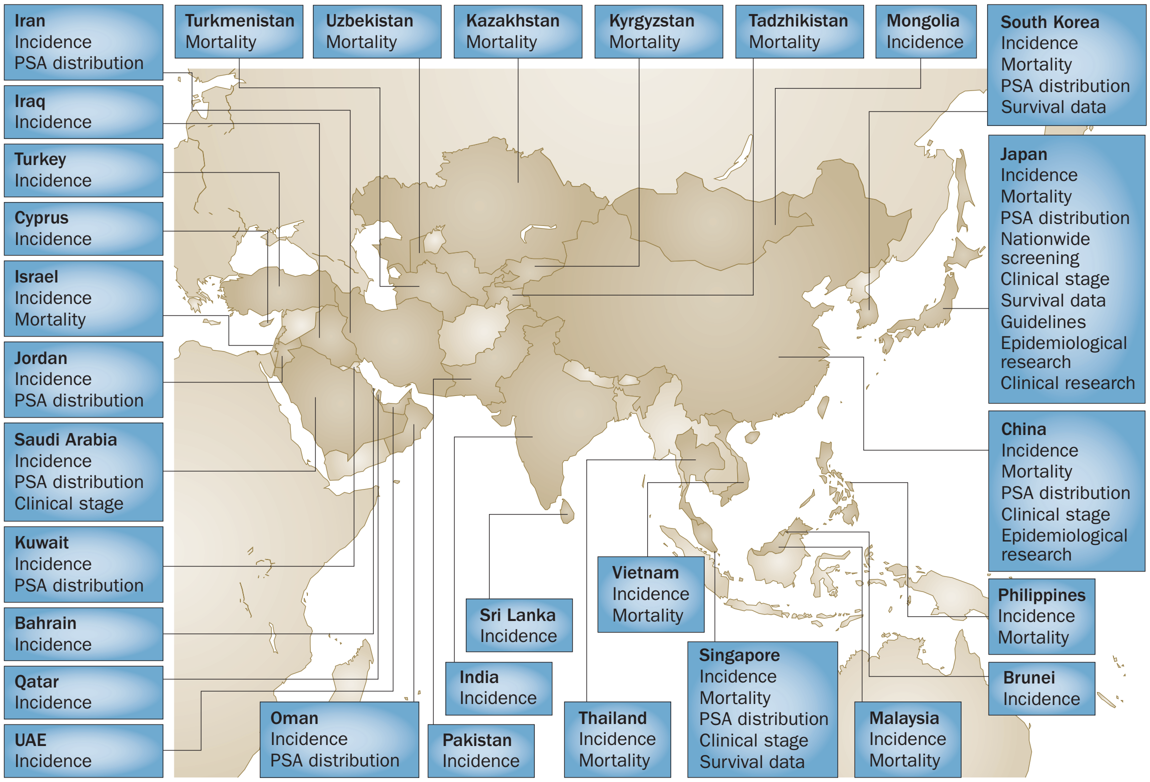

Figure 1 | Established data regarding prostate cancer in Asian countries. As indicated in this schematic, the data available on prostate cancer in many Asian countries are limited to incidence and/or mortality rates; however, additional or more detailed data have been studied in the populations of a few Asian countries, particularly in Japan, but also China, South Korea, and the Philippines. For example, stratification of serum PSA levels detected in population-based or hospital-based screening programmes by age (PSA distribution) has been performed in these countries as well as Iran, Jordan, Kuwait, Oman, and Saudi Arabia. Cancer registry data reporting the distribution of prostate cancer cases according to clinical stage are available in a limited number of Asian populations, as are data on relative, disease-specific, and/or overall survival published in international journals (survival data). In addition, 'Epidemiology research' and 'Clinical research' refers to the existence of head-to-head international cooperative studies in the field of epidemiology or clinical research, respectively, published in international journals. To date, nationwide screening programmes—that is, a large-scale screening database or reports that were declared by international or domestic publishers—and clinical guidelines on prostate cancer published in international journals have only been reported for the Japanese population.

in the USA, but threefold to fivefold higher than the incidence in corresponding native Asian populations (Table 1). However, whether genetic and/or environmental exposures, or access to health-care services underlie these differences remains unclear.

Additional support for the influence of PSA testing on prostate cancer prevalence comes from analyses of the annual percentage change (APC) in the incidence of this disease in nine Asian countries,[21,30] the Chinese administrative region of Hong Kong,[8] and the USA (Figure 2a).[31] Although joint-point analysis of reported prostate cancer incidences reveals no clear trend among Asian countries, the incidence in Japan and Hong Kong increased gradually during the early era of epidemiological investigation in each of these countries, followed by a rapid increase and a subsequent mild increase. The initial gradual change in incidence observed might reflect ageing of the society and, in part, the development of diagnostic procedures, whereas the subsequent rapid increase in the APC in reported cases might predominantly be attributable to the widespread introduction of PSA testing and technical developments in prostate biopsy. Supporting this explanation, a similar pattern was observed in the USA: exposure to PSA screening in the USA has been high since the late 1980s, potentially reflected in a large increase in the APC in prostate cancer incidence between 1988 and 1991, followed by smaller increases or even declines in the APC in the incidence of this disease (Figure 2a). In fact, a large decrease in disease incidence was recorded between 1991 and 1995 in the USA, which might be attributable to the rapid spread of PSA testing in the USA after FDA approval of PSA testing in 1986 for monitoring the progression of prostate cancer in men who had already been diagnosed with the disease and subsequent campaign for PSA screening throughout the country. However, such a large decrease in the AIR of prostate cancer has not been seen in any Asian country, and this difference might correspond to variation in the scale of the introduction of PSA screening or access to clinics offering this test. Indeed, anecdotal evidence suggests that the rates of exposure to PSA screening in most Asian countries are low[32] compared with those in the USA.[33] Together, these findings suggest that variations in PSA screening practices could explain the differences

Table 1 | Prostate cancer incidence and life expectancy in Asian countries stratified by regions

Geographical region	Country or race	Year or era analysed	AIR* of prostate cancer per 100,000 people	Life expectancy in 2000 (WHO)[100]	
				At birth	At age 60 years
South-Central Asia	Pakistan[19]	1998–2002	10.1	63	17
	Sri Lanka[20]	2001–2005	5.7	65	17
	India[21]	2000–2004	4.4	60	15
North-Western Asia	Cyprus[19]	1998–2002	40.8	75	19
	Turkey[4]	2006	22.8	68	17
	Iran[22]	2003–2006	9.6	68	18
	Iraq[23]	2005	1.0	68	17
South-East Asia	Thailand[19]	1998–2002	5.0	65	18
	Vietnam[19]	1998–2002	3.0	70	19
South-West Asia	Israel[21]	2000–2004	53.3	77	21
	Bahrain[24]	1998–2002	14.3	73	17
	Jordan[19]	1998–2002	12.1	71	18
	Oman[24]	1998–2001	10.5	73	19
	Kuwait[24]	1998–2002	10.5	75	19
	United Arab Emirates[25]	2000	4.5	73	18
	Saudi Arabia[24]	2001	3.4	72	18
	Qatar[24]	2006	3.0	78	22
North-East Asia	Japan[5]	2004	26.6	78	22
	Korea[26]	2000–2007	22.4	72	18
	China[21]	2000–2004	12.0	70	17
	Mongolia[27]	2003–2007	0.5	60	14
Peninsular islands of South-East Asia	Singapore[28]	2005–2009	26.7	76	20
	Philippines[21]	2000–2004	24.9	66	17
	Bruneiians[6]	Unknown	18.6	75	19
	Malaysia[19]	1998–2002	7.6	69	16
Hawaii (Asian populations only)	Filipinos[6]	1998–2002	78.0	ND	ND
	Japanese[7]	1998–2002	74.2	ND	ND
	Chinese[7]	1998–2002	69.1	ND	ND
USA (Asian populations only)[18]	Filipinos	1998–2002	121.9	ND	ND
	Japanese	1998–2002	115.0	ND	ND
	Asian Indian or Pakistani	1998–2002	98.4	ND	ND
	Chinese	1998–2002	84.8	ND	ND
	Vietnamese	1998–2002	59.1	ND	ND
	Korean	1998–2002	55.7	ND	ND
	Laotian	1998–2002	30.9	ND	ND
USA (reference populations)[29]	Black	1998–2002	178.8	74	20
	Non-Hispanic white	1998–2002	112.3	74	20

*All data were reported in AIR, which represents the incidence of disease adjusted according to age structure of the WHO 2000 World Standard Population[99] to normalize for variations in the age profiles of the populations that might otherwise confound the data, excluding those data for Oman, which report the crude rate per 100,000 population. Abbreviations: AIR, age-standardized incidence rate; ND, not determined.

in prostate cancer incidence observed among Asian populations; whether widespread introduction of this test would result in similar worldwide prevalence of this disease or whether fundamental differences in the genetic and environment influences underlie a lower predilection for this disease in Asian individuals, precluding rates that reach the levels seen in US populations, remains unclear.

Prognosis of prostate cancer in Asia

The 5-year relative survival rates in Asian patients with prostate cancer in three countries are shown in Table 2, together with the relative survival in the USA, where the PSA-screening rate is high and appropriate treatment strategies are available. In a Korean cohort,[34] relative survival rates in all patients with prostate cancer increased from 55.9% to 82.4% between 1993 and 2007, a finding that might primarily be attributable to a clinical stage shift caused by the introduction of PSA screening in Korea during this 15-year period. Likewise, in a cohort study comprising Singapore Chinese individuals,[35] 5-year relative survival rates in patients diagnosed with non-metastatic prostate cancer improved from around 50% to 76% between 1973 and 1992; however the 5-year survival plateaued at this level over the next decade and remained considerably lower compared with the rates of regional and localized prostate cancer derived from Japanese[36] and US cohorts,[2] which ranged between 95–100% (Table 2). Furthermore, 5-year survival in Singapore Chinese patients with metastatic cancer fluctuated considerably between 1973 and 2002,[35] but were generally comparable to those observed in US[2] and Japanese populations.[36]

In comparison with this US cohort,[2] the 5-year relative survival rate in patients with regional prostate cancer was slightly lower in the Japanese population,[36] comprising cases recorded in a large-scale database of population-based cancer registries during a similar era. By contrast, survival among patients with metastatic prostate cancer

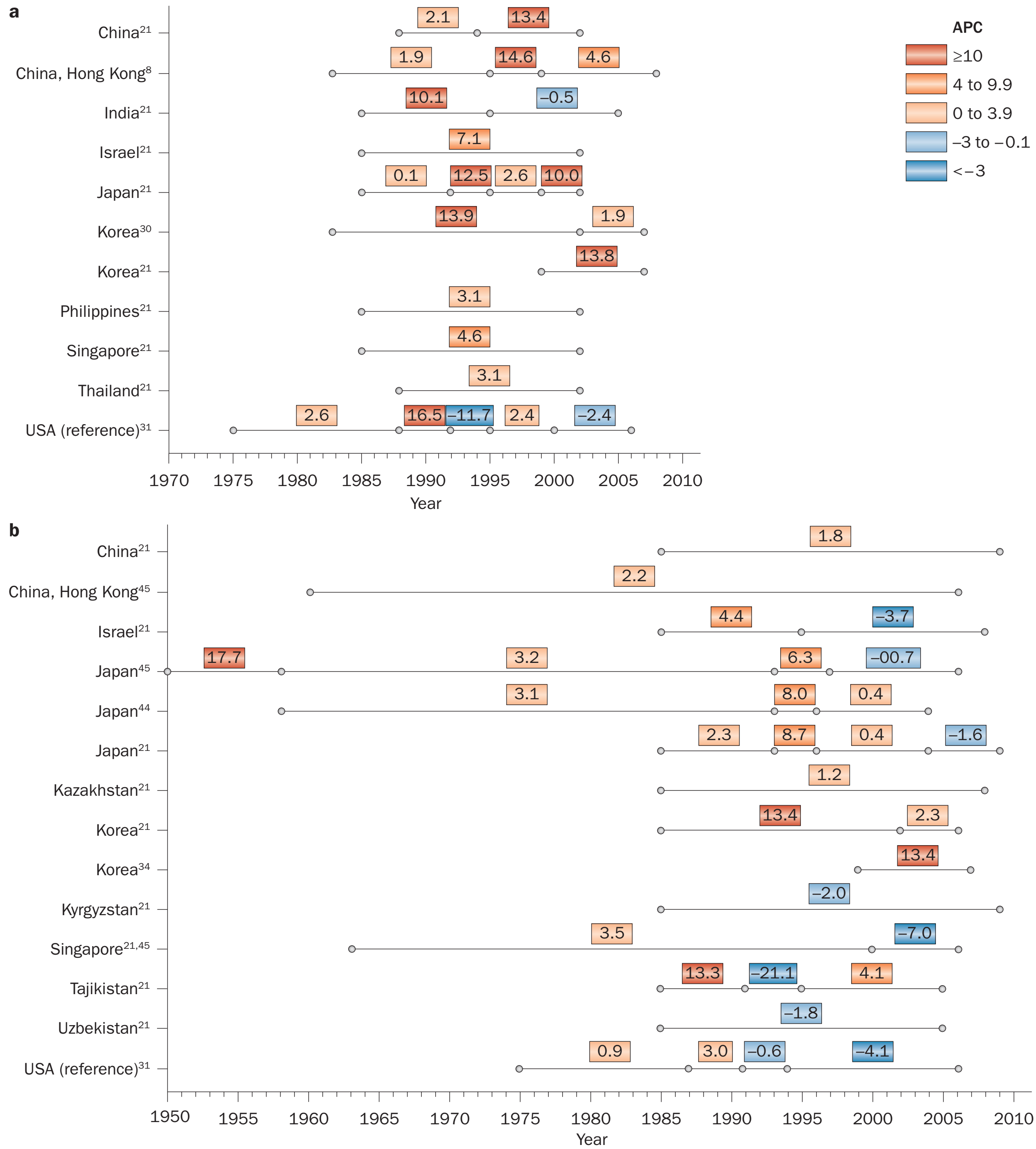

Figure 2 | Changes in prostate cancer incidence and mortality over time in Asian countries. **a** | The APCs in the incidence of prostate cancer over time are shown for nine Asian countries, as well as the Chinese region of Hong Kong. The variation in the annual incidence of prostate cancer in the USA is also shown for comparison. Gradual increases in the APC in prostate cancer incidence might reflect ageing of the society and, in part, the development of diagnostic procedures, whereas a rapid increase and subsequent rapid decrease in the APC in prostate cancer incidence, as shown in the USA, might predominantly be attributable to the widespread introduction of PSA testing and technical developments in prostate biopsy. Thus, variations in the APC in prostate cancer incidence, and potentially mortality, might be influenced by improved screening and/or management of the disease. **b** | The APCs in mortality due to prostate cancer in nine Asian countries and one region of China (Hong Kong) are shown, together with the figures for a reference population (USA). Considerably different APCs have been reported over similar periods for some populations, even within the same ethnic groups, mainly because eras between the joint-points varied among these studies. Abbreviation: APC, annual percentage change.

was substantially higher in the Japanese cohort than in the US cohort (45.2% versus 29.4%).[2,36] The difference in the survival rates among metastatic cases might reflect variations in the clinicopathological features of the tumours, as cancers that showed rapid progression during the screening interval were included in the metastatic cases in the US cohort.[2] In fact, the percentage of metastatic prostate cancer in the US cohort was 4.2%, compared with 12.5% in the Japanese cohort. This finding suggests that most cancers are detected before metastasis in the USA, with the remaining cases potentially representing those with a more aggressive

Table 2 | 5-year survival rates in populations of Asian men with prostate cancer

Study population stratified by clinical stage and/or era	Number of patients	5-year survival rates (%)*
Korean patients (all cases)[34]		
1993–1995	ND	55.9
1996–2000	ND	67.2
2001–2005	ND	78.6
2003–2007	ND	82.4
Singapore–Chinese patients[35]		
Nonmetastatic cancer; 1973–1977	40	51.3
Nonmetastatic cancer; 1978–1982	61	47.7
Nonmetastatic cancer; 1983–1987	82	55.7
Nonmetastatic cancer; 1988–1992	146	76.5
Nonmetastatic cancer; 1993–1997	306	76.3
Nonmetastatic cancer; 1998–2002	518	76.1
Metastatic cancer; 1973–1977	22	11.1
Metastatic cancer; 1978–1982	24	49.7
Metastatic cancer; 1983–1987	41	16.9
Metastatic cancer; 1988–1992	95	43.0
Metastatic cancer; 1993–1997	147	23.4
Metastatic cancer; 1998–2002	180	33.7
Japanese patients		
Localized cancer; 2003–2005[36]	6,204	100
Regional cancer; 2003–2005[36]	1,667	94.8
Metastatic cancer; 2003–2005[36]	1,520	45.2
Unknown stage; 2003–2005[36]	2,809	ND
M0; 2004[38]	8,746	OS: 93.3; DSS: 98.4
M1a; 2004[38]	39	OS: 56.5; DSS: 64.2
M1b; 2004[38]	1,090	OS: 61.8; DSS: 66.7
M1c; 2004[38]	66	OS: 51.9; DSS: 56.8
Mx; 2004[38]	339	OS: 91.0; DSS: 98.8
US patients[2] *(reference population)*		
Localized cancer; 1999–2007	325,810	100
Regional cancer; 1999–2007	46,331	100
Metastatic cancer; 1999–2007	16,990	29.4
Unknown stage; 1999–2007	13,613	73.1

*Relative survival rates are indicated unless otherwise stated. Abbreviations: DSS, disease-specific survival; ND, not determined; OS, overall survival.

phenotype that progress very rapidly, potentially between screening intervals. A second possible explanation for the lower survival rate observed in the US population is ethnic variation in the clinical outcome after hormonal therapy between Japanese and American individuals. Only one head-to-head comparative study has investigated the effectiveness of hormonal therapy in Japanese–American and white individuals resident in Hawaii.[37] Both overall and disease-specific survival rates were considerably higher in Japanese–American patients compared with white patients, despite similar background clinicopathological features.[37] Indeed, ethnicity was identified as an important prognostic factor after multivariate analysis.[37]

The overall and disease-specific survival rates in patients with prostate cancer recorded in the Japanese Urological Association (JUA) nationwide cancer registry in 2004[38] are also shown in Table 2. The frequency of metastatic prostate cancer in this population (M1a, M1b, and M1c) was 11.6%, and 5-year survival rates in non-metastatic and metastatic cases were excellent compared with those that have been recorded in developed Western countries.[2] Together, these data suggest that treatment of prostate cancer in Japan, and possibly Singapore, is comparable with, or even superior to, that observed in the USA, although improved screening might lead to further improvements in the identification of prostate cancer before metastasis occurs.

Prostate cancer mortality in Asia

The age-standardized mortality rate (AMR) of prostate cancer is high in Caribbean countries, the USA and Northern Europe, with AMRs per 100,000 individuals of 53.6 in Trinidad and Tobago, 34.3 among African–American individuals in the USA, 22.8 in Cuba, and 21.3 in Norway reported in 2012.[21] By contrast, the prostate cancer mortality rate in Asia as a whole was low, with an AMR of 3.1.[1,21] Figure 3 shows the AMRs for prostate cancer in Asia, stratified by region and in various Asian countries for which data have been published.[21,28,30,39–41] Regional differences in prostate cancer mortality rates are evident, with the highest AMR (7.5 deaths per 100,000 individuals) in Western Asia and the lowest (2.5 deaths per 100,000 individuals) in Eastern Asia.[1,21] Among Asian countries, the highest mortality rates due to prostate cancer were 9.1, 6.1, and 5.4 per 100,000 individuals in Israel, Kazakhstan, and Japan, respectively.[21] Conversely, the prostate cancer mortality rate in Thailand was extremely low, at 0.3 per 100,000 individuals,[40] although this country also had a low rate of prostate cancer incidence (AIR = 5.0 per 100,000 individuals in the years between 1998 and 2002; Table 1).[19]

As for the variation observed in incidence rates of prostate cancer, the difference in prostate cancer mortality in Asian countries might reflect differences in genetic features, dietary habits, and/or delays in the diagnosis of detectable prostate cancer. In addition, insufficient clinical management of prostate cancer and a lack of reliable official death certificates might be of particular relevance to the reported prostate cancer mortality rates in developing countries. These varied and complex influences complicate the identification of the factors underlying the racial and national differences in prostate cancer mortality. However, analysis of the mortality rate to incidence ratios (AMR:AIR ratios) could add insight into the effects of developments in PSA screening and subsequent access to appropriate treatments. Figure 4 shows the AMR:AIR ratio of prostate cancer in seven Asian countries;[42] data from five Asian–American groups and the non-Hispanic white population living in California, USA,[43] where availability of PSA testing and subsequent treatment is widespread, were also included in Figure 4 as reference populations. Although the mortality and incidence of prostate cancer in Asian–American populations

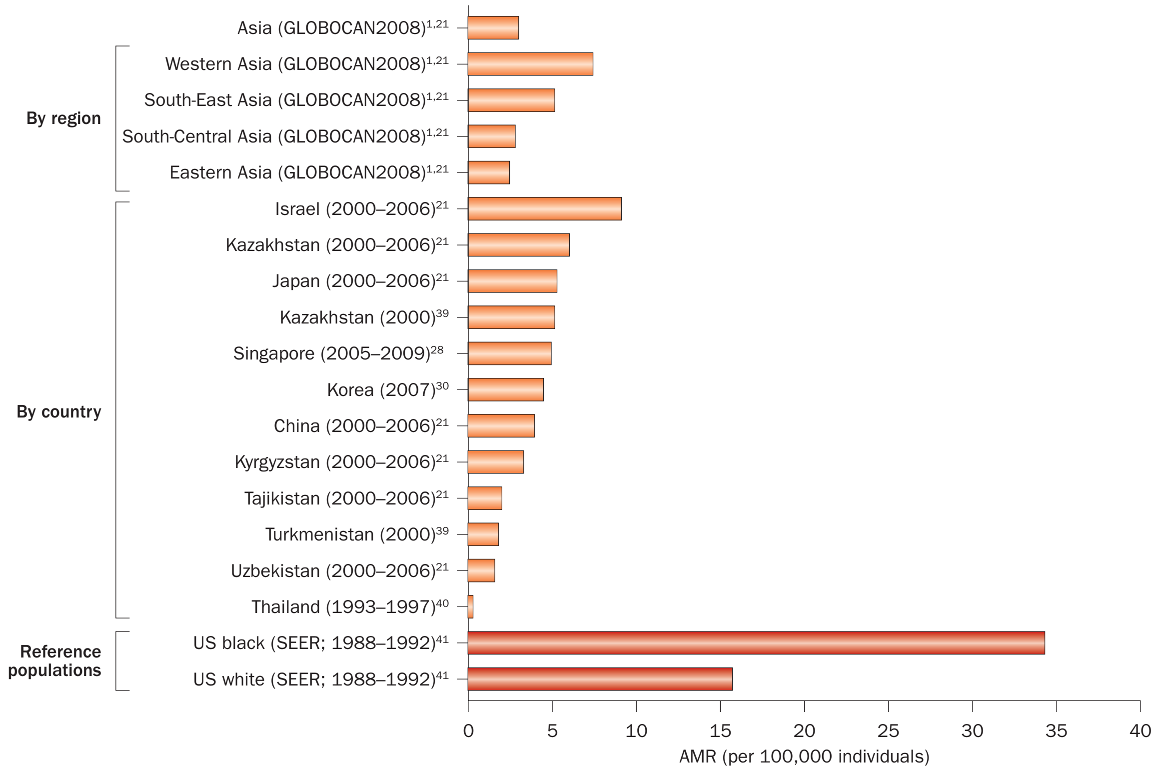

Figure 3 | Prostate cancer mortality in Asian regions and countries. The annual mortality rates—adjusted according to the age structure of the WHO 2000 World Standard Population[99] to correct for variations in the age profiles of the populations that might otherwise confound the data—among the populations of various regions or countries of Asia for which data are available are shown. These data clearly indicate that prostate cancer mortality is lower in all Asian geographical areas than reference populations from the USA. Abbreviation: AMR, age-standardized mortality rate.

were about one-third lower than those in non-Hispanic white individuals, the AMR:AIR ratios in the Californian populations of various ethnicities were all low and almost identical at 0.11–0.17.[43] In fact, this ratio was typically lower in Asian–American cohorts compared with white populations.[43] Asian countries could be divided into the following two groups: generally well-developed countries in which the AMR:AIR ratio was relatively low (0.18–0.22; Korea, Singapore, and Japan), indicating disease-specific survival rates comparable to those in US populations; and typically less well-developed nations, in which this ratio was high (0.42–0.63; China, Philippines, Vietnam, and Malaysia), suggesting poor survival compared with US populations.[42] The substantially lower absolute incidence and mortality rates, but high AMR:AIR ratio, in native Chinese and Filipinos compared with those reported in Chinese–Americans and Filipino–Americans resident in California might reflect large differences in the rate of PSA testing and access to appropriate treatment between these countries, although differences in the reliability of the cancer registry and death certificate systems might also contribute to these findings. Interestingly, the AIRs of prostate cancer in the Asian countries with high AMR:AIR ratios were generally more than two-fold lower than those observed in Korea, Singapore, and Japan. These observations again suggest that better access to screening leads to identification of more patients, but at earlier stages of disease, and/or that availability of treatment is greater in the developed Asian countries. Nevertheless, screening and/or reporting might remain suboptimal in Asian countries with low AMR:AIR ratios, as indicated by the large increases in the AIR of prostate cancer in Asian individuals originally from these countries resident in California compared with the corresponding native Asian populations; however, caution is needed in drawing such a conclusion considering the potential for genetic admixture and particularly the possible influence of Western environmental factors on the risk of this disease.

A joint-point analysis of changes in prostate cancer mortality rates in Asian countries and the USA are shown in Figure 2b.[21,31,34,44,45] Analysis of the APC in prostate cancer mortality over time reveals that Israel and Singapore had a high positive APC in deaths due to this disease before 1995 and 2000, respectively, but a relatively high negative APC in the years following this period.[21,45] A similar pattern was observed in the USA before and after 1994.[31] Japan had a relatively high positive APC in prostate cancer mortality during the early period of investigation and a relatively low or steady APC during the most recent period for which data is available.[21,44,45] The remaining Asian countries—with the exception of reports from Korea and Tajikistan, which demonstrated skewed changes in APC in prostate cancer mortality—experienced either a gradual increase or decrease in mortality rates throughout the period of investigation. These trends in Asian countries might provide insight into the potential influence of advances in screening or treatment

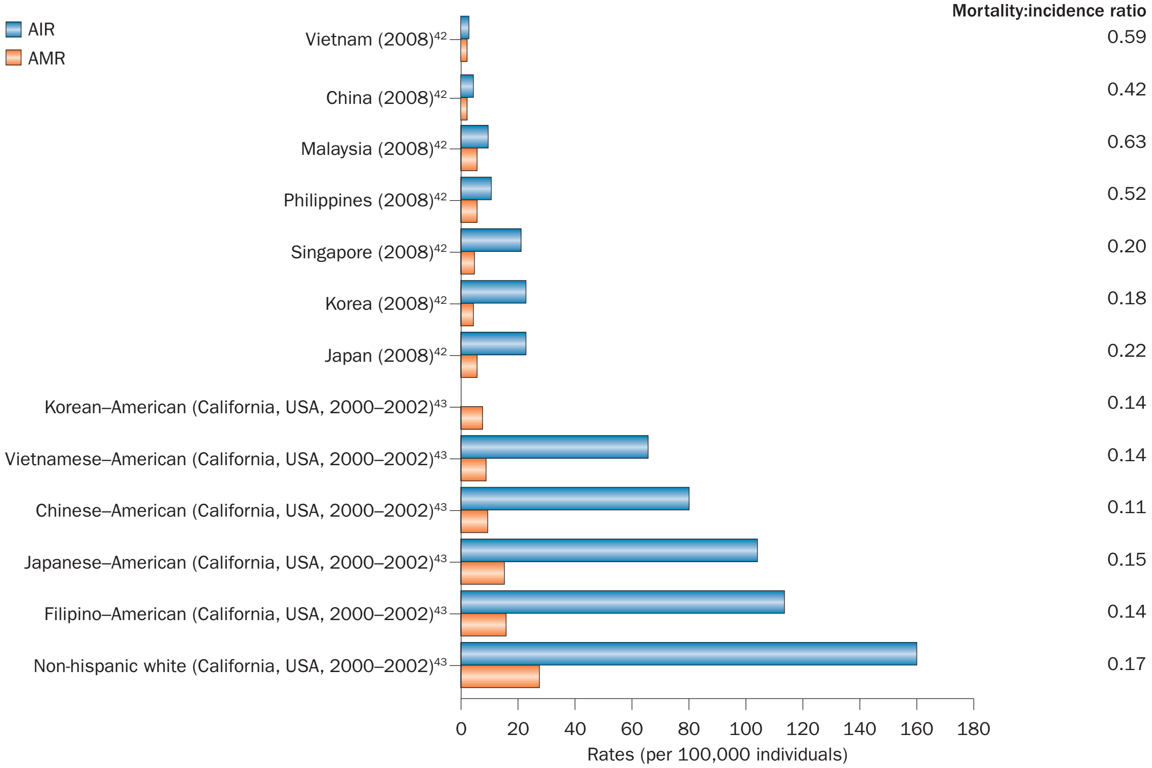

Figure 4 | Mortality rate to incidence rate ratio of prostate cancer in Asian and Asian–American populations. The annual incidence and mortality rates of prostate cancer (AIRs and AMRs, respectively), adjusted according to the age structure of the WHO 2000 World Standard Population[99] to correct for variations in the age profiles of the populations that might otherwise confound the data, are shown for seven Asian countries and five Asian–American populations, together with the ratios between the AMRs and AIRs for these populations. Asian countries could be divided into relatively low (0.18–0.22) and high (0.42–0.63) AMR:AIR ratio groups, which might reflect differences in access to screening and/or availability of appropriate treatment in Asian countries. Whereas the incidence of prostate cancer is generally markedly higher in Asian individuals in the USA compared with those of the same ethnicity who live in Asian countries, the mortality ratio is typically lower in Asian–American populations, and is similar to the ratio observed in the US non-Hispanic white reference population. Furthermore, the incidence of prostate cancer in Asian–American cohorts remains reduced compared with the rate reported for the non-Hispanic white population. Nevertheless, screening might remain suboptimal even in Asian countries with a low AMR:AIR ratio compared with corresponding Asian–American residents in California; however, drawing such a conclusion might be confounded by the potential for genetic admixture and the possible influence of Western environmental factors on the risk of prostate cancer. Abbreviations: AIR, age-standardized incidence rate; AMR, age-standardized mortality rate.

on mortality rates. As the countries with changes from high APCs to negative or stable APCs seem to be those with lower AMR:AIR ratios (Singapore, Japan, and presumably Israel), improved screening (resulting in detection of disease at early stages) and/or management of the disease could conceivably underlie these temporal changes in mortality. However, whether these factors underlie the observations described remains to be formally established.

Latent prostate cancer in Asian groups

The prevalence of latent prostate cancer generally increases with age and is estimated to be 13.0–26.5% in native Japanese men, Japanese men immigrated to Hawaii, and Colombian, white, and African–American individuals in the USA aged ≥50 years.[46–49] Epidemiological surveys have demonstrated less variation in the prevalence of latent prostate cancer among Asian, European, and American individuals compared with differences in the incidence of clinically manifested prostate cancer between these regions. A head-to-head comparison of the frequency of latent prostate cancer in African–American, white, Colombian, and Japanese people living in Hawaii, and a native Japanese population has been conducted using a uniform reference methodology for tissue handling and a standardized pathological evaluation protocol.[46] After adjusting for differences in the age distribution of these populations, the prevalence of latent prostate cancer was 36.9%, 34.6%, 31.5%, and 25.6% in African–American, white, Colombian, and Japanese populations living in Hawaii, respectively, and 20.5% in the native Japanese cohort.[46] When latent prostate cancer was classified into the latent invasive type (LIT) and latent noninvasive type (LNT), the prevalence of LNT prostate cancer did not differ considerably among the five populations;[46] however, the frequency of LIT tumours was markedly lower in native Japanese men compared with African–American, white, and Colombian groups, and slightly lower compared with the prevalence in the Hawaiian–Japanese individuals.[46] No direct evidence supports a link between LIT prostate cancer and clinical disease. However, the pathological differences in the prevalence of LIT disease among these ethnic groups could conceivably be closely related to the differences in the incidence of clinically detectable prostate cancer demonstrated by epidemiological surveys. Therefore, this finding suggests that Asian individuals could have a lower susceptibility to clinical prostate cancer, which in turn further supports the involvement of differential genetic or environmental factors, such as diet, in determining the observed rates of prostate cancer across ethnic groups.

Risk factors for prostate cancer

Basic science and epidemiological studies have demonstrated that ethnicity, diet, ageing, and genetic factors all have roles in the initiation, development, and progression of prostate cancer.[41,50–53] Therefore, differences in the prevalence of prostate cancer among African–American, white, and Asian individuals living in the USA (that is, men who are all typically exposed to a Western diet and who have almost identical access to screening) are probably primarily due to genetic factors associated with race or ethnicity.[50] Although the reported incidence of prostate cancer is increased in Asian–American populations compared with corresponding native Asian populations, whether due to increased screening, increased longevity, and/or the effects of a Western diet, the rates generally remain lower than in other ethnic groups within the USA (Figure 4; Table 1). Although remaining cultural differences due to incomplete integration might explain this observation, decreased genetic susceptibility in Asian individuals might also be a contributing factor. Indeed, genetic susceptibility factors for development of prostate cancer are known to exist, as familial aggregation accounts for 20–26% of cases and hereditary occurrence is evident for 5–10% of all clinically detectable prostate cancers.[51]

Genetic factors in prostate cancer in Asians

Only one epidemiological study has examined the prevalence of hereditary or familial prostate cancer in Asian individuals using reliable data from a regional cancer registry in Japan (death certificate only [DCO] rate <10%).[54] This study identified hereditary and familial forms of diseases using the criteria for hereditary and familial prostate carcinoma.[52] These criteria proposed that classification of hereditary carcinoma requires clustering of three or more affected relatives within a nuclear family (for example, father and two sons), two relatives affected at an early age (<55 years), or the occurrence of prostate carcinoma in each of three generations in either the paternal or maternal lineage (paternal grandfather, father, and son, for instance).[52] The criteria also proposed that classification of familial carcinoma requires at least two relatives affected by prostate carcinoma, in individuals who did meet the criteria for hereditary carcinoma.[52] According to these criteria, only 1.1% and 3.6% of 11,664 patients with prostate cancer were classified as having hereditary and familial forms of the disease, respectively.[54] This prevalence of hereditary forms of prostate cancer in Asians is considerably lower than the frequency in Western countries,[51] supporting the differential involvement of underlying inherited genetic susceptibility factors between ethnic groups. Genetic polymorphisms with low penetrance are generally considered to have an important influence on the diversity observed between individuals. Thus, genetic factors with low penetrance, including mutations in the androgen receptor[55] and 3-oxo-5-α-steroid 4-dehydrogenase 2 encoding genes,[56] as well as several known genetic polymorphisms,[57,58] might also contribute to the differences in prostate cancer incidence in different populations. In addition, the presence of equol-producing intestinal bacteria and extrinsic factors, including diet and socioeconomic status, might explain such variation in disease prevalence.

On the basis of a genome-wide linkage study in Japanese nuclear families identified through a reliable regional cancer registry, the region with the best available evidence of linkage was found on chromosome 8p23 in proximity to the linkage marker D8S550, and the second best available evidence of linkage was observed on chromosome 1p36 near the marker D1S2667.[59] Interestingly, the role of the gene located at the linkage marker D8S550, *FDFT1*, has been investigated in familial prostate cancer, revealing an association between the A allele of the single nucleotide polymorphism (SNP) rs2645429, a common variant in the promoter region of this gene, and disease risk in Japanese individuals.[60] This variant of rs2645429 was linked to increased expression of *FDFT1,*[60] which encodes the enzyme squalene synthase that has known roles in cholesterol and steroid metabolism. Furthermore, knockdown of *FDFT1* expression or inhibition of squalene synthase led to substantial decreases in the proliferation of prostate cancer cells *in vitro*.[60] Importantly, human prostate cancer specimens, particularly those from aggressive cancers, were shown to express markedly higher levels of *FDFT1* mRNA compared with noncancerous tissues.[60] Therefore, *FDFT1*-encoded squalene synthase might have an important role in the development of prostate cancer and characterize tumours with aggressive phenotypes in Asian populations.

With regard to a relationship between the risk of developing high-grade prostate cancer and genetic factors, previous epidemiological studies have demonstrated no difference in the clinical aggressiveness of prostate cancer among hereditary, familial, and sporadic cases in Asia.[54] However, limited evidence has suggested associations between germline mutations in *RNASEL* and high-grade prostate cancer in patients with hereditary prostate cancer (HPC-1).[61–63] In addition, two genetic risk factors for familial prostate cancer and aggressive disease have been identified within the 8q24 chromosomal region in Asian individuals.[64] Specifically, the –12 allele of the microsatellite marker DG8S737 and the A allele of the SNP rs1447295 were positively associated only with familial prostate cancer risk in a Japanese study in 134 patients with familial prostate cancer and 158 sporadic prostate cancer cases.[49] Both markers analysed were also associated with higher-grade cancers (Gleason score ≥7).[64]

Diet and prostate cancer in Asian populations

Most studies of the relationships between diet and prostate cancer have originated from Western countries. In particular, a systematic review of the associations between diet and cancer, published by the World Cancer Research Fund and the American Institute for Cancer Research in 2007,[53] demonstrated that foods containing lycopene or selenium, and purified selenium supplements, which have antioxidant effects, probably decrease the risk of prostate cancer, whereas pulses (legumes) and foods containing vitamin E or the related α-tocopherol might also have a limited role in preventing prostate cancer. The authors also reported that ingesting high levels of calcium probably increases the risk of prostate cancer, and that processed meat, milk, and dairy products might have at least a partial role in the development of prostate cancer.[53] As the effects of long-term dietary exposures and underlying genetic susceptibility on the risk of prostate cancer might differ between ethnic groups, an original study to investigate the potential protective effects of an Asian diet and the converse role of a Western diet should be conducted in Asian individuals. Although well-designed prospective or informative retrospective studies investigating this aspect are limited at present, particularly in Asian populations, the impact of isoflavones, soybeans, tofu, and green tea on the development of prostate cancer in such individuals has been investigated.

A meta-analysis of data from three prospective cohort studies and one case–control study in Japanese individuals, two case–control studies in Chinese cohorts, and one prospective cohort study in an American population found that Asian individuals who consumed green tea more frequently had a decreased risk of developing prostate cancer compared with Asian people who consumed green tea less frequently (OR 0.62; 95% CI 0.39–1.01).[65] However, no relationship with the risk of developing prostate cancer was observed in the American cohort who had ever consumed green tea compared with the population who had never consumed green tea (OR 1.47; 95% CI 0.99–2.19). In the seven studies analysed, the levels of exposure to green tea in the high-exposure groups varied from 'ever' to >10 cups per day, and consumption of green tea also varied in the low-exposure groups from 'never' to ≤1 cup per day. Thus, the observed influence of green tea in Asian and Western populations have limitations and, therefore, the effect of this dietary factor remains uncertain.

The effect of soy consumption on the development of prostate cancer has also been analysed in a meta-analysis that included eight studies on isoflavone consumption, eight studies on consumption of nonfermented soy foods, and six studies on consumption of fermented soy foods, which were conducted in the USA, European countries, China, and Japan.[66] The eight studies investigating an influence of isoflavone consumption on prostate cancer risk yielded a combined RR/OR of 0.88 (95% CI 0.76–1.02; $P=0.09$). However, according to meta-analyses of data stratified by ethnicity, the three studies in Asian populations reveal a significant RR/OR of 0.52 (95% CI 0.34–0.81; $P=0.01$) for the effect of isoflavone consumption.[66] On the other hand, the combined RR/OR based on the three studies in European and US populations was 0.99 (95% CI 0.85–1.16; $P=0.91$),[66] suggesting no significant effect of isoflavones on prostate cancer risk. Analysis of the six studies on the influence of consumption of fermented soy foods on prostate cancer, which included four studies in native Japanese individuals, one study in native Chinese men, and one study in Japanese–Americans living in the USA, reveal a combined RR/OR of 1.02 (95% CI 0.73–1.42; $P=0.92$).[66] However, the eight studies of the influence of consumption of nonfermented soy foods, which included five studies in native Japanese or Chinese populations, one study in Japanese–American individuals living in the USA, and two studies in multiple ethnic groups living in the USA or Canada, showed a significant RR/OR of 0.70 (95% CI 0.56–0.88; $P=0.01$).[66] These results suggest that consuming nonfermented, but not fermented, soy is associated with a reduced prostate cancer risk regardless of ethnicity. Isoflavone intake might also reduce the risk of developing prostate cancer, but only in Asian populations, who generally consume larger quantities of isoflavones than Western populations.

The influence of isoflavones on prostate cancer incidence in Asian individuals has also been investigated in a well-designed large-scale nested case–control study by the Japanese Public Health Centre (JPHC).[67] This study demonstrated that plasma levels of the isoflavone genistein tended to be inversely associated with the overall risk of prostate cancer, and plasma levels of equol—an isoflavandiol metabolite of the isoflavone daidzein—in the highest tertile were closely associated with a decreased total risk of prostate cancer.[67] Both of these inverse associations were strengthened in the subgroup of patients with localized prostate cancer. Indeed, the odds ratios for the risk of developing localized prostate cancer in the individuals with the highest tertile plasma genistein and equol concentrations compared with those with the lowest tertile levels of these compounds were 0.54 and 0.43, respectively. Thus, isoflavones seem to have a role in preventing the development of localized prostate cancer in Asian populations.

PSA-based screening in Asian cohorts

Temporal trends in PSA levels

Analysis of changes in PSA levels in Japan

Epidemiological surveys have demonstrated that the incidence of prostate cancer has increased in most Asian countries (Figure 2a). However, determination of the true incidence of detectable subclinical or clinical prostate cancer in Asia is difficult because of the low reliability of the cancer registry system and the inadequate availability of PSA screening in many Asian countries. Thus, the key influences underlying the trend towards increasing incidence of prostate cancer in Asian countries remain unknown. Several studies have demonstrated that baseline PSA levels could be an important objective factor predictive of prostate cancer development.[68–70] Thus, increasing PSA level among the male population of Asia, whatever the aetiological determinant, could explain the

Table 3 | Cumulative rate of freedom from PSA increases to >4 ng/ml over 4 years based on baseline PSA levels

Serum PSA concentration at initial screening (ng/ml)	Proportion of the population without increases in serum PSA levels to >4 ng/ml (%)			
	Dutch population (ERSPC Rotterdam cohort)[68]	Japanese population (Gunma Prefecture cohort)[68]	US black population[69]	US white population[69]
0.0–0.9	99.4	99.6	100	100
1.0–1.9	96.6	96.6	98.8	98.1
2.0–2.9	76.2	74.6	87.6	83.2
3.0–3.9	43.0	46.8	55.3	48.4

Abbreviation: ERSPC, European Randomized Study of Screening for Prostate Cancer.

trend in prostate cancer observed over the past three decades. Data addressing this possibility come from a study by Ohi and colleagues,[71] who conducted a unique retrospective longitudinal study investigating changes in the baseline PSA distribution in 32,274 Japanese men aged 50–79 years who were screened for the first time between 1988 and 2003. Linear regression analyses to calculate log10 PSA stratified by calendar year showed that the baseline PSA levels within each age group did not change during the 16-year period investigated. Therefore, using PSA levels as the key predictor of prostate cancer, the risk of developing the disease in 1988 might have been almost identical to that in 2003. Thus, the increasing trend in the incidence of prostate cancer demonstrated by epidemiological research in Asian countries does not seem to be due to a shift towards increased baseline PSA levels. If increased exposure to a Westernized diet had affected the true incidence of prostate cancer in Asian individuals, the slope of the linear regression analysis curve plotting age versus log10 PSA would have been steeper, suggesting that this factor is not a major determinant of the incidence of prostate cancer in Asian populations. Hence, this finding implicates the gradual spread of PSA-based screening and improved biopsy techniques in the increasing incidence observed in Asia.

Race and PSA increases from baseline levels

That ethnicity is a key factor in stratifying the risk of developing prostate cancer is clear, but more universal and objective predictive factors are desirable in the clinical setting. Two head-to-head comparative studies[68,69] have investigated the risk of development of prostate cancer if serum PSA levels increase above 4 ng/ml in different ethnic groups, stratified by baseline PSA levels. Table 3 shows the cumulative rates of freedom from PSA increases to levels >4 ng/ml during 4 years of observation in Japanese, Dutch, African–American, and American white men, stratified by baseline PSA levels. The proportion of individuals without PSA levels >4 ng/ml after 4 years of observation was not markedly different between populations, considering individuals with baseline PSA levels within the same range (Table 3). Indeed, the Japanese and Dutch populations had a similar degree of progression to PSA concentrations >4 ng/ml,[68] and the proportion of individuals surpassing this threshold was almost identical in the African–American and US white populations.[69] Although the data come from different studies,[68,69] which limits direct comparison, the proportion of the population who remained free of PSA levels >4 ng/ml was generally higher in the US populations (Table 3). Differences in the incidence of prostate cancer worldwide clearly exist; however, the cumulative probability of developing prostate cancer markedly increases with increasing baseline PSA levels independent of ethnicity, and the risk of developing prostate cancer might be almost equivalent among any populations that have similar baseline levels of PSA.

PSA distribution among Asian populations

Reports of PSA-based screening for prostate cancer in several Asian countries are available; however, conducting an objective comparison of screening results among these countries, particularly in terms of prostate cancer detection rate, might be problematic because adjusting for differences in the age distribution of the screened populations, the PSA cut-offs used, biopsy compliance, and the diagnostic accuracy of a prostate biopsy could be difficult. Nevertheless, comparison of PSA distributions stratified by age range in men among Asian countries who participated in domestic screening programmes could prove informative,[72–82] as PSA could be an objective predictive marker of the probability of present or future prostate cancer.[68,83] Analysis of the data from these screening programmes (Table 4) reveals that median PSA levels in the same age groups vary less than the incidence of prostate cancer reported in epidemiological surveys among the corresponding Asian countries (Table 1).

Of the countries in Asia, a nationwide review of PSA-based screening is available only for Japan, in the form of a Japanese Foundation for Prostate Research survey of prostate cancer screening between 2001 and 2005.[84] Of 1,719 municipalities in Japan, 252 (15%) participated in the survey and 249 (14%) provided completed data from screening to cancer detection;[84] 455,443 men were screened during the 5-year survey period, with 19.4%, 22.8%, and 20.5% aged 60–64, 65–69, and 70–74 years, respectively.[84] The percentage of men with serum PSA levels >4 ng/ml was 7.3% (33,363 of 455,443), and the percentages of men with PSA levels of ≤1 ng/ml and ≤2 ng/ml were 51.3% and 78.1%, respectively.[84] Most participating municipalities recommend a PSA threshold for biopsy of 4.0 ng/ml, and some recommend age-range-specific PSA cut-offs for biopsy of 3.0, 3.5, and 4.0 ng/ml for those aged <65, 65–69, and ≥70 years, respectively.[84] In total, the percentage of men who were recommended to proceed with a prostate biopsy was 8.0% (36,565 of

Table 4 | Racial differences in the median serum PSA levels in Asian men in screening studies*

Ethnicity and country	Era	Number of participants	Median serum PSA concentration (ng/ml) stratified by patient age			
			40–49 years	50–59 years	60–69 years	70–79 years
Chinese, China[72,73]	1999–2001 2001–2008	1,096 11,150	0.54 0.87	0.82 0.92	0.93 1.15	1.17 1.39
Chinese, Singapore[74]	2004	3,179	0.70	0.80	1.20	1.40
Indian, Singapore[74]	2004	84	0.80	0.90	1.20	1.80
Iranian, Iran[75]	2005–2007	900	NA	0.75	1.06	1.46
Japanese, Japan[76]	1990–1992	286	0.60	0.70	0.90	1.40
Korean, Korea[77,78]	1995–1997 1997–1998	5,805 8,966	0.80 0.89	0.90 0.96	1.00 1.22	1.30 1.25
Malay, Singapore[74]	2004	102	0.50	0.60	1.50	1.90
Singaporean, Singapore[79]	1992–1995	695	0.77	0.92	1.00	2.00
Jordanian, Jordan[80]	1993–2001	1,852	40–44 years: 1.54 45–49 years: 1.78	50–54 years: 1.30 55–59 years: 2.00	NA	NA

*Published data on PSA distribution in populations from Saudi Arabia,[81] Kuwait,[82] and Oman[82] were also available, but data on median PSA levels were not presented. Abbreviation: NA, not available.

455,443).[84] Of the men with PSA values above the cut-offs for biopsy, 34.5% (12,633 of 36,565) were actually biopsied.[84] The prostate cancer detection rate was 1.11% in all screened men and 40.0% in the biopsied men, and cancer was localized in 77% of the patients identified, locally advanced in 17%, and metastatic in 6%.[84] A Gleason score of ≤6 was observed most frequently, at 42%, followed by Gleason score 7 in 36%, and Gleason score 8–10 in 22% of patients.[84] These data suggest that the biopsy compliance in the nationwide Japanese cohort was low at around 35%. This large survey in Japan might be a reference for other Asian countries where screening for prostate cancer has not spread. Furthermore, comparing this prostate cancer screening effort with those in other countries or populations will be scientifically important.

PSA screening—associations with clinical stage

At present, only a limited number of surveys of prostate cancer clinical stage distribution in Asian populations are available. Several small-scale hospital-based registries or screening studies reporting the percentage metastases among prostate cancer cases in China,[85–89] Japan,[38,90–92] and Saudi Arabia[81] have been published. Table 5 shows the percentage of patients with distant metastases in these three Asian countries. The percentage of patients with prostate cancer with metastatic disease was 26.1–76.6% in China.[85–89] Data from a Japanese hospital-based registry showed that the percentage of metastatic prostate cancer among all recorded cases of the disease decreased from 56% to 26% between 1975 and 2002.[91] Furthermore, a large nationwide survey carried out by the JUA demonstrated that the percentage of metastatic prostate cancer among cases of the disease decreases from 21.3% in 2000[90] to 11.6% in 2004.[38] Together, these findings suggest that screening in Japan has improved in the past decades, resulting in earlier detection and prevention of metastatic disease, whereas this might not have occurred in China. Over this period, ageing of the population and/or Westernization might have increased the prostate cancer incidence in China, potentially explaining the trend towards increase metastatic disease in this country.

Only one Japanese study has compared the clinical stage distribution among patients diagnosed with prostate cancer in population-based screening programmes, either during the pre-PSA-screening era (1981–1991) or after PSA testing became available (1992–1996), or in outpatient urology clinics over the same period.[92] The percentage of metastatic prostate cancer was highest (58.7%) in patients diagnosed in outpatient clinics during the 1981–1991 era (Table 5), followed by 46.8% in those diagnosed in outpatient clinics between 1992 and 1996, 23.4% in those diagnosed in the earlier screening programme based on prostatic acid phosphatase levels and/or digital rectal examination, and was lowest (10.6%) in patients diagnosed by PSA-based screening.[92] In addition, an inverse relationship was found between population-based PSA-screening rates in the community and the percentage of prostate cancer cases that were metastatic in an assessment of a Japanese regional cancer registry.[93] Interestingly, the proportion of metastatic prostate cancer among all reported cases of the disease was 11% in municipalities where the exposure to PSA screening during the 10-year survey was >50%. This incidence of metastatic cancer was high compared with the rates reported in Asian–American individuals in the USA, which was only 3.1% based on data from a hospital-based registry in Washington DC,[94] despite the fact that native Japanese men might also consume larger amounts of foodstuffs associated with protection from prostate cancer, including nonfermented soy, and have less exposure to Westernized foods than Asian–American individuals. Together, these findings suggest that the introduction of PSA screening to Asia, specifically Japan, has resulted in detection of prostate cancer at early clinical stages of the disease; however, the lower proportion of metastatic cancers in Asian populations in the USA might indicate that screening rates in Japan could still be improved.

Table 5 | Proportion of patients with metastatic prostate cancer in Asian cohorts

Population	Number of patients	Proportion of patients with distant metastases (%)
Hospital-based registries		
Chinese/Taiwanese 1944–1997[85]	633	32.4
Chinese 2000–2004[88]	431	30.9
Chinese 2003–2005[86]	408	43.6*
Chinese 2005–2007[87]	90	76.6*
Japanese 1975–1988[91]	182	56*
Japanese 1988–1997[91]	301	37*
Japanese 1998–2002[91]	642	26*
Asian–Americans (Washington DC) 1989–2007[94]	583	3.1
Screening programme databases		
Chinese (era unknown)[89]	69	26.1*
Saudi Arabian 2008[81]	52	26.9*
Japanese Gunma regional cancer registry (DCO <10%) 1981–1991[92]	Screening-programme-detected‡ cases: 128 OPC-detected cases§: 312	Screening-programme-detected‡ cases: 23.4* OPC-detected cases§: 58.7*
Japanese Gunma regional cancer registry (DCO <10%) 1992–1996[92]	Screening-programme-detected‖ cases: 151 OPC-detected cases§: 312	Screening-programme-detected‖ cases: 10.6* OPC-detected cases§: 46.8*
Municipalities in Gunma Prefecture, Japan,[93] stratified by exposure to PSA testing¶		
<5% population coverage	ND	35
5–10% population coverage	ND	26
10–15% population coverage	ND	27
15–20% population coverage	ND	28
20–30% population coverage	ND	24
30–40% population coverage	ND	22
40–50% population coverage	ND	16
>50% population coverage	ND	11
National registries		
JUA nationwide hospital-based registry[90]	4,529	21.3
JUA nationwide hospital-based registry[38]	10,280	11.6

*Study population included patients with N stage and M0 stage cancers. ‡Screening programme was based on DRE and analysis of PAP levels. §Patients were identified in OPCs, outside of the screening programme. ‖Screening programme was based on PSA testing. ¶Population exposure rates of PSA screening were estimated by dividing the number of men who underwent PSA testing at least once between 1992 and 2001 (total of 4,072 individuals) as part of the population-based screening programme provided by each municipality in Gunma Prefecture, Japan, by the number of male inhabitants aged ≥50 years living in each corresponding municipality. Abbreviations: DCO, death certificate only; DRE, digital rectal examination; JUA, Japanese Urological Association; ND, not disclosed; OPC, out-patient clinic; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen.

Guidelines on PSA-based screening in Asia

In Asia, guidelines on prostate cancer screening that have been approved by a national urological association and published in an international journal are available only in Japan, at present. Indeed, the Committee for Establishment of the Guidelines on Screening for Prostate Cancer and the JUA published updated guidelines for prostate cancer screening in 2010.[95] Therein, the JUA recognized that the rate of prostate cancer PSA-based screening in Japan is low compared with uptake in the USA and Western Europe.[95] Furthermore, the prostate cancer mortality rate in Japan is expected to increase in the future; projections suggest that in 2020 mortality will be 2.8-fold higher than the rate observed in 2000.[3] Therefore, identification of the best available therapeutic approach to decreasing the number of deaths due to prostate cancer is an urgent requirement. PSA screening can reduce the risk of death due to prostate cancer,[96,97] and accordingly the JUA considers that this assessment should be offered to all men at risk of developing prostate cancer using up-to-date, comprehensible, and well-balanced brochures showing the benefits and drawbacks of prostate cancer screening. No official guidelines on screening for prostate cancer are available for Asian countries, except Japan. Priorities for the management for prostate cancer, socioeconomic status, penetration of PSA screening, and epidemiological features of prostate cancer might all be different between Asian and developed Western countries. Therefore, the development of general guidelines for prostate cancer screening in Asian individuals by specific Asian urological organizations, such as the Urological Association of Asia (UAA), or by a specific committee within International Urological Associations, such as the Société Internationale d'Urologie (SIU), is an urgent primary unmet need. Subsequently, revised domestic guidelines for use in each Asian country should be developed by individual urological associations or *ad hoc* committees based on these official Asian guidelines.

Ongoing studies of screening in Japan

The low rate of screening for prostate cancer in Asia could be of benefit to studies investigating the effect of screening programmes, in terms of minimizing contamination in the control cohort. The ongoing Japanese Prospective Cohort Study of Screening for Prostate Cancer (JPSPC),[98] is a cluster prospective cohort study that was initiated in 2002 to assess the effectiveness of prostate cancer screening using mortality rate as the primary end point. Various municipalities within the Hokkaido, Gunma, Hiroshima, and Nagasaki Prefectures form the screening and control cohorts. The screening group comprises around 100,000 men aged 50–79 years, who have been exposed to a yearly campaign aimed at increasing prostate cancer screening to an expected exposure rate >60% during the 5-year campaign. The control cohort includes well-matched male populations, in which prostate cancer screening has not been actively promoted.

The JPSPC has been conducted successfully, with high compliance with PSA testing protocols in the screening cohorts and relatively low uptake of the PSA test in the control cohorts.[98] The cancer registry for prostate cancer cases diagnosed between 2002 and 2010, both in the screening and control cohorts, will be completed by the end of 2014. To investigate clinicopathological features of prostate cancer before the widespread introduction of PSA screening, the study protocol also includes retrospective cancer registration between 1997 and 2001. The first analysis of changes in the incidence of metastatic prostate cancer over the total 14-year study period will be carried out in 2015. The results of this study are eagerly anticipated and could add clarification as to whether, and to what extent, differences in prostate cancer screening practices explain the variation in prostate cancer incidence and mortality observed worldwide.

Conclusions

The overall incidence of, and mortality from, prostate cancer in Asian countries are lower than the rates observed in cohorts of migratory Asians in Western countries, and considerably lower than those in native Western individuals. Although genetic factors and dietary issues might, to some extent, underlie these findings, the influence of such factors is unlikely to differ substantially within defined regions of Asia. Furthermore, age-stratified PSA levels are generally comparable between populations, suggesting they have similar susceptibility to prostate cancer. Thus, other factors probably contribute to the variation in the incidence of prostate cancer and mortality associated with this disease among Asian countries. For example, differences in life expectancy or exposure to PSA screening and access to urology clinics could potentially explain the marked discrepancies recorded. However, variations in life expectancies do not seem to be directly associated with prostate cancer incidence, except in a limited number of countries where the relatively short lifespans observed might influence approaches to screening and treatment of prostate cancer (Table 1), and no data showing a direct correlation between increased rate of screening and an increased incidence of prostate cancer are available. Additional studies are therefore needed to clarify these relationships.

According to data derived from cancer registries, the clinicopathological features of prostate cancer in Asian countries are more advanced and include a greater proportion of metastatic cancers compared with cases in developed Western countries. These findings suggest that the clinical stage of disease at detection varies geographically, supporting the theory that access to screening is inadequate in Asian countries, although differences in the aetiology of the disease might also partially underlie these observations. Nevertheless, at present, the appropriate approaches to the therapeutic management of prostate cancer in Asian countries are likely to be different from those used in Western countries. Thus, recommendations for prostate cancer screening and treatment strategies are urgently needed in Asia and should be based on the epidemiological features and socioeconomic status in each country.

Review criteria

PubMed was searched for English-language papers, and the websites of the Japan Medical Abstracts Society and the Japanese Foundation for Prostate Research were searched for Japanese-language literature relevant to this comprehensive Review. To identify relevant epidemiological data, we independently searched the PubMed database for article published since its inception in 1961 to May 2013 using the terms “prostate cancer”, “prostate”, “incidence”, “mortality”, “Asia”, “China”, “Japan”, “Korea”, and “statistics” in various combinations. Information on other aspects of prostate cancer in Asian individuals were identified in PubMed using the search terms “prostate”, “prostate cancer”, “PSA screening”, “diet”, “hereditary prostate cancer”, “familial prostate cancer”, “risk factor”, “survival”, “guideline”, “Asia”, “China”, “Japan”, and “Korea” in various combinations. Relevant studies were also selected from the reference lists of the publications identified and information from the websites indicated above.

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