Asia Cancer Trends Study

Prostate Cancer
Cancer is one of the leading causes of death globally, with annual new cancer cases projected to rise to 17 million by 2020. Almost half of the world’s new cancer cases will happen in Asia. In China, cancer is the leading cause of death in both urban and rural areas. An eight-year-old girl recently became China’s youngest lung cancer patient, with doctors attributing her condition to air pollution. Lung cancer is the most common cancer in Asia, followed by stomach cancer, breast cancer, colorectal cancer and liver cancer.

Across the world, more than a fifth of all deaths from non-communicable diseases are from cancer. South Koreans are more likely to die from cancer than from any other cause. In Singapore, where one in three people die of cancer, there are 13 deaths and 31 new diagnoses every day.

These statistics put into focus the impact cancer has on the health of Asia’s population; they also highlight the importance of the industry’s understanding of the incidence, risk factors, past trends, and emerging trends in the development of the most prevalent types of cancer in this region. This report on prostate cancer is one in a series developed by Swiss Re Asia, which aims to grow this understanding. It leverages existing data sources, including cancer registries, published research and other publicly available data, and draws on the knowledge and experience of the many life and health experts within Swiss Re.

We hope that you find this report of value to your business.
Executive summary

Prostate cancer is a type of cancer that occurs mainly amongst the elderly male population. The prognosis of prostate cancer is one of the best among all cancers. It has attracted extensive attention in the Asian insurance industry in recent years, as observed incidence rates have increased rapidly during the past decade and continue to rise today.

Despite the increasing trends, both incidence and mortality of prostate cancer in most Asian populations are still much lower than in Western populations. It has been proposed that different ethnic groups may have different genetic predisposition to developing prostate cancer, and recent genetic research seems to support this hypothesis. Autopsy studies have also found that the prevalence of asymptomatic prostate cancer is much higher in men over the age of 70 in the United States (US) than in Japanese men over the age of 80 (81–83% vs. 48%).

However, genetics alone does not explain the difference in incidence rates. A Western diet rich in red or processed meat with high total and saturated fat content tends to elevate the risk of prostate cancer, while elements of an Eastern diet including green tea and soybean may have a protective effect. Driven by strong economic growth and the resulting increase in family incomes, many countries in Asia have experienced a shift from a more traditional Asian diet to a more Western diet, which may be one reason for the increase of prostate cancer in Asia, and it seems this trend is continuing.

The introduction of blood screening for PSA (prostate specific antigen) is believed to be the key factor contributing to the rapid increase in observed prostate cancer incidence in both the United States and Europe since the late 1980s. The recommendations from mainstream professional bodies representing medical practitioners in Western countries are mostly against mass screening using PSA as the potential drawbacks are considered to be greater than the benefits. It has been estimated from a European study that PSA screening leads to around 67% more men being diagnosed with prostate cancer than would be diagnosed without screening. This over-diagnosis tends to result in over-zealous treatment and subsequently higher rates of complications from therapy. In the US, at least 20% to 30% of men undergoing surgery or radiation therapy for prostate cancer suffer long-term side effects.

PSA testing is not popular in Asia, resulting in more prostate cancers in Asia being diagnosed at an advanced stage. However, unlike the US and Europe, medical experts in Asia tend to be more positive in promoting PSA screening. It will be important to monitor PSA screening behaviour in Asia, as it could cause a rapid increase in the incidence of early stage prostate cancer within a short period and consequently higher claim costs for the insurance industry.

Going beyond PSA testing, a new generation of prostate cancer biomarkers is already under development. These biomarkers are able to detect even smaller cancers and can also differentiate between aggressive and non-aggressive cancers. Insurance companies may need to reconsider their existing product designs, exclusion wordings and risk stratification systems as the incidence of prostate cancer may rise with many newly diagnosed clinically indolent cancers requiring only active surveillance without treatment.
The prostate gland is part of a man’s reproductive and urinary systems. A normal prostate is about the shape and size of a walnut, sits under the bladder and in front of the rectum, and surrounds part of the urethra. The prostate is not essential during the course of a man’s life but is important for reproductive purposes. Its main function is to make seminal fluid, the liquid in semen that protects, supports and transports the sperm.

The prostate gland is divided into 3 zones: peripheral, central and transition. The peripheral zone is the largest zone and closest to the rectum. It can easily be felt during a digital rectal examination (DRE). About 75% of prostate tumours are found in this zone. The central zone is farthest from the rectum, tumors in this zone cannot be felt during a DRE. The transition zone is between the peripheral and central zones, and is the main area of developing benign prostatic hyperplasia (BPH), a non-malignant lesion that increases the size of the prostate.

Prostate cancer is the second most common cancer affecting the male population worldwide, accounting for 15.4% of all cancers in men. Australia and New Zealand have the highest incidence rates in the world, while Asian populations have some of the lowest observed incidence rates of prostate cancer (see Table 1). In Asia, prostate cancer ranks sixth, accounting for 5.8% of all Asian male cancers. It is believed that both ethnic differences and the lower usage of prostate specific antigen (PSA) testing account for the lower rates of diagnosis.

Table 1
Age-standardised incidence rate (ASIR) and age-standardised mortality rate (ASMR) of prostate cancer

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASIR</td>
<td>All cancer</td>
</tr>
<tr>
<td>World</td>
<td>36.0</td>
<td>15.4%</td>
</tr>
<tr>
<td>North America</td>
<td>97.2</td>
<td>28.3%</td>
</tr>
<tr>
<td>Europe</td>
<td>64</td>
<td>22.8%</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>111.6</td>
<td>31.2%</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>69.1</td>
<td>24.6%</td>
</tr>
<tr>
<td>Asia</td>
<td>11.6</td>
<td>5.8%</td>
</tr>
<tr>
<td>East Asia</td>
<td>13.2</td>
<td>5.1%</td>
</tr>
<tr>
<td>China</td>
<td>7.0</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>29.8</td>
<td>11.6%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>29.7</td>
<td>8.8%</td>
</tr>
<tr>
<td>Japan</td>
<td>36.1</td>
<td>12.1%</td>
</tr>
<tr>
<td>Korea</td>
<td>34.9</td>
<td>9.2%</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>13.3</td>
<td>8.1%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>13.0</td>
<td>8.0%</td>
</tr>
<tr>
<td>Philippines</td>
<td>20.2</td>
<td>13.1%</td>
</tr>
<tr>
<td>Singapore</td>
<td>38.5</td>
<td>15.4%</td>
</tr>
<tr>
<td>Thailand</td>
<td>8.8</td>
<td>5.3%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>18.1</td>
<td>11.8%</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>3.7</td>
<td>2.0%</td>
</tr>
<tr>
<td>South-central Asia</td>
<td>5.4</td>
<td>5.0%</td>
</tr>
<tr>
<td>India</td>
<td>5.1</td>
<td>4.9%</td>
</tr>
<tr>
<td>Iran</td>
<td>15.3</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

Notes:
- Hong Kong and Taiwan data are extracted from local cancer registry report or a query system for 2012. Data for other regions or countries are extracted from a Globocan 2012 online analysis.
- ASIR and ASMR are both calculated using WHO 2000 standard population and are on a per 100,000 person-years basis.
Histologically, 90–95% of prostate cancers are a type called acinar adenocarcinoma, developing from gland cells in the prostate. Many of these cancers grow extremely slowly and are not likely to spread. In survival analyses for 455,296 cases of prostatic cancer diagnosed from 1988 to 2003 taken from the US SEER registry, only 0.19% of total prostate cancer in the United States (US) exhibited poor survival, and all of these were non-acinar carcinomas. Five-year relative survival rates from the US SEER registry were over 99% for prostate cancers diagnosed from 2006–12. In contrast, Asia’s five-year relative survival rates were 85% or above in Japan, Korea and Singapore, but between 30% to 40% in China and Thailand.

Survival rates are heavily affected by the distribution of prostate cancers at diagnosis stage. Both localised and regional prostate cancers have a much better survival rate than those cancers that already have distant metastasis at diagnosis (table 2a). 80% of prostate cancer patients in the US are diagnosed at localised stage, while only 54.3% Korea patients and 61.6% Singapore patients respectively were diagnosed at localised stage, increasing the average survival rates in the US. In Japan, only 50% of prostate cancers are diagnosed at a localised stage, while in China, 68% already had metastasis at diagnosis.

<table>
<thead>
<tr>
<th>Stage Distribution at Diagnosis (%)</th>
<th>USA (SEER data)</th>
<th>Korea</th>
<th>Singapore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td>100</td>
<td>99.2</td>
<td>89.6</td>
</tr>
<tr>
<td>Regional</td>
<td>100</td>
<td>94.7</td>
<td>85.2</td>
</tr>
<tr>
<td>Distant</td>
<td>29.3</td>
<td>36.4</td>
<td>36.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>79.4</td>
<td>87.9</td>
<td>–</td>
</tr>
</tbody>
</table>

2.1. Age-specific incidence rates

Using publicly available national cancer registry data, we have compared age-specific prostate cancer incidence rates in the United States, Australia and Eastern Asia (see Figure 1)\(^7\). We found:

1. The shapes of age-specific incidence curves are similar across populations, however incidence rates start to increase at earlier ages and peak incidence rates are higher in Australians, US Whites and US Blacks compared to Asians. For every age-group until age 80, US Blacks had the highest incidence rates, while Chinese men had the lowest rates.

2. Prostate cancer before age 40 is extremely rare. In Australia and the United States, incidence rates start to increase in the 40–44 age band, while in Asia, incidence rates start increasing 10 years later in the 50–54 age band.

3. Australian and US men reach peak incidence around age 65, 10 years earlier than Asian men. Taiwan shows the oldest peak at the age of 80. Most of the observed populations exhibit a reduction in incidence rates after the peak, except Singapore.

4. Although Japan has the highest incidence rate in Asia, it is still significantly lower than in the US and Australia.

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**Figure 1**
Age-specific incidence of prostate cancer in East Asian areas and United States in 2012
2.2. Incidence trends

In the US, the incidence of prostate cancer rapidly increased by 108% for White males between 1986 and 1992 and by 102% for Black males between 1986 and 1993. Part of this increase reflected the one-off effect of introducing PSA screening to a previously unscreened population. Because of this one-off effect, incidence rates dropped significantly after 1992 but stabilised at a level still significantly higher than pre-PSA incidence rates. Partly as a result of recommendations against PSA screening, from 2002 to 2011 the overall incidence rate of prostate cancer decreased by around 3.4% per year (see Figure 2).

By contrast, reported prostate cancer incidence in Asian countries has been increasing rapidly at a rate of 7.2% per year from 2004 to 2009, with no clear flattening or turning point observed to date. Korea showed the fastest increase with an annual percentage change of 12.8%, age-adjusted incidence increased from 8.4 per 100,000 in 1999 to 24.4 per 100,000 in 2011. The annual increases in Taiwan and Shanghai were 4.9% and 4.8% respectively, while the incidence in India has been relatively stable during the same period based on data from both the Mumbai and Bangalore cancer registries (see Figure 3).
Risk factors

Our current understanding of prostate cancer suggests that it is caused by a complex interplay between genetics, environment and behavioural factors. This means that differences in incidence by ethnicity may not only be due to differences in genetics, but also to differences in environmental exposures, diet, lifestyle and attitudes towards healthcare.

3.1. Genetics

Although most prostate cancers are “sporadic” (driven by random genetic changes as opposed to inherited mutations), it has been recognised that some patients have a hereditary basis to their disease. A man with a family history of prostate cancer is at a higher risk of developing prostate cancer (see Table 3). A recent epidemiological study in Japan found that the prevalence of prostate cancer classified as having hereditary form in Japan is 1.1%, considerably lower than the 5–10% prevalence in Western countries, suggesting that different ethnic groups may have different genetic drivers for developing prostate cancer.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>RIR for prostate cancer (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father with prostate cancer</td>
<td>2.35 (2.02–2.72)</td>
</tr>
<tr>
<td>Brother(s) with prostate cancer</td>
<td>3.14 (2.37–4.15)</td>
</tr>
<tr>
<td>Two or more affected first-degree relatives</td>
<td>4.39 (2.61–7.39)</td>
</tr>
<tr>
<td>Second-degree relatives with prostate cancer</td>
<td>2.52 (0.99–6.46)</td>
</tr>
</tbody>
</table>

Table 3
Relative Risk (RR) for those with Family History of Prostate Cancer vs those without any Family History

There are many types of genetic variations that can cause prostate cancer, and some of them are found to be substantially different between Caucasians and East Asians.

Improper repair of DNA replication errors can result in both intra- and inter-chromosome rearrangements. TMPRSS2:ERG, a fusion of two different genes (TMPRSS2 with ERG) is perhaps the best studied of these in prostate cancer. This rearrangement occurs in nearly 50% of all primary prostate cancers in Caucasians, but is much rarer in East Asian populations (8%–21%). This genetic difference may be linked to the different incidence rates in different ethnic groups.

Point mutations involving tumour suppressor, oncogenes and others have also been identified in prostate cancer. Ethnic differences have been found in some of these point mutations. For example, the Asp541Glu mutation at the HPC1 gene increases the risk of prostate cancer in some Japanese men but this mutation has not been found in European studies. Another mutation example is HOXB13 G84E variant, unique to European patients, and conferring a significantly increased risk of prostate cancer (Odds Ratio (OR) of 20.1, 95% CI 3.5–803.3)*.

*European patients with a HOXB13 G84E variant were 20.1 times more likely to be diagnosed with prostate cancer than those without, with a 95% confidence interval of 3.5 to 803.3 times.
3.2. Diet

Green tea and soybean

It has been suggested that green tea, a traditional drink in East Asia, can inhibit cell growth and induce apoptosis through a variety of pathways. Zheng et al. conducted a meta-analysis on 13 independent studies and found that green tea (but not black tea, which is more popular in Western population), may have a protective effect with respect to developing prostate cancer. For East Asian populations, high green tea consumption was associated with a borderline significant decrease of 38% for prostate cancer risk (OR = 0.62; 95% CI: 0.38–1.01).

A prospective study in Japan covering 49,920 men aged 40–69 years and followed for more than 10 years showed that advanced prostate cancer was more sensitive to the effects of green tea, and that the protection was dose-dependent. For men drinking 5 or more cups/day, the risk of developing prostate cancer was reduced by 50% compared with those drinking less than 1 cup/day (RR 0.52; 95% CI: 0.28–0.96)**.

The above studies were mainly performed in China and/or Japan, further research are needed to understand the potential protective effects of green tea in other regions.

Soybean, another traditional food in East Asia, has also been investigated for possible beneficial effects. A meta-analysis including 15 epidemiologic studies on soy consumption suggested that non-fermented soy foods (tofu and soy milk) intake can reduce the prevalence of prostate cancer by about 30% (combined RR/OR = 0.70; 95% CI: 0.56–0.88), but not fermented soy foods including miso and natto (combined RR/OR = 1.02; 95% CI: 0.73–1.42).

** For men drinking 5 or more cups of green tea a day, there was 48% less risk of being diagnosed with prostate cancer with a 95% confidence interval of 0.28 to 0.96.
Fat and meat
Western diets tend to be higher in red or processed meat with higher total and saturated fat content. Driven by strong economic growth and the resulting increases in family incomes, many countries in East Asia have experienced a shift from a traditional East Asian diet to a more Westernised one, accompanied by lower levels of physical activity and increased obesity.

Per capita consumption of meat increased by over 330% in East Asia over the 30 years from 1966 to 1999, while for industrialised countries, the corresponding increase was 43% within the same period. A further increase of 55% has been predicted for East Asia by 2030. Consumption of meat in South Asia has increased more slowly but is expected to accelerate in the next 15 years (see Table 4).

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>East Asia</td>
<td>8.7</td>
<td>37.7 (+333%)</td>
<td>58.5 (+55%)</td>
</tr>
<tr>
<td>South Asia</td>
<td>3.9</td>
<td>5.3 (+36%)</td>
<td>11.7 (+121%)</td>
</tr>
<tr>
<td>Industrialized</td>
<td>61.5</td>
<td>88.2 (+43%)</td>
<td>100.1 (+13.5%)</td>
</tr>
<tr>
<td>countries</td>
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</tr>
</tbody>
</table>

In an epidemiologic review of 22 publications, 16 studies showed a positive relationship between prostate cancer and high consumption of red meat, with a RR of 1.3 or more. Animal studies have shown that consumption of meat cooked at high temperatures, by panfrying, grilling, or barbecuing can result in the formation of carcinogens in the prostates of animals.

Whittemore et al. conducted a multi-ethnic (Blacks, Whites, Asian Americans) study across populations drawn mainly from the US. Results show a positive statistically significant association between prostate cancer risk and saturated fat intake for all ethnic groups. However, intake of saturated fats by Asian Americans was found to be associated with higher RR factors than in US Blacks and US Whites. The elevation of prostate cancer risk in Asian Americans could also have been due in part to related decreases in the intake of cancer protective compounds common to traditional Asian diets.

In summary, traditional East Asian diets are generally associated with a lower risk of prostate cancer compared to Western diets, but a trend towards more Westernised diets with higher saturated fat content is likely to result in an increase in the underlying trend of prostate cancer incidence in Asia.
3.3. Other risk factors

Age
The risk of being diagnosed with prostate cancer increases with age. The US SEER data shows that only 0.33% of men who are now 40 years old will be diagnosed with prostate cancer during the next 10 years, while 7.52% of those men who are now 70 years old will be diagnosed with prostate cancer by the age of 80\(^3\). East Asian countries are facing a much faster pace of ageing compared to the rest of the world. It is reasonable to assume that the crude rate of prostate cancer incidence will continue increase in this region\(^3\).

Tobacco and alcohol use
The evidence on the association between tobacco and alcohol consumption and prostate cancer incidence is mixed. One study found positive associations among those who reported smoking 40 or more cigarettes per day for both US Black males (former smokers: OR, 1.1; 95% CI, 0.6–2.0; current smokers: OR, 1.9; 95% CI, 0.9–4.2) and US White males (former smokers: OR, 1.5; 95% CI, 1.0–2.2; current smokers: OR, 1.3; 95% CI, 0.7–2.4)\(^3\). Other studies found no or weak positive associations between smoking and prostate cancer risk.

Weak positive association between alcohol consumption and prostate cancer have been reported (OR, 1.2; 95% CI, 0.9–1.7) when comparing those who reported any alcohol intake to those who never drink\(^3\).

Sexually transmitted infections
It has been reported that the risk of prostate cancer increases among men who reported a history of gonorrhoea or syphilis (OR = 1.6; 95% CI 1.2–2.1) or showed serological evidence of syphilis (OR = 1.8; 95% CI 1.0–3.5)\(^3\). The Harvard’s Health Professionals Follow-up Study covering 29,342 men between the ages of 46 and 81 revealed that high ejaculation frequency seems to protect against prostate cancer\(^3\). So far, no firm conclusions have been reached.

Hormones
A collaborative analysis of 18 prospective studies from around the world found that the serum concentrations of sex hormones were not associated with the risk of prostate cancer\(^3\).
4.1. PSA test and prostate cancer

PSA is a protein produced by the prostate gland, and higher blood PSA levels are often noted in men with prostate cancer and/or noncancerous disorders of the prostate. For persistently elevated PSA levels, a prostate biopsy is usually recommended. This involves a rectal ultrasound and the use of a needle to obtain tissue samples from the prostate gland.

The PSA test is widely accepted for ongoing surveillance of patients after diagnosis of or treatment for prostate cancer. However, there is continued debate among experts over when and how often PSA tests should be used to screen asymptomatic men.

4.2. Recommendations on prostate cancer screening

The mainstream view of the worldwide medical profession is that mass public screening of prostate cancer for men without symptoms should be avoided. This is especially so for men under the age of 50–55 or above the age of 70–75 or any man with a life expectancy of less than 10–15 years.

In 2012, the United States Preventive Services Task Force (USPSTF) gave the strong recommendation: "do not use PSA–based screening for prostate cancer in asymptomatic men". The USPSTF pointed out that "the reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years", and "many men are being subjected to the harms of treatment (including erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death) for prostate cancer that will never become symptomatic".

A shared decision-making approach is strongly recommended by almost all expert organisations. Clinicians are requested to inform men about the potential benefits and harmful effects, limitations, and uncertainties associated with prostate cancer early detection and treatment to allow a truly informed decision about whether to be screened.

In the United Kingdom (UK), “the National Health Service (NHS) will not be implementing a national screening programme until there is clear evidence showing that it will offer more benefit than harm to the general population”, however “men over 50 who decide to have a PSA test based on balanced information can do so for free on the NHS”.

In Europe, the European Association of Urology suggested in 2013 that “a baseline serum PSA should be offered to all men 40–45 years of age to initiate a risk-adapted follow-up approach with the purpose of reducing prostate cancer mortality and the incidence of advanced and metastatic prostate cancer”. In contrast, the European Society for Medical Oncology (ESMO) recommendation in 2015 states that “population-based PSA screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended.”
In Japan, the Japanese Urological Association (JUA) recommends PSA screening for men at risk of prostate cancer to reduce the risk of death as a result of prostate cancer. Here the men at risk defined by JUA are men aged 50 years or older in general, and 40 years or older in men with a family history. In individual-based screening, checking baseline PSA at the age of 40 years would not contribute to cancer detection at the time of the measurement, but might be valuable in terms of minimizing the likelihood of missing clinically important prostate cancer in patients in their early 50s. A patient’s individual PSA kinetics measured since his 40s might be very helpful to predict the aggressiveness of the prostate cancer and to select the appropriate treatment. The National Cancer Center of Japan does not recommend either PSA or DRE for population-based screening programs due to insufficient evidence that such screening reduces mortality. With respect to opportunistic screening, if individuals request for screening, they should be given appropriate information, and the decision making should be made at the individual level.

In China, there are no recommendations or guidelines issued by the government or expert organisations. However, researchers have noted that the mortality-to-incidence rate ratio (MR/IR) of prostate cancer in China (MR/IR = 0.63) is higher than the average in Asia (MR/IR = 0.57) and much higher than that in North America (MR/IR = 0.13). They believe that in China most prostate cancers are in the advanced stages at the time of diagnosis, and that patients have a short survival time thereafter. As a result of this finding, they suggested mass PSA screening should be performed annually for Chinese men over the age of 50 years to achieve early diagnosis and treatment.

Recommendations for other Asian countries are summarised in table 5.

Table 5
Prostate cancer screening by expert organizations

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Recommendations on PSA screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>The United States Preventive Services Task Force (USPSTF)</td>
<td>Do not use prostate-specific antigen (PSA)-based screening for prostate cancer.</td>
</tr>
</tbody>
</table>
| The American Urological Association (AUA) | - Men aged 40 or under: no PSA screening;  
- 40–54 years: No routine screening in men at average risk;  
- 55–69 years: Strongly recommends shared decision-making process;  
- Men aged 70+ years or any man with less than a 10 to 15 year life expectancy: No PSA screening. |
| The American Cancer Society (ACS) | Men should not be screened unless they have been fully informed of the risks and benefits of screening and treatment, and made a shared decision with their doctors. The discussion about screening should take place at:  
- Age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years.  
- Age 45 for men at high risk of developing prostate cancer.  
- Age 40 for men at even higher risk. |
| The Clinical Guidelines Committee of the American College of Physicians (ACP) | Against screening for prostate cancer in  
- Average-risk men under age 50  
- Men over age 69  
- Men with a life expectancy less than 10 to 15 years.  
Men aged 50 to 69 should be fully informed of the limited potential benefits and substantial harms of prostate cancer screening and only screen men who express a clear preference for being screened. |
<p>| The Canadian Task Force on Preventive Health Care | No screening for prostate cancer with the prostate-specific antigen test. |</p>
<table>
<thead>
<tr>
<th>Organisation</th>
<th>Recommendations on PSA screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>The European Society for Medical Oncology (ESMO)</td>
<td>No population-based PSA screening for prostate cancer. No testing for prostate cancer in asymptomatic men over the age of 70 years.</td>
</tr>
<tr>
<td>The European Association of Urology</td>
<td>A baseline serum PSA should be offered to all men 40–45 years of age to initiate a risk-adapted follow-up approach with the purpose of reducing Prostate Cancer mortality and the incidence of advanced and metastatic Prostate Cancer. In the future, the development and application of multivariable risk-prediction tools will be necessary to prevent over diagnosis and over treatment.</td>
</tr>
<tr>
<td>The United Kingdom National Screening Committee</td>
<td>The NHS will not be implementing a national screening program until there is clear evidence showing that it will offer more benefit than harm to the general population.</td>
</tr>
<tr>
<td>The Australian Cancer Council</td>
<td>There are no tests available with sufficient accuracy to screen populations of men for early signs of prostate cancer.</td>
</tr>
<tr>
<td>The Japanese Urological Association</td>
<td>PSA screening should be offered to all men at risk of developing prostate cancer to reduce the risk of death as a result of prostate cancer.</td>
</tr>
<tr>
<td>National Cancer Center of Japan</td>
<td>Both PSA and DRE were not recommended for population-based screening programs, but they could be conducted as individual-based screening if basic requirements were met.</td>
</tr>
<tr>
<td>The Korean Urological Oncology Society</td>
<td>PSA screening may be useful for detection of prostate cancer in Korea.</td>
</tr>
<tr>
<td>Singapore, the Ministry of Health Clinical Practice Guidelines on Cancer Screening</td>
<td>No routine screening of men younger than age 50. An informed decision-making approach is recommended for men aged 50 to 75, or at higher risk of developing prostate cancer.</td>
</tr>
<tr>
<td>Hong Kong SAR Government’s Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)</td>
<td>No population-based screening for prostate cancer in men without any symptoms. Recommends an individual-based informed decision approach.</td>
</tr>
<tr>
<td>Indonesia</td>
<td>No PSA screening system, and PSA is assayed in patients who display symptoms.</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Population screening is not recommended, and PSA is to be assayed in men with risk factors.</td>
</tr>
<tr>
<td>China</td>
<td>No recommendations or guidelines issued by the government or expert organisations. Some medical professionals suggest “mass screening should be performed in the whole of China using serum PSA to facilitate early diagnosis and treatment of prostate cancer”, because most prostate cancers in China are diagnosed in the advanced stages and with a short survival time.</td>
</tr>
</tbody>
</table>
4.3. Screening rate and reported prostate cancer incidence

Little data on prostate cancer screening rate in Asia is available.

A population-based telephone survey was conducted in Hong Kong in 2007. A total of 1,002 men aged 50 or above took part in the study, and the uptake rate of PSA testing was found to be 9.5\%\textsuperscript{53}, which is much lower than the screening rate in the United States\textsuperscript{54} (see Table 6). The three main reasons cited by respondents for having the most recent PSA test were regular physical check-ups (39\%), prompted by local signs and symptoms (34\%) and physician’s recommendation (21\%). The three most common reasons for never having had a PSA test was that they did not think it was necessary (44\%), did not know it was available (33\%) and they regarded themselves as healthy all along (8\%).\textsuperscript{53} These results imply that the uptake of PSA screening is more likely to increase if individuals are made aware of the availability of the test.

<table>
<thead>
<tr>
<th>Hong Kong (ever had a PSA test in/ before 2007)</th>
<th>United States (had a PSA test in 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8% (age 50–59)</td>
<td>31.0% (age 50–54); 38.5% (age 55–59)</td>
</tr>
<tr>
<td>10.7% (age 60–69)</td>
<td>47.4% (age 60–64); 52.0% (age 65–69)</td>
</tr>
<tr>
<td>13.8% (age 70–79)</td>
<td>52.1% (age 70–74); 47.6% (age 75–79)</td>
</tr>
<tr>
<td>10.6% (age &gt; 80)</td>
<td>45.5% (age 80–84); 27.2% (age 85–89)</td>
</tr>
</tbody>
</table>

In China, a mass screening exercise in 1999 using PSA found 780 prostate cancers per 100,000 persons, which was much higher than the national average incidence of 16 per 100,000 persons in 2002\textsuperscript{55}.

The data in the United States for an aging cohort of men 65 years and older tracked from 1988 to 1994\textsuperscript{56} showed that the trend of prostate cancer incidence was almost perfectly parallel to the trend of first-time PSA tests, both trends increased from 1988 to 1992, followed by a decline from 1992 to 1994 (see Figure 4).

PSA testing has also shifted the diagnosis of prostate cancer to an earlier histological stage on average. The US SEER data demonstrated that mostly as a result of the introduction of PSA screening, the rate of distant disease diagnosis fell by 56\% from 14.9 in 1985 to 6.6 per 100,000 in 1995, but the rate of localised stage disease diagnosis roughly doubled during the same period from around 50 to 90 per 100,000\textsuperscript{8}.

\*Data adopted from\textsuperscript{57}.
In Japan, a review in Gunma prefecture showed an inverse correlation between the PSA exposure rate and the proportion of advanced cancer. In 9 municipalities with less than 10% exposure to PSA screening, 23.9% of prostate cancers were diagnosed at metastatic stage, while only 13.9% were diagnosed at metastatic stage in those municipalities with exposure rate to PSA screening higher than 30.1%.

4.4. Autopsy studies

An autopsy study provides useful information on the true prevalence of prostate cancer. Bell et al., reviewed 29 studies published from 1948 to 2013, covering 17 countries including Japan and China, on incidental prostate cancer rates in men who died of other causes. They found that the prevalence of prostate cancer under autopsy did not change over time, but showed substantial variation between the different countries.

Other autopsy studies reviewed by Gabriel P. Haas, et al. showed that prostate cancer has the highest prevalence among US men of Caucasian and African origin, and lower prevalence among men of Asian and Mediterranean origin. In older age groups, over 80% US men and nearly 50% Japanese were found to have prostate cancers in an autopsy (see Table 7). The results of these studies also show prostate cancer being identified at a much younger age via autopsy than would be expected using current diagnostic methods for live patients. This implies that many prostate cancers are histologically present in the body without clinical symptoms for 15 to 20 years, or even longer before they would be detected using current screening and diagnostic techniques.

Table 7

<table>
<thead>
<tr>
<th>Age</th>
<th>US white</th>
<th>US black</th>
<th>Japan</th>
<th>Greece</th>
</tr>
</thead>
<tbody>
<tr>
<td>21–30</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>31–40</td>
<td>31</td>
<td>31</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>41–50</td>
<td>37</td>
<td>43</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>51–60</td>
<td>44</td>
<td>46</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>61–70</td>
<td>65</td>
<td>70</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>71–80</td>
<td>83</td>
<td>81</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>81–90</td>
<td>48</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It has been suggested that approximately 75 percent of newly diagnosed prostate cancers would never be diagnosed if clinical incidence remained at levels that existed prior to the introduction of PSA testing in the population. In the UK, it is estimated that if population-based PSA screening were introduced, prostate cancer diagnosis rates in men aged 50 to 69 years would increase by more than 20-fold compared to the current rates.
4.5. Overdiagnosis and overtreatment

Overdiagnosis is the term used when the diagnosed condition does not lead up to symptoms or death. Patients may experience significant morbidity and loss of quality of life from the overtreatment of clinically indolent prostate cancers. Based on autopsy studies and US SEER data on lifetime risk of death, Welch et al estimated the probability of over diagnosis for prostate cancer would be around 87–94% in men over age 60 years. A prior European publication compared the incidence of prostate cancer between a PSA screened group and a non-screened control, and estimated that over diagnosis due to PSA screening was about 67%. It is estimated that the ability to avoid treating the 80% of men with low-grade disease who will never die of prostate cancer would save $1.32 billion per year in the US.

The United States Preventive Services Task Force (USPSTF) noted that nearly 90% of men with PSA-detected prostate cancer go on to have surgery, radiation or hormone therapy. Up to 5 in 1,000 men will die within 1 month of surgery, and at least 20% to 30% of men getting surgery or radiation therapy will have serious long-term side effects such as urinary incontinence, erectile dysfunction or bowel dysfunction. Hormone therapy is also associated with erectile dysfunction, breast enlargement and hot flashes. The task force changed its recommendation in 2012 to “do not use PSA–based screening for prostate cancer in asymptomatic men”.

4.6. Definition and impact on claims

In many cancer and critical illness products a lump sum benefit is provided upon diagnosis of cancer. However, exclusions to the rule are not uncommon, especially for early prostate cancer diagnosis because subclinical prostate cancer is common in older men and most of them will never suffer clinical symptoms. As mentioned earlier, if population-based PSA screening were introduced, prostate cancer diagnosis rates in men aged 50 to 69 years could increase by more than 20-fold compared to the current rates. Without an exclusion for early prostate cancer, insurance companies face the potential risk of a very significant increase in prostate cancer claims, especially in Asia where PSA screening rate is still low.

Many markets selling critical illness and/or cancer insurance have a standardised definition for cancer with varying exclusions imposed for prostate cancer. There are broadly three types of exclusions commonly used around the world: exclude prostate cancer with a TNM classification of T1N0M0 (T1a, T1b, T1c); exclude only T1a and T1b; exclude up to T2N0M0 (inclusive) or up to a Gleason score of 6 (inclusive) (see Table 8).

Table 8
Exclusions of prostate cancer in markets with standardised cancer definition

<table>
<thead>
<tr>
<th>Country</th>
<th>Exclusion of prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>China, 2015</td>
<td>cT1 (T1a, T1b, T1c)</td>
</tr>
<tr>
<td>Singapore, 2014</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Malaysia, 2010</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Thailand, 2013</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>India, 2013</td>
<td>Up to T2N0M0 (inclusive) or up to Gleason score 6 (inclusive)</td>
</tr>
<tr>
<td>Israel, 2014</td>
<td>Up to T2N0M0 (inclusive) or up to Gleason score 6 (inclusive)</td>
</tr>
<tr>
<td>Canada 2013</td>
<td>Stage A (T1a or T1b)</td>
</tr>
<tr>
<td>UK, 2011</td>
<td>Up to T2N0M0 (inclusive) or up to Gleason score 6 (inclusive)</td>
</tr>
<tr>
<td>South Africa</td>
<td>Up to T2N0M0 (inclusive) or up to Gleason score 6 (inclusive)</td>
</tr>
</tbody>
</table>
TMN staging of prostate cancer is divided into clinical and pathological, and is preceded by the letter of “c” or “p” to clarify. A stage given before surgery based on clinical examination and imaging is clinical, while after surgery based on microscopic findings is pathological. T1 is a clinical stage only, which means doctor cannot detect any tumours on the prostate through digital rectal examination and/or imaging. A needle biopsy confirmed prostate cancer due to increase PSA level without clinical detectable tumour is classified as T1c, if total prostatectomy has been done as a result of the positive biopsy, the classification will be upgraded to pT2, however if the patient decides to receive active surveillance without further surgery, the classification will remain as T1c.

Based on the exclusions shown in Table 8, T1c cases followed by surgery would be payable in China, Malaysia, Singapore, Thailand and Canada (where the exclusion applies only to T1 cancers), but could be excluded in India, Israel, the UK and South Africa (where the exclusion is up to T2N0M0 (inclusive)). It has been reported that 34.7% patients had higher pathological T stage, while only 2.5% had lower pathological T stage compared to clinical stage.

It should also be noted that stage T1 prostate cancers cannot be felt upon digital rectal examination or identified on any imaging, so that any prostate cancer identifiable on MRI, CT or other imaging would be automatically classified at least stage T2. Increasing in radical prostatectomy is predicted especially in East Asia as many robot systems has been installed in this region. The potential for reclassification to stage T2 after surgery and the increasing usage of advanced imaging techniques in cancer diagnosis suggest that the existing exclusion for early prostate cancer used by insurance companies in many countries may not be effective in case of increased uptake of screening for prostate cancer.

The Gleason score is an important prognostic tool for prostate cancer, the lower the score the less aggressive the tumour. A Gleason score of 6 or less represents a low probability of spread of the tumour beyond the gland and a better prognosis than for higher scores. Five year survival for a prostate cancer with lower Gleason score is almost 100%, therefore the combination of TNM classification and Gleason score could provide a more reasonable basis for severity based risk stratification of prostate cancers.
Looking into the future

One of the main limitations of PSA screening is that it cannot determine which prostate cancers are aggressive and need treatment, and which are not likely to cause problems. To address this issue, new generations of prostate cancer biomarkers are emerging, that may supplement PSA testing, or replace it over time. These new biomarkers may help us to identify the virulence of the disease if present, and therefore help clinicians to determine whether to biopsy, when to re-biopsy, and whom to treat or not to treat. There are many new biomarkers currently under development. PCA3 and TMPRSS2-ERG genetic testing are two of the most promising biomarkers as alternatives to PSA diagnostic tests for prostate cancer.

- **Prostate cancer antigen 3 (PCA3) gene test:**
  PCA3 gene testing is used to detect genetic changes specific to prostate cancer. PCA3 is the most specific prostate cancer gene identified to date, its expression is 60- to 100-fold greater in cancerous than in benign prostate tissues, and the accuracy of separating between benign and malignant prostate cells approaches 100%. PCA3 gene test is a urine-based test without the need for taking blood\(^\text{69,70}\).

- **TMPRSS2-ERG gene test:**
  Another urine based gene test. Specific for prostate cancer and can even detect pre-cancerous stages, such as prostate intraepithelial neoplasia (PIN)\(^\text{71}\).

These new generations of prostate cancer biomarkers could help detect more sub-clinical cancers, but could also better differentiate between aggressive with non-aggressive cancers, leading to more personalised diagnosis and treatment.

Should these new biomarkers come into common usage, the current stage and grade based risk stratification systems may need to be revised.

It should also be noted that, since most new biomarkers have a genetic basis, the effectiveness of these biomarkers may vary between ethnicities. Those which have been validated in Caucasians may need to be validated again in Asian populations before being applied for clinical use in Asia.
Conclusion

Although the incidence of prostate cancer is lower in Asian men than in Western populations, a continuous increase in incidence has been observed over the past two decades in Asia, with no signs of reversal to date. The introduction of PSA testing for prostate screening is believed to be a key reason behind this rapid increase, but the Westernisation of Asian diets may also have contributed to this increase.

Although autopsy studies suggest that the underlying prevalence of prostate cancer is also much lower in Asian men than in the West, there is still an enormous gap between the prevalence of prostate cancer observed from autopsy studies and the current reported incidence. The next generation of urine based prostate cancer biomarkers may allow these subclinical cancers to be detected more easily, but they are also likely to differentiate better between aggressive and indolent cancers.

In turn, this might mean that prostate cancer can be detected at a much earlier stage with many such cancers requiring only active monitoring without treatment. With the emergence of new biomarkers, we may need to reconsider the current stage based early prostate cancer concept.

For insurance companies, it is important to understand the impact of possible screening scenarios on their business, including allowance for advances in screening methods. Besides consideration of future scenarios in pricing, further refinement of definitions and product design (such as the introduction of like severity based benefit) will also play an important part in mitigating the risk.
References

Bibliography


