Epidemiological and Molecular Features of Prostate Cancer in Asian Men Living in Asian Countries: Implications in Screen and Management

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Abstract

Prostate cancer is the most common cancer, and second leading cause of cancer death in men in the United States. Incidence and mortality of prostate cancer in most Asian countries are much lower. With dramatic economic development and exposure to westernized lifestyle and increased PSA testing, the incidence of prostate cancer has recently surged rapidly in Asian countries. For the screen and management of prostate cancer, most Asian countries adopt the guidelines and recommendations from Western countries, yet there has been limited data to either support or against such a practice. This review discusses epidemiology, screen and management of prostate cancer in Asian men living in their native Asian countries. In particular, it focuses on the difference of genetic, environment and lifestyle factors and screen program between Asian and Western populations.

Introduction

Prostate cancer is one of the most common cancers in the world with close to 1.1 million new cases diagnosed globally in 2012 [1,2]. Incidence of prostate cancer is very high in the United States, Australia and Scandinavian countries. Although there is a rapidly trend of rising incidence in some Asian countries, the incidence of prostate cancer overall remains relatively low in these countries [3]. For example, the age-standardized incidence rate (AIRs) in Australia and Northern America is 111.6 and 97.2 per 100,000 respectively, and it is only 10.5 and 4.5 in East and South-Central Asia respectively [4]. The incidence in the United States is about 90 fold higher comparing to that in China. In comparison to other cancers, prostate cancer has overall relative low mortality, and it is a less prominent cause of cancer death with about 307,000 deaths globally in 2012 [2]. The overall mortality rates are also higher in North America and Europe, and lower in Asian populations [2]. For example, mortality in the United States is about 26 fold higher than that in China. However, the survival rate of clinically diagnosed prostate patients is lower in Asian population, and the mortality-to-incidence ratio (MR/IR) in Asia is as high as 40% compared to 18% in Europe, 10% in Northern America and 25% worldwide [5]. In particular, the overall MR/IR ratio at Northern America and developed countries has been decreased gradually over the last decade. The ratio at rural China, however, is about 3 times higher relative to developed and urban area with an increasing trend [2]. With recent dramatic economic growth and exposure to westernized diet and lifestyle over the last decades, the incidence and mortality rates of prostate cancer in some Asian countries are rapidly increasing. Prostate cancer is going to be a more serious healthcare and socio-economic problem for Asian countries. Currently, diagnostic and treatment guidelines in Asia are largely based on clinical studies from Western countries.

There has been consistent evidence showing racial differences in the incidence and mortality of prostate cancer, in which Asian men, especially men from East Asia countries (Chinese, Japanese, and Korean), have a substantially lower risk of developing and dying from prostate cancer relative to Non-Hispanic Whites and African Americans. A study using data from the California Cancer Registry from 1995 to 2004 found that even with less favorable prognostic factors such as tumor stage, histological grade, etc., East Asians with prostate cancer have significantly better overall survival than Non-Hispanic Whites with prostate cancer [6]. After controlling other prognostic factors, the multivariate Hazard Ratio for death of prostate cancer in Chinese men was 0.51 (95% CI 0.43-0.62) compared to the Non-Hispanic Whites [6]. As most prostate cancer researches to date have been focusing on Caucasians and African Americans, few studies have been devoted for Asians at genomic and post genomic levels.
The major challenge for prostate cancer management is early detection of aggressive prostate cancer, at the same time to prevent unnecessary biopsy, over-diagnosis and overtreatment of indolent prostate cancer. Overall, Asian men have different prostate cancer genetic variants and biological behavior in comparison with Western population [7-9]. Since most prostate cancers are detected clinically rather than through PSA-based screen in Asian countries, the cancers are often more advanced; therefore, it may be important for Asian countries to have wider exposure to screening program to detect early stage aggressive prostate cancer. However, the current PSA based Risk Calculator for Western countries screen program overestimates the risk of prostate cancer in some Asian countries. Asian countries need to develop their own specific screen programs to prevent unnecessary biopsies and over-diagnosis. Active surveillance is becoming an important management strategy for prostate cancer patients, which is critical to prevent overtreatment. Identification of patients with indolent prostate cancer is the key for success of active surveillance. Criteria and nomograms for selection of patients used in western countries again might not work in Asian countries. The selection criteria and nomograms for active surveillance specific for Asian countries still remain to be developed and validated. Further studies are necessary to develop novel biomarkers as potential screening marker replacing or in addition to PSA, to use genetic profiling of individual prostate cancer for stratifying patients for different therapeutic modality in both Western and Asian populations.

Epidemiology

Despite extensive studies, the etiology and pathogenesis of prostate are not well understood. Like other cancers, both genetics and environment exposure seem play important roles. Asian men moving to USA have a dramatic increase in prostate cancer incidence, which implicates the importance of environmental component. Yet the annual incidence for all the generations of Asian-Americans, however, is only half of that for whites born in the USA, which suggests that prostate cancer is a genetic disease, and genetic variants are critical in the pathogenesis [10].

Diet and lifestyle factors have been long known to be associated with prostate cancer [11,12]. Animal studies link epithelial injury caused by environmental carcinogens and ensuring chronic inflammation to development of prostate cancer [13,14]. Both Epidemiological and animal studies strongly support that dietary intake of red meat and animal fat are risk factors for prostate cancer, which may be associated with the formation of polycyclic aromatic hydrocarbon carcinogens [15,16]. It is believed that the exposure to and metabolism of estrogens, and the dietary intake of phytoestrogens, combined with fat intake, obesity, and burned food processing may all be related to hormonal carcinogenesis and oxidative DNA damage [7]. Several studies indicate that tea may have a preventative effect on prostate cancer with odd ratio around 0.6 in one study [17,18]. Studies have shown that polyphenolic anti-oxidants derived from green tea protect epithelium from injury [19]. Interestingly, dietary Vitamin E, calcium, beta-carotene and selenium intake do not have any significant protective effect on prostate cancer, as shown in randomized clinical trials [20]. As to lifestyle habits, some studies found that physical activity is weakly linked to decreased risk of prostate cancer [21], and lowering the testosterone concentration by vitamin E, calcium, beta-carotene and selenium intake do not have any significant protective effect on prostate cancer, as shown in randomized clinical trials [20]. As to lifestyle habits, some studies found that physical activity is weakly linked to decreased risk of prostate cancer [21], and lowering the testosterone concentration by physical activity seems to be a possible explanation [21].

Asian populations vary greatly on diet and lifestyle habits. Generally, East and Southeast Asian consume more vegetables and tea, less red meat and fat in their daily intake than Western populations, and the diet in East Asian is also relative low in calories. Prostate cancer incidence in native Asian population is only about one-third prostate cancer of Asian-American, which suggests diet and lifestyle habits are important contributing factors to the lower incidence of prostate cancer in native Asian population. With the dramatic economic development and adoption of Western lifestyles in some Asian countries, incidence of prostate cancer is expected to increase substantially. In fact, the incidence of prostate cancer in developing East Asia countries has been grown at a rate of 7.2% per year from 2004 to 2007 [22]. However, more widely use of PSA testing in Asian countries, besides lifestyle/diet changes, may contribute to this rapidly growing trend.

Molecular Characteristics

The clinical behavior of prostate cancer is highly variable, partly due to substantial molecular heterogeneity among prostate cancers. Prostate cancers can be sub types based on molecular signatures, which can be used to predicate aggressiveness of the tumor in some cases [23-25]. Data from The Cancer Genome Atlas (TCGA), largely from Western population, reveals that 74% primary prostate cancers can be sub classified into seven subtypes by specific gene fusions or mutations: ERG fusion (46%), ETV1/ETV4/FLLI1 fusions or over expression (8%, 4%, 1%, respectively), SOP mutation (11%), FOXA1 mutation (11%), and IDH1 mutation (1%). Overall, the majority of primary prostate cancers harbor ETS gene rearrangements. Furthermore, PTEN and TP53 tumor suppressors are deleted or mutated in 20-40% primary cancers; SPOP is mutated in 10% of primary prostate cancer [26]. In comparison with non-metastatic prostate cancer, metastatic cancers have a significant increase in mutations in PTEN and other PI3K pathway components, and Androgen receptor signaling is also more frequently altered. In contrast, only non-metastatic cancers contain IDH1 mutations [27,28]. These data underscore the importance of personalized molecular and genetic profiling to distinguish indolent from aggressive prostate cancer. Yet whether such a classification also applies in Asian population remains to be determined. Two types of genetic variations are important in the pathogenesis of prostate cancer. One is germline common polymorphisms conferring genetic predisposition as a risk factor for prostate. The other is cancer somatic alterations involving prostate cancer initiation, progression, metastasis and drug resistant.

Prostate cancer is associated with numerous germline variants conferring susceptibilities and risk. Early linkage analysis only consistently identified a few loci associated with prostate cancer risk such as 22q and 8q24 [29,30]. Genome-wide association studies (GWAS) have identified more than 70 single nucleotide polymorphisms (SNPs) on various genes or chromosomal loci that are associated with prostate cancer susceptibilities [31]. Individually, each SNPs allele only confers small additional risk for prostate cancer; however, there is evidence that their combined effects on risks are multiplicative [32]. Some of these SNPs have important genetic functions in regulating metabolism and inflammation, which has been associated with carcinogenesis. Most of these GWAS are done in Western and European populations, and more studies recently have been performed in Asian populations. Many SNPs identified in European populations are confirmed in Asian populations [33,34]; however, difference does exist in SNPs between these two populations with some unique SNPs identified in Asian populations. For example, a GWAS on Chinese prostate cancer patients found two new foci at...
The differences in germline variations contribute to the variance of incidence in different population, though it is hard to predict the extent of its effect.

For somatic variations, prostate cancer, like all cancers, is caused by the activation of oncogenes and/or inactivation of tumor suppressors. As a result of development of next-generation sequencing technologies, more and more somatic alterations are identified in prostate cancer. Substantial racial differences of mortality between patients from Western countries and East Asian have been reported, whereas genetic differences may play a role. For example, One common genetic alteration in prostate cancer is gene fusion involving the untranslated region of androgen-regulated gene TMPRSS2 and members of ETS family of oncogenic transcription factors including ERG, ETV1, ETV4, ETV5 and FLI1 [36,37]. Among all the fusion mutations, TMPRSS2-ERG fusion is the most common. In animal study, fusion product ERG enhances prostate cancer development, and the majority of clinical studies also associate TMPRSS2-ERG fusion with unfavorable prognosis [38-40]. The frequencies of TMPRSS2-ERG fusion in Caucasian prostate cancer patients are from 50% to 70%, and it is the most common mutation [40]. While in Asian patients the frequencies are only form 8% and 21% [41,42]. The similar difference between Western and Asian populations is also present with PTEN mutation. PTEN mutation is identified in about 60% to 80% Caucasian prostate cancer patients, only in 10% to 34% East Asian patients in comparison [9]. PTEN loss of function mutation leads to the activation of PI3 kinase pathway. Animal study shows that prostate-specific deletion of the murine PTEN leads to metastatic prostate cancer [43], and it is also a well-established prognostic marker associated with poor clinical outcomes [44]. PTEN genomic deletion has been associated with androgen receptor signaling in hormone refractory prostate cancers [44,45]. On the other hand, RAS/RAF/MAPK pathway mutations are much more common in Asian prostate cancer populations, KRAS mutations are found in 17% Asian patients [46], and BRAF copy number gains are identified in 29% Asian patients [47]. In Western countries patients, KRAS mutations and BRAF copy number gains have been reported in only 3% and 9.2% of patients respectively [46,47]. RAS/RAF/MAPK pathway mutations are critical in the pathogenesis of some cancers such as colon and thyroid carcinoma, its role in development of the prostate cancer is less established. KRAS mutations does not appear to be associated with prognosis or clinical outcomes [46].

Overall, it seems that PI3K pathway mutations are more common in prostate cancer patients from Western population, while RAS/RAF/MAPK pathway mutations are more frequent in Asian prostate cancer patients.

Screen and Early Detection

Like all the cancers, early diagnosis is the key for the control of prostate cancer. Serum PSA has been used in prostate cancer screening, diagnostic and prognostic purposes. PSA-Based population screen was introduced in mid-1980 in most Western developed countries, and only a few Asian countries adopt the program. The incidence of clinical diagnosed prostate cancer in Western countries is about 10 fold higher than that in Asian countries. On the other hand, incidental prostate cancer found in cystoprostatectomy specimens is only about 5 fold higher in Western countries, with 50% in Western countries [48], and 10% in men from Asian countries [49]. These data suggest that international difference of PSA screen programs significantly contribute the worldwide difference of prostate cancer incidence. The role of PSA-based population screening for prostate cancer is controversial. The European Randomized Study of Screening for Prostate Cancer finds that there is modest reduced mortality from prostate cancer with PSA screen [50]. Such a difference could be partially explained by the variations of treatment method in screened versus non-screened prostate cancer (with prostatectomy versus non-surgical means, respectively). No mortality reduction was identified in the large scale longitudinal Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in United States [51].

Population PSA-based screen detects more latent, early-stage cancers, which is thought to be the reason why survival of prostate cancer is significantly higher in countries with PSA-based screen [52]. In a multicenter study, 68% of Chinese patients with newly diagnosed prostate cancer had metastatic disease [53], this really underscores the importance of some screen program for early detection of prostate cancer and improvement of survival in some Asian countries. Interestingly, the relationship between prostate cancer detection rate and PSA levels varies greatly between Asian and Caucasian populations. For examples, prostate cancer detection rate of men with PSA of 4 to 10ng/ml in Americas is about 40% [54]. In contrast, prostate cancer detection rate is only about 20% in Asian men with same PSA levels [55]. The major problems with PSA-based population screen include unnecessary biopsies, over diagnosis and overtreatment of low-stage low-risk prostate cancer [56]. Prostate cancer risk calculators, which include ultrasound volume, digital rectal exam, and transrectal ultrasound in addition to the PSA, were developed in Western countries to reduce the number of unnecessary biopsies. Among them, The European Randomized Study of Screening for Prostate cancer Risk Calculator (ERSPC-RC) [57] and The Prostate Cancer Prevention Trials Risk Calculator (PCPT-RC) [58] are the most widely validated and adopted. However, these two RCs have been found to overestimate the risk of prostate cancer in some Asian countries by more than 20%, given the different genetic and environmental background [59,60]. Recently, a Chinese Prostate Cancer Consortium Risk Calculator (CPCC-RC) was constructed and validated, and it performs well and has higher accuracy compared with ERSPC-RC and PCPT-RC [61]. Overall, screen program based on specific risk calculator is important for Asian countries to decrease the prostate cancer mortality, at the same time, not overwhelmed with unnecessary biopsy and over diagnosis.

There are other prostate cancer biomarkers, which have potential to be used for prostate cancer screen/diagnosis, such as PCA3, TMPRSS2: ERG, AnnexinA3 and Sarcosine [62]. Among these biomarkers, urine PCA3 analysis is most well-studied. PCA3 is a non-coding mRNA. Since PCA3 is highly expressed in prostate cancer relative to normal prostate and benign prostatic hyperplasia [63], theoretically, it can be a better screen marker than PSA for prostate cancer screen. However, PCA3 is measured by quantitative real time PCR [63], which is cumbersome and expensive. Also, there are problems with determining appropriate PCA3 cut-off levels for prostate cancer [64]. Overall, with the current measurement technology, the PCA3 test cannot replace PSA as initial screen/diagnostic test, though it has been approved by the United States Food and Drug administration for use in decision-making regarding rebiopsies when the initial biopsy is negative [65]. The effectiveness of PCA3 need to be validated in Asian population before it can be put to clinical use.
Management

Multiple modalities are available for management of prostate cancer. Treatment strategies include active surveillance, radiation therapy either via an external beam source or by brachytherapy, radical prostatectomy, androgen deprivation therapy and chemotherapy. For men with newly diagnosed prostate cancer, treatment selection is dependent on risk stratification. The National Comprehensive Cancer Network (NCCN) has guidelines for risk stratification [66]. Basically, patients are categorized into different risk groups: very low risk, low risk, intermediate risk, high risk, very high risk and metastatic. The stratification takes into account factors such as anatomic extent of disease (tumor, node, metastatic stage), histologic grade (Gleason score/grade group) of the tumor, and serum PSA. Different initial treatment strategies are recommended to patients in different category. For men with NCCN very low risk prostate cancer and with a life expectancy less than 20 years, active surveillance is usually recommended. For men with NCCN very low risk and with a life expectancy more than 20 years, or men with NCAA low risk prostate cancer, treatment options include active surveillance, radiation therapy and radical prostatectomy with optional lymph node dissection. For men with NCCN intermediate risk prostate cancer, standard treatment options include radiation with or without combination of androgen deprivation, radical prostatectomy with pelvic lymph node dissection. For NCCA high risk patients, treatment options include radiation with long-term androgen deprivation therapy, and radical prostatectomy with extended pelvic lymph node dissection. For NCCA very high risk men, external beam radiation therapy with long term androgen deprivation, or radical prostatectomy with extended pelvic lymph node dissection is recommended. For patients with clinical lymph node involvement, they are usually treated with definitive radiation therapy plus androgen deprivation therapy. Androgen deprivation therapy with or without docetaxel chemotherapy are recommended for men with metastatic prostate cancer. Overall, the risk stratification is based on the understanding that prostate cancer is a disease with prolonged natural history and has risk for progression to disseminated, potential fatal disease [66,67]. These guideline and treatment recommendations are mostly based on clinical evidences from Western countries. Most Asian countries so far basically adopt the guideline assuming similar clinical outcomes. Given the potentially large differences in epidemiological and molecular characteristics as well as prognosis of prostate cancer between Western and Asian populations, more controlled clinical studies from Asian population are indeed needed to determine what guidelines and treatment recommendations best serve the Asian populations. Below, we focus our discussion on the active surveillance as a management strategy, which is critical to prevent overtreatment of prostate cancer with the adoption of screen program, which underscores the importance to develop regional specific guidelines for management of prostate cancer in Asian countries.

Active surveillance is becoming an important management strategy for prostate cancer patients. Patients undergo regular follow-up with serum PSA tests and repeat biopsies, rather than receiving immediate definitive treatment with curative intent. Active surveillance is an accepted option for patients with localized, well-differentiated prostate cancer which have low-risk for progression [68]. With the PSA screen, prostate cancer is often detected when it is not clinically significant. In men less than 40 years dying without a known prostate cancer, about 30% of them are found to have latent prostate cancer at autopsy, in men 60 to 80 years of age, the percentage is as high as 70 to 80% [69]. These autopsy evidences indicate that, in contrast to other cancers, the growth rate of many well differentiated prostate cancers is slow and appears to be relative constant over time. Active surveillance plays a key role in overcoming overtreatment of indolent prostate cancer detected by screen. Multiple observational studies have found that active surveillance is feasible and safe, the majority of patients did not require definitive therapy; there is also a low rate of progression to metastatic disease or death from prostate cancer which is comparable to patients managed with initial definitive treatments; in addition, active surveillance is associated with a higher quality-adjusted life expectancy [70-72].

Identification of patients whose disease will not progress for extended period is a critical issue in the choice of active surveillance for prostate cancer. Multiple criteria have been proposed for identifying patients with a favorable prognosis who are candidates for active surveillance. The criteria vary in different studies. Overall, criteria include patient age, serum PSA level, Gleason score, number of positive biopsy cores, and the extent of prostate cancer in any core [73]. Nomograms have been developed to replacing a single set of criteria to predict the probability of indolent prostate cancer for an individual patient [74,75]. Most of these nomograms include parameters such as serum prostate specific antigen, ultrasound prostate volume, clinical stage, prostate biopsy Gleason grade, and total length of cancer and non-cancer tissue in biopsy cores.

The Success of active surveillance as a management option for prostate cancer patients is dependent on appropriate patient selection based on these criteria or nomograms. Again the majority of these criteria and nomograms are derived from Western countries, and based on evidence from Western population. These criteria and nomograms might not work for Asian population, giving the biological behavior difference of prostate cancer in difference population. For example, in a Western population study, 93% of men meeting Epstein criteria on biopsy have organ confined disease, and 20% have aggressive pathologic features such as Gleason score 7 and extra prostatic extension [76]. In contrast, a study on Korean prostate cancer patients has shown that 30.5% of Korean prostate cancer patients who meet all the conditions of the Epstein criteria for prediction of clinically insignificant prostate cancer might actually harbor prostate cancer with aggressive pathological features [77]. Another study in Korean patient also found that the rate of inaccuracy of the contemporary Epstein criteria is 42.1% in that population [78]. These studies underscore the importance to develop specific criteria or nomograms for Asian countries. A nomogram has recently been proposed to predict insignificant prostate cancer at radical prostatectomy in Korean men in a multi-center study, and the resulting nomogram was reported to have excellent discrimination accuracy, with a bootstrapped concordance index of 0.827 [79]. It is important to note that active surveillance should be applied only if there is an active PSA-based screen program. The selection criteria and nomograms for active surveillance specific for Asian countries still remained to be developed and validated. With the development and increased understanding of genetic profiles for prostate cancer, genetic biomarkers are expected to predict tumor aggressiveness, in particular for Gleason 3 cancer. The genetic profile for prostate cancer is expected to be an important parameter to choose patients for active surveillance; more studies are needed in this front for both Western and Asian population.
Conclusion

The overall prostate cancer incidence and mortality in Asian countries are lower than that in Western countries. Genetic variances, environment and lifestyle factors, and screening programs all contribute to the difference. 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, and the mortality to incidence ration (MR/IR) of prostate cancer in Asian countries is much higher compared to that in Northern America. Yet the overall mortality of prostate cancer is still much lower in Asian countries. These data underscore the importance of developing appropriate screening programs in Asian countries with aim to detect aggressive prostate cancer in early stage but avoid the issue of over-diagnosis and overtreatment of latent, biologically indolent or less aggressive prostate cancer. The current PSA based Risk Calculator for Western countries screen program overestimate the risk of prostate cancer in some Asian countries. Given the differences of prostate cancer risk and prognosis between Western and Asian populations, clinical studies from Asian population are needed to determine the best screen guidelines and treatment recommendations that fit better in Asian population. From a broader perspective, the definition of prostate cancer is unique—it is largely based on changes of histological patterns rather than the identification of invasive mass lesions as typically seen in other cancer types. This may contribute to the problem we are facing today with over diagnosis and over treatment of this disease. Thus, a more defined, probably molecular biomarker driven approach may be needed to replace PSA-driven approach for prostate cancer screen and detection in either Asian or Western population.

References

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