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Changing demography of prostate cancer in Asia

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Abstract

There has been a recent trend in Asia towards increasing incidence of prostate cancer, with some low-risk regions, such as Japan and Singapore, reporting a more rapid increase than high-risk countries. In this study, age-specific and age-standardised (world) incidence rates and mortality rates for prostate cancer in Asian countries for 1978–1997 were retrieved and compared. The results confirm that the incidence of prostate cancer has risen by 5–118% in the indexed Asian countries. Incidence at centres in Japan rose as much as 102% (Miyagi 6.3–12.7 per 100,000 person-years) whilst the incidence in Singaporean Chinese increased 118% from 6.6 to 14.4 per 100,000 person-years. The lowest incidence rate recorded was in Shanghai, China and the highest rates were in Rizal Province in the Philippines, although still much lower than those in the United States of America (USA) and many European countries. Whilst the absolute value of the increase is not comparable to North American and European populations, the incidence ratio in many Asian centres is similar to that of the high-risk countries. The mortality data for prostate cancer showed a similar rising trend. The increases in age-adjusted mortality rates per 100,000 person-years, adjusted to the world standard, ranged from 50% in Thailand to 260% in Korea. The difference may be partly due to genetic polymorphism in the androgen receptor and androgen metabolism pathway enzymes as well as to dietary or environmental factors. In particular, phytochemicals, such as isoflavonoids and tea polyphenols, which are common in Asian diets showed promising anti-mitotic activity in animal and clinical studies. In conclusion, with gradual Westernisation, many Asian countries may be losing their cultural protective factors and acquiring high-risk ones. A better understanding of how these factors interact to cause prostate cancer through further studies with a multi-ethnic perspective will facilitate appropriate public health strategies to minimise high-risk factors and maintain protective factors and keep prostate cancer at bay.

Keywords: Incidence rate; Mortality rate; Asian; Prostate cancer; Risk factor; Association; Epidemiology; Aetiology

1. Introduction

Prostate cancer remains one of the most common cancers afflicting men today. It is the third most common cancer in the world and the most frequently diagnosed male cancer in the United States of America (USA), with a world age-standardised rate of 104 per 100,000 [1]. Prostate cancer rates are highest in Western countries and lowest in Asian countries. With ageing populations and increasing use of prostate-specific antigen (PSA) screening, the incidence of prostate cancer in the high-risk countries has risen sharply in the past decade [2–4]. In Asia, however, the incidence of prostate cancer is significantly lower and it often plays second fiddle to lung, stomach and colon cancer. It is thus revealing that recent data from Asia have shown a general trend towards increasing incidence of prostate cancer, with some low-risk regions, such as Japan and Singapore, reporting a more rapid increase than some high-risk countries [5]. Understanding the genetic and environmental basis for this difference and the changing demographics of Asian prostate cancer has emerged as an important field of

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study. Several epidemiological studies involving multidisciplinary and multi-centre collaboration to investigate suspected environmental factors for prostate cancer are ongoing. This review critically examines available data regarding changing epidemiological trends in Asian prostate cancer and discusses the possible reasons behind these trends.

2. Material and methods

Age-specific and age-standardised (world) incidence rates per 100,000 man-years for prostate cancer over a 20-year period (1978–1997) in Asian countries were retrieved from the four volumes (V–VIII) of *Cancer Incidence in Five Continents*, published by the International Agency for Research on Cancer (IARC), covering the periods 1978–1982, 1983–1987, 1988–1992 and 1993–1997 [6–9]. These data were derived from contributions from various cancer registries over the years. The criteria for selection of data from these centres included availability of 5-year data from all four volumes of IARC publications, large number of cases for analysis and high percentage of histological verification.

Mortality rates for prostate cancer from Asian countries during the period 1978–1997 were obtained from the World Health Organisation (WHO) mortality data bank via their website [10].

The selected countries were ranked according to the incidence and mortality rates during the periods 1978–1982 and 1993–1997, respectively, and the rate of change was calculated from the 1993–1997 figures relative to the 1978–1982 figures.

Our search strategy included MEDLINE, the Cochrane Cancer Database and the Cochrane Database of Systematic Reviews. We used the key words 'prostate cancer', 'Asian', 'epidemiology' and 'risk factor' to look for clues to the epidemiological differences between Western and Asian populations.

3. Results

3.1. Changing demographics – is it for real?

National and regional cancer registries are pivotal in providing an in-depth look at the epidemiological map of prostate cancer across Asia. The number of cases of prostate cancer reported in the listed Asian countries ranged from 24–558 during 1978–1982 to 146–1654 during 1993–1997. Age-standardised incidence rates per 100,000 man-years for prostate cancer from Asian countries over a 20-year period from 1978 to 1997 confirmed that the incidence of prostate cancer has risen 5–118% in most of the indexed Asian countries (Table 1).

Incidence at centres in Japan rose as much as 102% (Miyagi 6.3–12.7 per 100,000 person-years) whilst the incidence in Singaporean Chinese surged 118% from 6.6 to 14.4 per 100,000 person-years. The lowest incidence rate was in Shanghai, China and the highest rate was found in Rizal Province in the Philippines, although this rate is still much lower than the incidence in the USA and many European countries. Whilst the absolute value of the increase is not comparable to North American and European populations, the percentage change in incidence rates (incidence ratio) in many Asian centres is quite similar to the high-risk countries. The rising incidence trend is shown in Fig. 1. The age-specific incidence rates correlate well with age both during 1978–1982 and 1993–1997, with exponential increases in incidence rates beyond the age of 55 years (Figs. 2 and 3).

The mortality data for prostate cancer show a similarly rising trend (Table 2). The number of reported deaths from prostate cancer ranged from 99–1894 during 1978–1982 to 99–8819 during 1993–1997. The increases in age-adjusted mortality rates per 100,000 person-years, adjusted to the world standard, ranged from 50% in Thailand to 260% in Korea. Unfortunately, complete mortality data on prostate cancer were not

Table 1
Age-adjusted incidence rates of prostate cancer in seven Asian countries

Country	1978–1982			1993–1997			% change[a]
	Cases (*n*)	Incidence[b]	Rank	Cases (*n*)	Incidence	Rank	
Philippines, Rizal	230	11.1	1	662	16.6	1	49.5
Singapore, Chinese	179	6.6	4	717	14.4	2	118.2
Japan, Miyagi	277	6.7	3	1274	14.1	3	110.4
China, Hong Kong	558	6.2	5	1654	8.6	4	38.7
India, Mumbai	414	8.2	2	960	7.4	5	10.8
Thailand, Chiang Mai	60	4.0[c]	6	146	4.2	6	5.0
China, Shanghai	265	1.8	7	940	3.0	7	66.7

Data for 1988–1992.
[a] Percentage change from 1978–1982 to 1993–1997.
[b] Per 100,000 person-years, age-adjusted using the world standard.
[c] Data for 1983–1987.

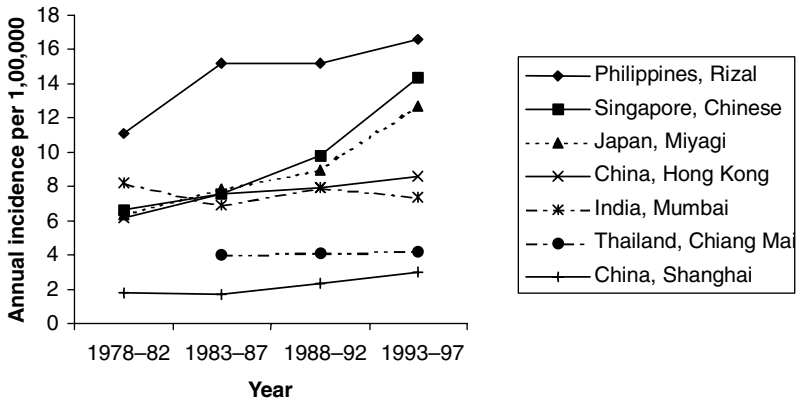

Fig. 1. Incidence rate of prostate cancer over time in seven selected Asian regions.

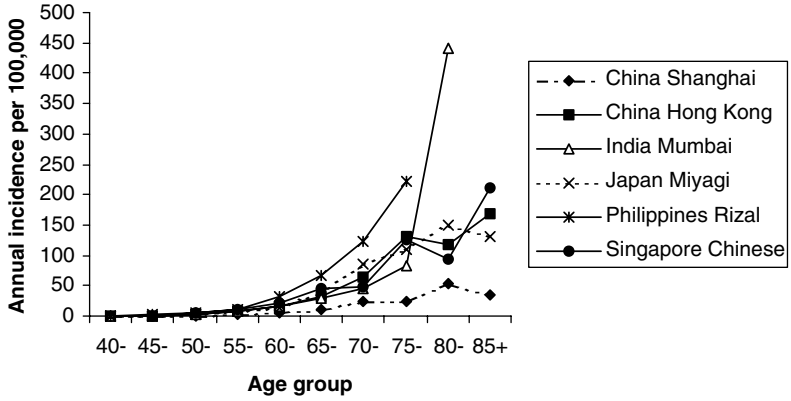

Fig. 2. Annual incidence rate of prostate cancer by age group in six Asian centres between 1978 and 1982. Data were not available from Thailand.

available from India, Indonesia and China, three of the largest Asian countries. The trend in prostate cancer mortality is illustrated in Fig. 4.

The apparent dramatic increases in incidence rates need to be analysed in the context of several possible confounding factors. The denominator for the incidence and mortality rates is the study population and this is dependent on the accuracy and comprehensiveness of the population census. In certain areas, such as parts of India, China, Indonesia or the Philippines, obtaining an accurate population census is a challenging task. In other areas, such as Hong Kong and Singapore, migration patterns may dilute or increase the incidence rates of the native population. In some countries, cancer notification is voluntary or by administrative order and year-to-year changes can vary due to differences in reporting patterns. In addition, there can be startling differences in incidence rates between different provinces

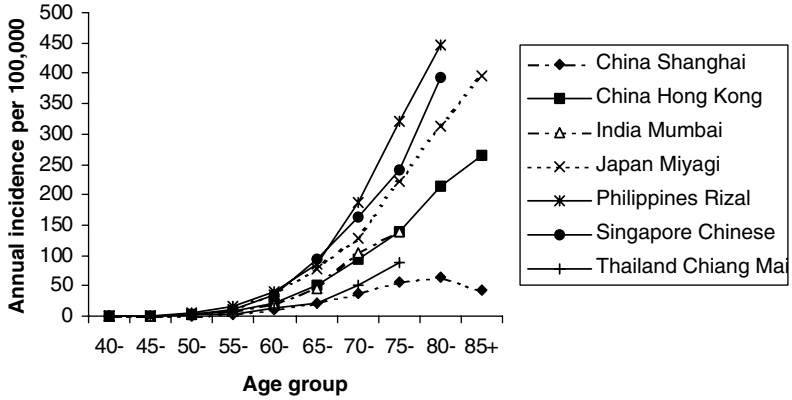

Fig. 3. Annual incidence rate of prostate cancer by age group in seven Asian centres between 1993 and 1997.

Table 2
Age-adjusted mortality rates of prostate cancer in five Asian countries

Country	1978–1982			1993–1997			% change[a]
	Cases (*n*)	Incidence[b]	Rank	Cases (*n*)	Incidence	Rank	
Singapore	99	1.9	3	353	5.2	1	173.7
Japan	8819	2.4	1	26651	4.8	2	100.0
China, Hong Kong	208	2.1	2	522	3.6	3	71.4
Korea	148[c]	0.5	4	1267	1.8	4	260.0
Thailand	105	0.2	5	55	0.3	5	50.0

[a] Percentage change from 1978–1982 to 1993–1997.
[b] Per 100,000 person-years, age-adjusted using the world standard.
[c] Data for 1983–1987.

and between rural and urban populations within the same country. A prime example would be China, where the difference can be up to 7.8 times between Hong Kong and Qidong County (Table 3).

3.2. Raison d'être for the surge in incidence of prostate cancer

3.2.1. Ageing population

Age is a well-known risk factor for prostate cancer. With increasing sophistication of medical care and better nutrition, more Asians have longer life expectancy. More men therefore live long enough for prostate cancer to be diagnosed. The age-specific incidence curve in Fig. 2 clearly shows an exponential increase in prostate cancer incidence rates after 55 years of age.

3.2.2. Diagnostic intensity and screening bias

Availability of serum PSA as a rapid and convenient outpatient screening test may have contributed to the apparent increase in incidence of prostate cancer in the late 1980s and early 1990s. Screening programmes, prostate cancer awareness programmes, media attention and testimonies from celebrity patients have increased public awareness and attention to prostate cancer and led to increased screening and detection of clinically asymptomatic cancers. In the USA, data from the Surveillance, Epidemiology and End Results (SEER) programme showed that the prostate cancer incidence rates for white men doubled between 1983–1987 and 1993–1997, during the period when PSA screening was introduced [11]. In Asian countries, the availability of transrectal ultrasound and extended systematic biopsies in the late 1990s increased the number of cancers detected, from a positive predictive value (PPV) of 8.9% with sextant biopsies in the early 1990s to between 24.6% and 29.3% with 10-core biopsies in 1999–2002 [12–14].

3.2.3. Genetic polymorphism

Prostate cell division is influenced by the actions of steroid hormones, namely testosterone, dihydrotestosterone and vitamin D, mediated through the prostate cell androgen receptor (AR) and vitamin D receptor, respectively. The *androgen receptor gene* is located in the Xq11.2-q12 chromosome and consists of eight exons. In particular, exon 1, which codes for the ligand-independent AF-1 domain, is well studied with regards to prostate cancer risk [15].

Exon 1 contains a polymorphic CAG repeat sequence, which ranges normally from 8 to 30 repeats and averages about 20 [16]. This CAG repeat sequence encodes a polyglutamine chain in the region of the AR associated with DNA transcription. Men with exceptionally long CAG repeat lengths experience clinical androgen insensitivity because of reduced transcriptional activity of the AR. Irvine proposed that men with

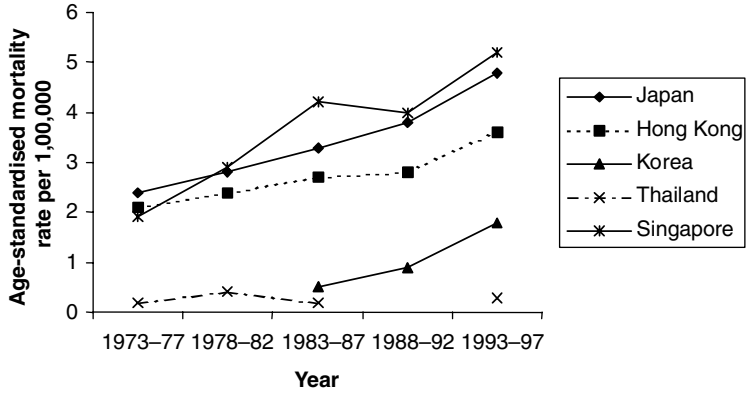

Fig. 4. Mortality rate of prostate cancer over time in five selected Asian regions. The mortality rates for India and China were not available.

Table 3
Age-adjusted incidence rates of prostate cancer in China

Region	Cases (*n*)	Incidence[a]
Hong Kong	1654	8.6
Shanghai	940	3.0
Beijing	266	2.9
Tianjin	224	2.0
Wuhan	178	2.0
Jiashan	16	1.9
Qidong County	33	1.1

[a] Per 100,000 person-years, age-adjusted using the world standard.

shorter repeat lengths are therefore at a higher risk of prostate cancer [17]. Data from 587 men in the Physician's Health Study suggest that men with CAG repeat lengths less than or equal to 18 were at particularly high risk of higher grade and advanced stage of prostate cancer at diagnosis, and metastasis and mortality from the disease [18]. Sartor and colleagues [19] showed that CAG repeat length varies with different ethnic groups; African–Americans have the highest incidence of prostate cancer but a shorter median CAG repeat length of 19, whilst non-Hispanic white men have a longer median CAG repeat lengths of 21. In a study of 190 Chinese men with prostate cancer, the median CAG repeat length was 23. Chinese men with CAG repeat lengths shorter than 23 had a 65% increased risk of prostate cancer [20]. This was further confirmed by an analysis of 116 Chinese men in northern China, which showed that the frequency of CAG repeats greater than or equal to 22 was higher in the Chinese population (80.4%) compared with American white men (52.1%) and African–American men (25%) [21]. However, several other studies showed no difference in CAG repeat lengths between Chinese and Caucasian men [22,23].

Vitamin D modulates prostate cancer growth via the vitamin D receptor (VDR). Several studies on *VDR gene* polymorphism have shed conflicting results, with some researchers in Taiwan and Japan showing higher risks with vitamin D *Bsm*I genotype [24,25] and others showing no difference with *Bsm*I, *Apa*I, *Taq*I, or *Fok*I genotypes [26–31]. As vitamin D increases insulin-like growth factor binding protein (IGFBP1) levels, Chokkalingam and colleagues [32] postulated that vitamin D and IGF regulatory systems might work together to influence prostate cancer risks.

Other gene variants involved in androgen biosynthesis have also been studied in relation to prostate cancer risks. The *CYP17* gene, which encodes for the enzyme P450c17 that catalyses the conversion of progesterone and pregnenolone into precursors of potent androgens, was postulated to affect prostate cancer risk. The A2/A2 allele, which contains a T-to-C polymorphism in the 5′ promoter region that creates a Sp1-type (CCACC box) promoter site, was shown to occur in higher frequencies than the A1/A2 and A1/A1 alleles in Caucasians with prostate cancer (70%) than in controls (57%) [33]. This finding was supported by results from other authors [34,35]. In Asian populations, Yamada and colleagues [36] found that the A2 allele conferred a higher risk of prostate cancer, but Habuchi and colleagues [37] found that the A1 allele posed a higher risk. Madigan and colleagues [38], however, found no difference in prostate cancer risks in Shanghainese patients in China with the CYP17 genotype. This was supported by a similar study in Taiwan by Lin and colleagues [39].

The *SRD5A2* gene encodes for the steroid 5α-reductase II, which is involved in the conversion of testosterone to dihydrotestosterone (DHT), the active metabolite associated with androgen activity that leads to prostate cell division and prostate cancer. Four types of polymorphism have been documented: A49T (a substitution of threonine for alanine at codon 49), V89L (a substitution of leucine for valine at codon 89), R227Q (a substitution of glutamine for arginine at codon 227), and a (TA)n dinucleotide repeat. The V89L leucine (L) allele, which involves substitution of valine with leucine at codon 89, was found to be associated with lower DHT levels and lower prostate cancer risk than the valine (V) allele. In a nested, matched, case-control study involving 320 Caucasian men without prostate cancer who underwent prostate biopsy, Nam and colleagues [40] found that the adjusted odds ratio for having prostate cancer for patients with at least one V allele was 2.53 compared with patients with the L/L genotype. Hsing and colleagues [41] showed, in a study involving 191 Chinese men, that the frequency of the lower risk L/L allele was higher at 35% compared with 10% in the high-risk Caucasian population in Nam and colleagues's study. However, Febbo and colleagues [42] found no association between V89L polymorphism with prostate cancer risk. The higher frequency of lower risk L/L allele may thus be a contributing factor to the lower prostate cancer risks in Asians, but direct comparison studies may be needed.

3.2.4. Hormonal factors

Androgens play an important role in normal prostate growth and function. Testosterone diffuses into prostate cells where 90% is irreversibly converted by 5-reductase to the more active metabolite DHT. Both testosterone and DHT bind to androgen receptors in the cytoplasm and the androgen–androgen receptor complex then initiates DNA transcriptional activity and prostate cell division [43]. The pivotal role that androgens play in normal prostate growth also extends to the progression of prostate cancer, where remission is induced by surgical castration, as shown by Huggins and Hodges [44]. However, the influence of androgens on the risk of development of prostate cancer is more controversial.

Many studies have attempted to link prostate cancer risk with high levels of circulating serum androgen, including free and total testosterone, DHT, sex-hor-

mone binding globulin (SHBG), 3α-androstanediol glucuronide (AAG), androsterone glucuronide, oestradiol and 5α-reductase. In assays of circulating steroid hormone levels in healthy white and black college students in Los Angeles, CA, USA, Ross and colleagues [45] pointed out that African–Americans had a 15% higher total testosterone level and a 13% higher free testosterone level. This 15% difference in circulating testosterone levels could readily explain a 2-fold difference in prostate cancer risk between these two ethnic groups. However, when they assayed serum testosterone concentrations in young adult Japanese men with those of young adult whites and blacks, they found no significant differences. Nevertheless, they noted that these white and black men had significantly higher values of AAG and androsterone glucuronide than Japanese subjects. As these androgens are downstream products of 5α-reductase activity, there was a suggestion that reduced 5α-reductase activity may have resulted in the lower prostate cancer incidence rates among Japanese subjects [46]. Wu and colleagues [47] found that the DHT:testosterone ratio was highest in African–Americans, intermediate in whites and lowest in Asian–Americans, corresponding to the respective incidence rates in these groups and providing indirect evidence for ethnic differences in 5α-reductase enzyme activity.

Subsequent longitudinal, population-based case-control studies on androgen levels and prostate cancer risks using pre-diagnostic sera yielded conflicting results. Gann and colleagues [48] analysed sera obtained from the Physicians' Health Study and demonstrated that high levels of circulating testosterone and low SHBG, but not DHT and AAG, were associated with increased risks of prostate cancer. Demark-Wahnefried and colleagues [49] showed that high free testosterone levels but not total testosterone, SHBG, AAG or DHT: testosterone levels were associated with prostate cancer risks. Shaneyfelt and colleagues [50] performed a meta-analysis on hormone predictors of risks for prostate cancer and found that men with serum total testosterone in the highest quartile are 2.34 times more likely to develop prostate cancer. Data from the case-control studies from the Janus serum bank in Norway, Finnish Mobile Clinic Health Examination Survey, Massachusetts Male Aging Study, Carotene and Retinol Efficacy Trial in Seattle, Washington and Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study showed no association between high levels of circulating androgens and prostate cancer risk [51–55].

Insulin-like growth factors (IGF-I and IGF-II) are polypeptides functioning both as growth factors and endocrine hormones. IGF-I has been found to have strong mitogenic and anti-apoptotic effects on normal and transformed prostate cells *in vitro* and *in vivo*, suggesting that it may play a role in the development of prostate cancer in humans [56–59]. It is produced in the liver, together with at least six IGF-binding proteins (IGFBP). In circulation, more than 90% of IGF-I is bound to IGFBP-3.

Chan and colleagues [60] first noted a strong positive association between IGF-I levels and prostate cancer risk in a nested case-control study involving 152 men with prostate cancer within the Physicians' Health Study. Men in the highest quartile of IGF-I levels had a relative risk of 4.3 compared with men in the lowest quartile. IGF-II and IGFBP-3 were not associated with prostate cancer when examined individually, but IGFBP-3 showed an inverse relationship with prostate cancer risk when controlled for IGF-I levels. Wolk and colleagues [61] found a moderately strong positive association between IGF-I and prostate cancer and Stattin and colleagues [62] noted higher risk association in men younger than 59 years of age at the time of blood collection. Djavan and colleagues [63] further noted that IGF density and IGF-I:PSA ratio were significantly higher in men with prostate cancer than in controls. Li and colleagues [64] undertook a sibling-matched case-control study with 408 cases and showed that the molar ratio of IGF-I:IGFBP-3 was associated with prostate cancer and high IGF-I was associated with less advanced disease at diagnosis. These findings were supported by a systematic review and meta-regression analysis of IGF-I, IGFBP-3 and risks of prostate, colorectal, breast and lung cancer by Renehan and colleagues [65]. However, Woodson and colleagues and Aksoy and colleagues [66,67] did not find any correlation between IGF-I and IGFBP-3 levels and prostate cancer risk, but their studies were limited by the small sample size.

In Asian populations, Chokkalingam and colleagues [68] conducted a population-based case-control study in 128 men with prostate cancer and 306 population controls in Shanghai, China and demonstrated that men in the highest quartile of IGF-I levels had a 2.6-fold higher risk of developing prostate cancer and men in the highest quartile of IGFBP-3 had a 46% decrease risk relative to the lowest quartile. Men in the highest quartile for IGF-I:IGFBP-3 molar ratio had a 2.5-fold higher risk of developing prostate cancer. Unfortunately, there are currently no studies comparing IGF-I and IGFBP-3 levels between Caucasian and Asian populations.

Studies on serum hormone levels and disease association need to be interpreted with caution. Often, these studies are based on single readings of serum hormones that did not factor in the confounding variables of diurnal changes and person-to-person variations. Furthermore, serum levels may not adequately reflect intra-prostatic hormone levels. All these confounding factors may have led to imprecise hormone level measurements that might have contributed to the lack of association between androgen levels in men with prostate cancer and healthy men [69].

3.2.5. Environmental and dietary factors

The huge difference in prostate cancer incidence rates between Asians and Caucasians has led investigators to compare differences in lifestyle and diet between Asians in their native countries and Asian migrants to high-risk countries.

Dunn and colleagues [70] first reported that the risk of developing prostate cancer in successive generations of early Japanese migrants to the USA gradually approaches that of white men. Santner and colleagues [71] further compared androgen levels between Caucasian men in Pennsylvania, USA and Chinese men in Beijing, China and found that the Caucasian men excreted significantly higher levels of AAG and androsterone glucuronide than their Chinese counterparts. When the Pennsylvanian Chinese men were compared with Pennsylvanian Caucasian men, no difference was detected. Cook and colleagues [72] reviewed data from the Surveillance, Epidemiology and End Results Program in the USA and observed that Chinese and Japanese men in the age range 45–69 years, born in China and Japan, respectively, had half the annual incidence rates of their counterparts who were born in the USA. In the older age group (age 70–84 years), Japanese men born in Japan continued to have half the incidence rates of those born in the USA, but Chinese men born in China had nearly the same incidence rate as those born in the USA. These findings suggest that lifestyle or dietary factors may have contributed to the difference in androgen production and incidence of prostate cancer and that Asian–American men may have retained some of these characteristics that continue to make their prostate cancer risk less than that of white residents in the USA.

3.2.6. Obesity

Obesity is often associated with a more sedentary lifestyle and decreased frequency of exercise. The association between obesity and prostate cancer stems from its influence on increasing circulating oestrogen level and decreasing androgen levels as androgens are aromatised to form oestrogens in adipose tissues. This may increase the prostate cell sensitivity to androgens and increase the risk of prostate cancer, following observations that androgen receptors in canine prostates were upregulated by oestradiol [73].

Andersson and colleagues [74] found that body mass index (BMI) was positively associated with excess mortality from prostate cancer but not cancer incidence in 708 prostate cancer deaths from a registry of 135,000 Swedish men. Rodriguez and colleagues [75] examined data from 1590 deaths from prostate cancer in male participants in two cancer prevention studies and observed that obesity (defined as BMI $\geqslant 30$) conferred a higher risk. Hsing and colleagues [76] interviewed 238 Chinese men with prostate cancer and 471 controls in Shanghai during 1993–1995 and measured their height, weight, BMI, waist, hip, right upper arm circumferences and waist-to-hip ratio (WHR). They found that men with the highest quartile of WHR, an indicator of abdominal adiposity, were conferred a 2.71 times risk compared with men in the lowest quartile. BMI was not associated with excess risk in this study. Data from the Health Professionals Follow-up Study, Baltimore Longitudinal Study of Aging and Swedish Twin Registry, however, did not demonstrate a statistically significant excess risk of prostate cancer with BMI or other measures of obesity [77–79]. It thus appears more likely that obesity confers an excess risk of prostate cancer mortality rather than incidence.

3.2.7. Dietary factors

Many dietary factors have been studied with regards to prostate cancer risk, but their role may be summarised as two contributing factors: (i) as an influence on circulating androgens or oestrogens, and (ii) as a general protective effect against mitogens. Dietary factors that have been cited as possible contributing factors to the low incidence in Asians included low dietary fat, isoflavonoids in soybeans, polyphenols in green tea, lycopene from tomatoes, selenium and vitamin E.

3.2.7.1. Dietary fat. Early epidemiological studies suggested a possible causal association between dietary animal fat and prostate cancer [80–84]. However, the evidence was less obvious in later studies. Questionnaire-based studies showed a tendency for weak positive association between total fat consumption and prostate cancer risk, but serum-based studies did not. There was inconsistent correlation for saturated fat, but unsaturated fat showed an increased risk in questionnaire-based studies. Linoleic acid showed no risk association whereas α-linolenic acid showed inconsistent correlation. Only oleic acid showed some positive association with prostate cancer risk [85].

To assess the influence of dietary fat on ethnic differences in prostate cancer risk, Whittemore and colleagues [86] interviewed 1655 black, white, Chinese–American and Japanese–American case patients in Los Angeles, San Francisco, Hawaii, Vancouver and Toronto, and found that saturated fat intake was associated with higher risks for Asian–Americans than for blacks and whites. Among foreign-born Asian–Americans, risk increased independently with years of residence in North America and with saturated fat intake. Crude estimates suggest that differences in saturated fat intake account for about 10% of black–white differences and about 15% of white–Asian–American differences in prostate cancer incidence. Lee and colleagues [87] interviewed 133 cases and 265 controls in 12 cities in China and observed that the daily fat intake and percentage energy

from fat was 3.6 times higher in cases than controls. These data suggest that whilst saturated fat may be a factor contributing to prostate cancer risks, other factors may be more important in accounting for the inter-ethnic differences.

Communities with high fish consumption, such as the Japanese, were thought to have a reduced risk of prostate cancer because of protective effects of marine fatty acids [88]. Marine fatty acid consumption, particularly the long-chain eicosapentaenoic and docosahexaenoic acids, have been found to be associated with decreased risk of prostate cancer in several studies [89,90].

The available epidemiological evidence demonstrated several methodological limitations [91]. Dietary fat is highly correlated with total caloric intake in most Western populations and only a few studies adjusted for energy intake in their analyses. When data collection allows for proper adjustment of total energy intake, the results are less likely to implicate animal fat as a risk factor for prostate cancer. Case-control studies possess the potential for recall bias. In addition, the dietary information was often obtained at a single arbitrary point in adult life at entry into the cohort studies. Much of the evidence centred on diets with high levels of red meat, which is also often associated with lower consumption of plant foods that may contain protective factors against prostate cancer. A high meat/high fat diet often included high intake of dairy products with high calcium content and other substances such as zinc, which have some association with increased prostate cancer risks. Furthermore, the manner in which food is prepared (steamed/boiled or grilled/fried) was not factored in. Traditional Asian dishes, especially Japanese and Chinese dishes, are often steamed, boiled or stir-fried and are seldom grilled or smoked. Smoking or grilling at high temperatures commonly generates carcinogens such as polycyclic aromatic hydrocarbons and heterocyclic amines.

3.2.7.2. Isoflavonoids. Dietary phyto-oestrogens are broadly grouped into two types: lignants and isoflavonoids. Lignants occur in seeds, berries, wholegrain bread, vegetables and tea, whereas isoflavonoids are found in soybean and related products.

Soybean products are commonly found in traditional Chinese and Japanese diets. Lee and colleagues [92] assessed 133 prostate cancer cases and 265 controls in China on consumption of soy foods and isoflavones using a food frequency questionnaire and observed a reduced risk of prostate cancer associated with consumption of soy foods and isoflavones (such as tofu and soybean). Sonada and colleagues [88] observed decreased prostate cancer risks in Japanese men who consumed beancurd (tofu) and natto (fermented beans) in a case-control study of 140 men with prostate cancer and 140 age-matched controls in four different geographical areas in Japan (Ibaraki, Fukuoka, Nara and Hokkaido). In the USA, Seventh-Day Adventist men who drank soy milk more than once a day had a 70% decreased risk of prostate cancer compared with those who did not [93]. The exact mechanism of the protective effect of isoflavonoids is not clear, but Onozawa noted that genistein (a type of isoflavonoid found in soybean) suppressed DNA synthesis and inhibited apoptosis in LNCaP cell lines [94]. It was noted that PSA expression was also suppressed. Other investigators observed that isoflavonoids decreased circulating oestrone concentrations and plasma DHT levels in human and rat models, respectively, but further work is needed to clarify the mechanism of action [95,96].

3.2.7.3. Green tea. Green tea is a popular beverage in China and Japan, and has been postulated to be a factor in reducing prostate cancer risks in these populations. Specifically, epigallocatechin-3-gallate (EGCG), the main polyphenol present in green tea, is a potent antioxidant and has been shown to induce apoptosis in human prostate carcinoma cells by concurrent effect on two important transcription factors, p53 and NF-κB, and to shift the balance between pro- and anti-apoptotic proteins (Bax and Bcl-2) in favour of apoptosis [97,98]. Jian and colleagues [99] conducted a questionnaire-based case-control study in Hangzhou, a south-eastern Chinese city famous for production of Long Jin green tea, involving 130 cases of prostate cancer and 274 controls. He observed that prostate cancer risk declined with increasing frequency (odds ratio (OR) 0.27, 95% confidence interval (CI) 0.15–0.48 for those drinking more than three cups per day), duration (OR 0.12, 95% CI 0.06–0.26 for those who drank tea over a period of 40 years) and quantity of green tea consumption (OR 0.09, 95% CI 0.04–0.21 for those consuming more than 1.5 kg of tea leaves per year).

3.2.7.4. Lycopene. Lycopene, a fat-soluble acyclic isomer of beta-carotene with anti-oxidant properties is present in many fruits, including watermelon, papaya, pink grapefruit and pink guava, but its richest source is in tomatoes (*Lycopersicon esculentum*) [100]. Early studies by Stahl [101] established that heat and mechanical processing increased the bioavailability of lycopene by releasing them from intracellular compartments. Ingestion of the highly lipophilic lycopene with oil or fat results in micelle formation and facilitates its absorption.

Gann and colleagues [102] compared the plasma lycopene levels in 578 men with prostate cancer with 1294 age- and smoking status-matched controls and observed an inverse correlation between plasma lycopene levels and prostate cancer risk. The 5th quintile OR was 0.75

(95% CI 0.54–1.06) for all prostate cancers and 0.56 (95% CI 0.34–0.91) for aggressive prostate cancers. This inverse relationship between lycopene and prostate cancer was also found in Chinese men by Binns and colleagues [103] who noted an adjusted OR of 0.18 (95% CI 0.08–0.41) for the highest quartile compared with the lowest quartile for lycopene in a questionnaire-based case-control study. However, Etminan and colleagues [104] performed a meta-analysis of 11 case-control and 10 cohort or nested case-control studies on intake of tomato products and found only a weak inverse association with prostate cancer risk for high intake (5th quintile) both raw tomatoes (relative risk (RR) = 0.89, 95% CI 0.80–1.00) and cooked tomatoes (RR = 0.81, 95% CI 0.71–0.92).

3.2.7.5. Micronutrients and vitamins. Selenium is a biological trace element and micronutrient that is derived from food grown in selenium-rich soil. It is essential for the normal growth and function of the prostate and is involved in immune system function and spermatogenesis. Willet [105] first demonstrated that low levels of serum selenium were found in 111 subjects with prostate cancer and gastrointestinal cancers compared with 210 matched controls. Subsequent cohort studies and case-control studies involving both serum levels and selenium concentration in nail clippings suggest an inverse relationship between selenium levels and prostate cancer risk [106–110]. Nomura and colleagues [111] confirmed this relationship and extended it to include Asians with a case-control study of 249 Japanese–American men with pre-diagnostic serum collected 20 years ago.

Vitamin E, and its most biologically active and common form α-tocopherol, has significant anti-oxidant properties that help to reduce DNA damage and carcinogenesis. In the alpha-tocopherol beta-carotene (ATBC) trial involving 29,133 male smokers in Finland, Hartman and colleagues [112] observed a 40% decrease in incidence of clinically apparent prostate cancer and 41% decrease in prostate cancer mortality. This finding was supported by another study by Giovannucci and colleagues [115] who found a 53% risk reduction in metastatic or fatal prostate cancer among current smokers and recent quitters on daily vitamin E supplementation (RR 0.47, 95% CI 0.24–0.92). However, when a post-intervention follow-up study was performed for participants in the ATBC trial, the beneficial effects of vitamin E were no longer observed [114]. A major randomised, prospective, double-blind cancer prevention trial with selenium and vitamin E supplementation involving recruitment of 32,400 American men with non-suspicious digital rectal examination and PSA less than 4 ng/ml is ongoing and may help to clarify the long-term beneficial effects of these nutrients [113].

4. Conclusion

Prostate cancer incidence and mortality rates have shown a rising trend over the last two decades but still remain lower in Asia than in Western countries. The difference may be the result of genetic factors and certain protective lifestyle, dietary or environmental factors. However, with globalisation and gradual Westernisation, many Asian countries may be losing their protective cultural factors and acquiring high-risk ones. A better understanding of how these factors interact to cause prostate cancer through further studies with a multi-ethnic perspective will facilitate appropriate public health strategies to minimise high-risk factors and maintain the protective factors that keep prostate cancer at bay.

Conflict of interest statement

None declared.

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