 doi:10.20944/preprints201811.0571.v2

Revisiting Prostate Cancer in India: A Genomic View

Prameesha Perera[a#], Ayam Gupta[c,f#], Nidhi Shukla[b], Mamta Nehra[c], Mukesh Sharma[d], Sneha Mishra[d], Vikram Singh Chauhan[d], Maneesh Kumar Vijay[d], Suresh Kumar Jatawa[f], Archana Tiwari[f], Krishna Mohan Medicherla[b,c], Praveen Mathur[e], Devendra Sharma[d*], and Prashanth Suravajhala[b,c,*]

[a] Department of Botany, University of Jayawardenapura, Nugegoda, Colombo, Sri Lanka

[b] Bioclues.org

[c] Department of Biotechnology and Bioinformatics, Birla Institute of Scientific Research, Statue Circle, Jaipur 302001, RJ, India

[d] Rukmani Birla Hospitals, Gopalpura bypass, Jaipur 302018 RJ, India

[e] Department of Pediatric Surgery, SMS Medical College and Hospital, Jaipur 302001, RJ,India

[f] School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya, State Technological University of Madhya Pradesh, Bhopal, Madhya Pradesh, India.

#Equal contributing authors

*Correspondence: prash@bisr.res.in and devendra.sharma@rbhri.in

Abstract

In the recent past, there has been a rise in Prostate Cancer (PCa) in Asia, particularly India. Although systematic reviews on PCa have dealt on the genetics, genomics and the environmental influence in causal of PCa, no predictive analytics in comparing the PCa from Caucasian, American to Asian population was attempted. In this review article, we have attempted to elaborate this aspect of PCa and deliberated on challenges related to next generation sequencing methods of PCa's manifestation when compared to the west.

Keywords: Prostate cancer, Prostate-specific antigen, incidence, genomics, next generation sequencing

1. Background

Concern for the global epidemiology of Prostate cancer (PCa) is substantially growing (Chen et al. 2017) as it accounts to the second most common cancer worldwide (GLOBOCON 2012, 2018)(Haas et al. 2008) and third most prevalent cancer in India (Ferlay et al. 2015). PCa cases are diagnosed in over one million annually and the mortality rate has grown to more than 300,000 deaths per year. Incidence and mortality differ among geographic regions and populations showing multifactorial impacts of genetic variation, diet, lifestyle, environmental factors and use of prostate specific antigen-based screening policies (Bashir 2015). In 2012, 1.1 million men were diagnosed with PCa worldwide, a total of 759,000 cases were recorded, (Figure 1) with Europe having the highest estimate of PCa cases (37.8%) followed by Northern America (28.4%), Asia (15.8%), Latin America and Caribbean (11.5%), Africa (4.0%) and Oceania (2.4%) (2012). Reported PCa incidence rates varied over 25-fold worldwide (Wong et al. 2016), where awareness about PCa is lacking men may not come forward for the diagnoses itself. On the other hand, the Prostate-specific Antigen (PSA) screening serves as one of the most common non-invasive biomarkers to detect PCa (Hernández and Thompson 2004). As described by Chen *et al.*, 2017, the world mortality-to-incidence ratios (MIR) for PCa was 28.1% wherein less developed

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

regions demonstrated high MIR for PCa with the highest MIR of 71.9% found in Africa. Countries with higher levels of human development and per capita gross domestic product (GDP) had been accounted with higher PCa incidence but not in mortality rates. In addition, the PCa incidence and mortality correlation with socioeconomic development of country showed a simple linear regression between PCa incidence/mortality and human development index (HDI) (Wong et al. 2016). On the other hand, Asians who immigrated to the western countries have been accounted for higher incidence of PCa when compared to the people in their native country. Reason for the higher occurrence of the PCa among Asian migrants could be due to diffident health care systems and more importantly the diet (Whittemore et al. 1995). However, it can be speculated that the westernized diet in Asian countries may have an influence on high risk of PCa, but it is difficult to show the impact of diet on PCa (Hwang et al. 2009).

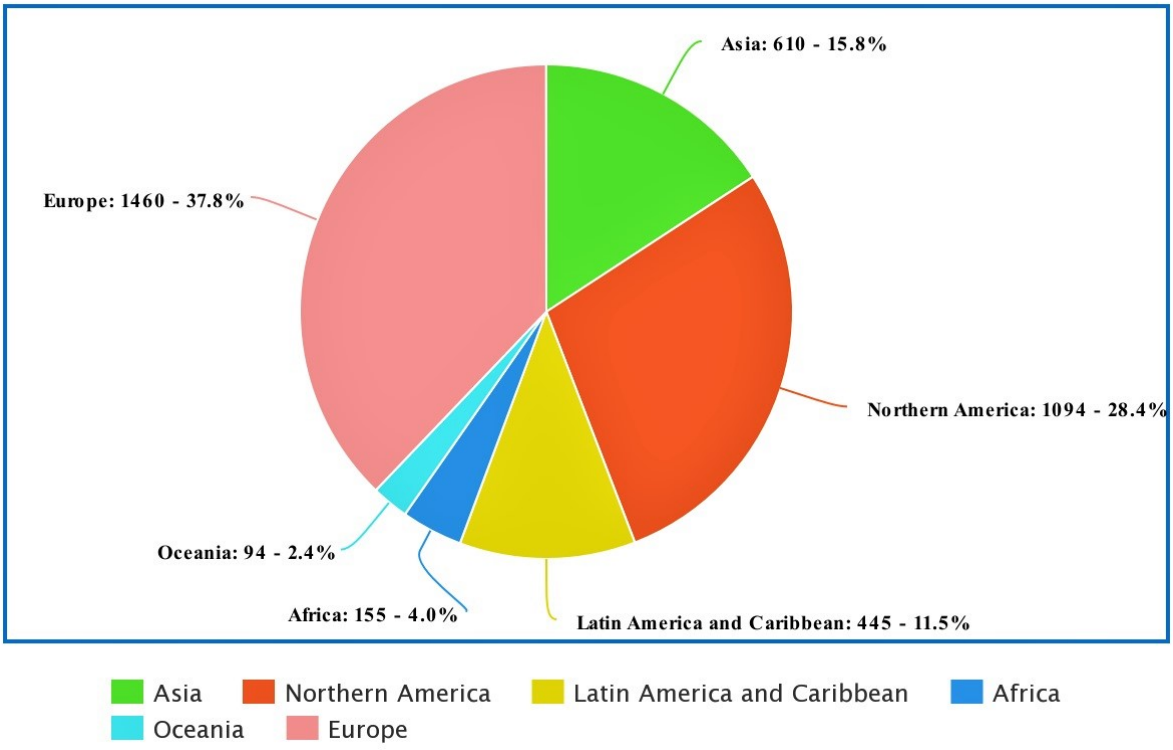

Figure 1: Estimated five year prevalence of PCa cases (*1000), adult population. Source: *GLOBOCAN*, 2012.

1.1. *PCa in India and South Asian Population*

The census of India released on July 15, 2011 revealed interesting statistics relevant to the pattern of prevalence and other disease characteristics of PCa (Sinha et al. 2003). Though the prevalence and characteristics of PCa have been studied in India, its true incidence is limited, perhaps owing to the lack of exposure of patients to clinic and the unavailability of diagnoses with cancer registries. In the recent past, the population of India in general and that of the areas covered by the registries have displayed rapid changes in life styles, dietary practices and socio-economic milieu, with scope for diagnostic and detection technologies to be improved for people to access and afford it. The most recent Population Based Cancer Registries (PBCRs) of different cities for the time period (2008–2011) shows that PCa has ranked among top ten leading sites of cancer in many cities including Bangalore, Barshi, Bhopal, Chennai, Delhi, Mumbai, Kamrup, Ahmedabad, Kolkata, Kollam, Nagpur,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

Pune, Trivandrum and Wardha (Figure 2). Some reports illustrate several genetic mutations associated with decreased risk of certain cancers in South Asians and polymorphism at *GSTM1* and *GSTP1* gene loci for PCa (Tran et al. 2018). In south Asians found to be higher prevalence of polymorphisms in DNA repair systems XRCC1 and XPD in which responsible for DNA repair and reduce cancer susceptibility.

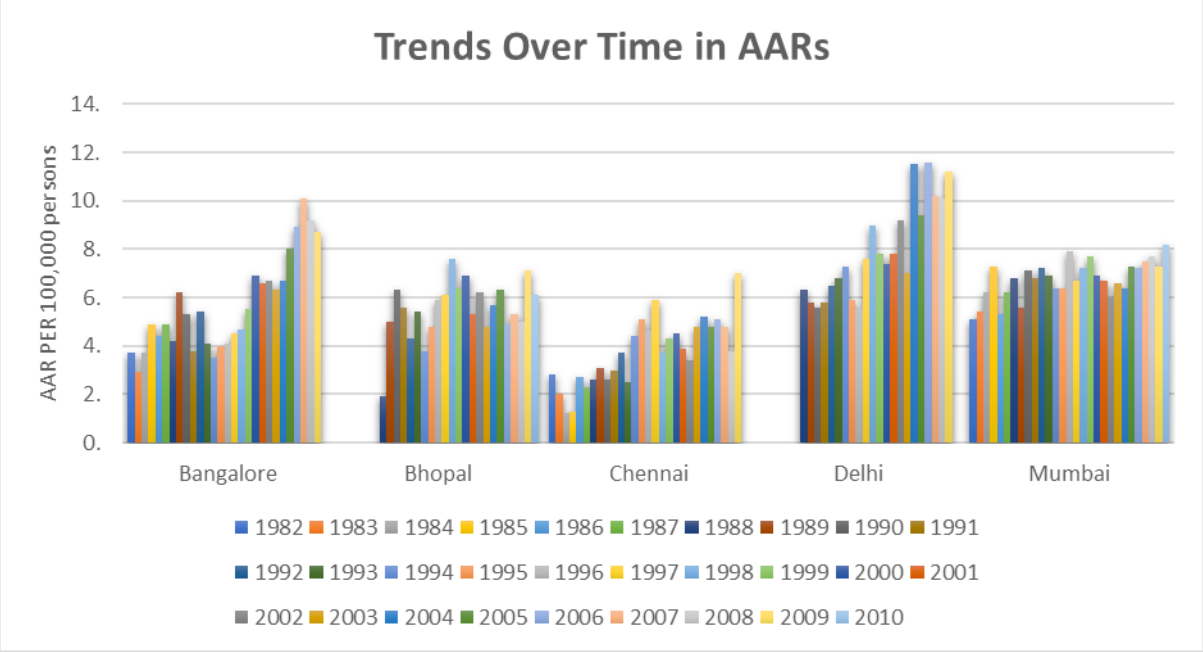

Figure 2: Graph showing trends over time in age adjusted rates for five population-based cancer registries. Image adapted from Jain, Saxena and Kumar, 2014.The incidence of PCa is relatively low in some states like Gujrat (Ahmedabad and Wardha PBRCs) and Madhya Pradesh (Bhopal PBCR) with the lowest being north east region of India [12]. PCa is the second leading cancer among males in large Indian cities like Delhi, Kolkata, Pune and Thiruvananthapuram, third leading site of cancer in cities like Bangalore and Mumbai and it is among the top ten leading sites of cancers in the rest of the PBRCs of India. The cancer projection data shows that the number of cases will become doubled by 2020.

1.2. *Identifying PCa mutations using Next Generation Sequencing methods*

In the recent past, next generation sequencing (NGS) has allowed the simultaneous identification of millions of short stretches of nucleic acids (Barbieri et al. 2013)screening a large number of genes with greater sensitivity and cost effectiveness (Stratton 2011). The NGS studies branched towards understanding the cancer genome of several tumor types (MacConaill and Garraway 2010). An attempt to perform diagnostic, prognostic, predictive biomarkers and biomarker-designed clinical trials is on the anvil (Stratton 2011). Application of NGS has led towards easier identification of the PCa variants by exposing hidden information through genomic and transcriptomic landscape, especially on key biological and molecular components of progression and potential therapeutic opportunities of castration-resistant PCa (CRPC), a type of PCa that keeps growing at the cost of reduced levels of testosterone (Robinson et al. 2015). In other words, early-stage PCa need optimal levels of testosterone for growth, but CRPCs do not need optimal testosterone levels.

As far as mutations are concerned structural genomic rearrangements (Barbieri et al. 2012) due to deletion of tumor suppressors such as *PTEN*, *TP53*, *NKX3-1 (Barbieri et al. 2017)* and *CDKN1B* (Shen and Abate-Shen

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

2010) and BRCA mutations identified in patients with PCa were found to be somatic with ca. 15% of patients with metastatic CRPC (mCRPC) (Robinson et al. 2015). The genome-wide profiling in the plasma of patients having PCa revealed multiple copy numbers, such as losses in 8p and gains in 8q in addition to identification of *TMPRSS2-ERG* rearrangement associated 3-Mbp deletion on chromosome 21 (Heitzer et al. 2013). Thus, determining somatic copy number alterations (SCNA) serving as mutational hotspots could be helpful. A novel mutational hotspot at the *KCCAT42*, *FENDRR*, *CAT1886* and *STCAT2* loci at the 16q23.1-q24.3 loss were identified as alterations of lincRNA sequences (Camacho et al. 2017). Tomlins *et al.*, 2005 described that, in approximately 50% of all PCas' have gene fusions and rearrangements of ETS family of transcription factors (*TMPRSS2-ERG*). Moreover, other ETS family members such as *TMPRSS2-ETV1*, *TMPRSS2- ETV4*, *TMPRSS2-ETV5*, and *SLC45A3-ERG* frequently rearranged and overexpressed in PCa. This phenomenon is found only in prostatic tumors and occasionally present in high-grade prostatic intraepithelial neoplasia.

From *in vitro* and *in vivo* assessments of gene and protein expression, Ren *et al.*, 2018 showed that the *PLXNA1* protein as an effective therapeutic target to treat advanced PCa. Enhanced reduce representation bisulfite sequencing (ERRBS) can detect genome-wide DNA methylation at single-base resolution including CGI shores and allele-specific methylation (ASM) at various regions (Lin et al. 2013). Based on the ChIP-Seq, Chen *et al.*, 2013 showed that ERG restores an androgen receptor (AR) transcriptome in PTEN-deleted PCa. In addition, methylated DNA immunoprecipitation sequencing (MeDIP-Seq) method involves isolation of methylated fragments of the genome by using an antibody (Thu et al. 2009). This involves epigenetic mechanisms such as DNA methylation and histone modification that play an important role in PCa development and progression associated with molecular and cellular alteration (Li et al. 2005). Various DNA methylation markers have been found in PCa, *viz.* CpG island hypermethylation of *glutathione-S-transferase P* (*GSTP1*) promoter DNA, resulting in the loss of *GSTP1* expression (Lin et al. 2001). A number of methylation profiles have been developed and are being evaluated as potential markers for early diagnosis and risk assessment (Chen et al. 2013). In the recent-past, iCLIP-Seq methods to infer RNA-Protein interactions at a higher resolution is made available (Huppertz et al. 2014).

1.3. *Screening PCa using PSA*

After the first discovery of Prostate Specific Antigen (PSA) in prostate tissue in late 1970s, it has been widely used as a tumor marker for PCa detection albeit has become bit controversial in use (Giunta 2013). The PSA is a glycoprotein with enzymatic protease activity secreted by prostatic epithelium and due to the enzymatic activity, the PSA liquefies the semen and increases the sperm motility (Held-Warmkessel 2006). PSA is a serine protease of approximately 33 kDa in size and is secreted by epithelial cells of prostate. In normal prostate, PSA is secreted into the luminal fluid whereas in case of PCa, it gets leaked into circulation due to disruption of basal cell layer resulting in an increase in PSA level (Lilja et al. 2008). The drawback of PSA test is its low specificity since PSA levels can be elevated in benign prostatic hyperplasia (BPH), prostatic infarction and in prostatitis (Liu et al. 2012) even as PSA does not differentiate between different stages of PCa (Hessels and Schalken 2013). To distinguish cancerous form from benign conditions and slow-growing from aggressive cancers, improved PSA tests in the form of PSA density, PSA velocity, detection assays for checking molecular forms of PSA, and precursor or pro-PSA, human glandular kallikrein 2 (hK2) and urinary marker uPM3 have been in use

 doi:10.20944/preprints201811.0571.v2

(Catalona and Loeb 2010). However, the most widely accepted method is the Gleason grading system (Gleason 1981).

1.4 *Enhancement of the PSA tests*

Many efforts are being done to increase the diagnostic accuracy of PSA, including measurement of different molecular forms of PSA and rate of PSA increase. Total PSA (tPSA) refers to the sum of free PSA (unbound) and bound PSA (complexed predominantly to α-1-antichymotrypsin). The percentage free PSA test is approved for use in men which helps discriminate between the presence of PCa and BPH that serves as a predictor for biopsy (Catalona et al. 1998). In this process, laboratory tests in the form of Prostate Health Index (PHI), Digital Rectal Examination (DRE) have been helpful for primary screening the patients depending on the PSA test result (Eckersberger et al. 2009).

2. Role of Metabolic diseases associated with PCa

Metabolic diseases such as diabetes have a major role to play towards an increased risk of several human malignancies such as cancers of the pancreas, colon, endometrium, breast, kidney, liver, biliary tract and esophagus (Meyer et al. 2007). However, association of diabetes with decreased risk of PCa in depth only long-term diabetes has a protective effect on PCa have been reported from several studies (Meyer et al. 2007; Baradaran et al. 2009), nonetheless some literatures have been provided evident for opposite opinion (Meyer et al. 2007). There are several mechanisms to describe the protective effect of diabetes on PCa whereas protection against the PCa is due to the hormonal alterations; insulin and testosterone (T) in diabetes patients (Pitteloud et al. 2005). Initially insulin level of diabetes patients seems to be higher, then on decrease gradually with disease progression due to progressive beta cell burn out while T and sex hormones binding globulins (SHBG) levels also drop with the time (Shaneyfelt et al. 2000). Numerous human and animal studies have shown that both androgens (Travis et al. 2007) and insulin (Hsing 2001) have an effect on prostate cell growth and malignant transformation. Therefore, it is believed to be low risk of PCa is due to the decline of T and or insulin in patient with diabetes. However, the results of all the epidemiological studies rely on sex hormones not consistent (Shaneyfelt et al. 2000). Baradaran *et al.*, 2009 demonstrated that a small, albeit significant drop of PCa risk for increasing level of T/SHBG ratio and further Will, Vinicor and Calle, in 1999 observed PCa risk to have doubled more than 5 years of diabetes diagnosis. However, steroids are not only the key factors for protective effect on PCa in diabetes patients but there could be an influence of hormonal environment also apart from testosterone, Insulin, insulin like growth factors (IGF) and leptin have effect on this inverse relationship (Baradaran et al. 2009). Alterations in serum testosterone and IGF-I concentrations result by diabetes mellitus, have influence on PCa risk reduction among men with genetic background of diabetes seems biologically plausible (Mantzoros et al. 1997). Another explanation based on the existence of a genetic factor that promotes diabetes risk and let fall the PCa risk. Genetic variation in peroxisome proliferator-activated receptor-gamma (PPARG) has association with a higher incidence of diabetes mellitus (Hegele et al. 2000) and also expressed in human prostate adenocarcinomas and derived cell lines. Inhibition of PCa cell growth is expected to be the activation of this receptor with specific ligands (Mueller et al. 2000). As described by Hsing, Sakoda and Chua Jr., 2007 long term diabetes condition results in insulin resistance. Insulin is a potent mitogenic and anti-apoptotic factor and stimulates the prostate growth further, DNA polymorphisms in the insulin gene may be linked with increased PCa risk. Pro-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

gressive insulin resistance and B-cell failure along with insulin depletion arising with long-standing diabetes may limit insulin actions and reduce the PCa risk. However, declined androgen levels in severe diabetes cases are probably due to a toxic effect of hyperglycemia on the Leydig cells of the testis (Barratt 2018).

The PCa incidence and mortality rates around the world highly demonstrate correlation with average level of fat consumption. It is speculated that, western diet associate with some life style factors, i.e. physical activity influence on increase level of PCa risk. With western diet full of calories especially polyunsaturated fats, it lacks certain essential nutrients as animal products and processed refined foods are mainly consumed by them resulting in higher intake of processed polyunsaturated fats and refined carbohydrates. Conversely, the consumption of fresh vegetables comparatively low, hand meats and dairy products rich in some constituents such as Zn and Ca have been shown risk of development of PCa. Some reports revealed men who consume higher levels of Ca via food intake or as supplement may prone to develop advanced PCa, nonetheless all the reports are not consistent (Kovács and Hoskin 2013). In contrast, many south Asians practice vegetarianism by avoiding the consumption of meat and fish products. It has been suggested that vegetarian diets have been related with decreased risk of PCa (Sinha et al. 2003) even as fresh vegetables, fruits, pulses and whole grains resulting in a low intake of fiber and phytonutrients may protect against PCa (Kovács and Hoskin 2013). Furthermore, spices and food additives used by south Asians play an important role in protection against cancer. For example, disease prevention capability of Turmeric has been widely discussed revealing its antioxidant, anti-inflammatory and chemo-preventive capacity. In addition, turmeric suppresses tumor initiation, promotion, and metastasis in experimental studies, in deep, turmeric may block the activity of nuclear factor kappa-B (NF-kB), responsible for cancer cell growth in many cell types. On other hand, screening behavior and access to care are followed by south Asians are important in cancer prevention (Sinha et al. 2003).

3. Genetic Biomarkers for PCa

Urine, a waste product of kidney, has become one of the most attractive bio-fluids in clinical proteomics (Fernandez-Serra et al. 2015). Urine is non-invasive, harmless and can be collected in large quantities without any significant proteolytic degradation (Eric Thomas et al. 2010; Ploussard and De La Taille 2010). Since prostate cells can be detected in urine (Fujita et al. 2009), different biomarkers specific to PCa has been identified through urine and used as serological marker in diagnostic test, which are described below:

3.1 *Non-coding RNA as biomarkers*

MicroRNAs (miRNAs) are naturally-occurring, small (18-22 nucleotides) non-coding RNAs (Bartel 2009) that control the expression of more than 60% of protein-coding genes, have regulatory function on various molecular signaling pathways in the cell and are therefore potential diagnostic indicators of tumor formation and metastasis(Jansson and Lund 2012). Differential expression of miRNA in PCa can be firmly correlated with its clinical expression suggesting that miRNAs are promising potential biomarkers and can be used in the detection of PCa (Catto et al. 2011). At present, over 10000 human miRNAs have been reported out of which more than 200 common miRNAs have been analyzed from urine exosomes. There have been a large number of studies to prove the usefulness of urinary miRNAs in combination with clinical parameters for enhancing the accuracy of classification of PCa. Among all the miRNAs reported, *miR-141, miR-21, miR-200b, miR221, miR-106b* and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

miR-375 have been the most frequently investigated in urine from PCa patients(Bryant et al. 2012) (Bryant et al. 2012; Jackson et al. 2014). Further analysis revealed that all these miRNAs were overexpressed in PCa serum samples compared with healthy controls which are in agreement with other studies. Together all these data suggest that use of miRNAs for non-invasive and specific detection of PCa can be very promising and can significantly improve the prediction level of the presence of PCa.

Prostate cancer antigen 3 (PCA3), also known as Differential Display code 3 (DD3), a prostate-specific long non-coding RNA is dramatically overexpressed in human PCa tissue relative to normal prostate tissue (Bussemakers et al. 1999). The PCA3 score is calculated as the ratio of PCA3 to PSA mRNA (PCA3 mRNA/PSA mRNA x 1000) (Gou et al. 2014). Compared to PSA test which gives false positives, PCA3 is more accurate in predicting clinically significant PCa and could be used as a diagnostic tool for PCa screening, grading and recurrence monitoring (De Kok et al. 2002; Tinzl et al. 2004). The limiting factor with PCA3 is that it does not correlate with Gleason score and clinical tumor staging which restricts its use in the medical field. Recent studies, however has enabled identification of other urinary long non-coding RNAs such as metastasis-associated lung adenocarcinoma transcript 1 (*MALAT-1*) a multiple cancer-associated lncRNA (Wang et al. 2014), and *FR0348383*, a PCa-associated lncRNA (Zhang et al. 2015). Whereas *MALAT-1* or *FR0348383* have great potential as independent predictors of PCa, a large multi-center study has validated the clinical utility of a 3 protein-coding gene panels (*HOXC6, TDRD1*, and *DLX1*) in urine (Leyten et al. 2015). Surprisingly, these three gene panels were known to have higher accuracy compared with urinary PCA3 or PSA in predicting aggressive PCa and combining them with PSA further improved the predictive accuracy. lncRNAs in plasma do not exist in their full-length form, though few stable fragments can be highly expressed and detectable in human plasma (Ren et al. 2013)

3.2. *Gene fusion biomarkers*

Gene fusion is the process of combining two or more distinct genes into a single chimeric gene or transcript and a major mechanism in driving carcinogenesis (Berger et al. 2011). The *TMPRSS2-ERG* fusion gene is a PCa-specific fusion gene comprising androgen-related transmembrane protease serine 2 gene (*TMPRSS2*) and ETS-related gene (*ERG*), which results in aberrant expression of the transcription factor *ERG* and inhibits normal prostate differentiation (St. John et al. 2012). The diagnostic accuracy of combining *TMPRSS2-ERG* and *PCA3* into a urine test is significantly higher than that of the PSA test (Mikhaĭlenko et al. 2014). This combination can also reduce more than half of repeat biopsies with no notable negative consequences suggesting that a large number of men could avoid unnecessary invasive procedures by applying this approach (Merdan et al. 2015).

A different approach was carried out by Liong group which can differentiate between PCa samples from normal samples by using blood-based microarray analysis (Liong et al. 2012). Through quantitative real time PCR, a panel of seven genes *(CTAM, CXCR3 (CD183), FCRL3, KIAA1143, KLF12, TMEM204, SAMSN1)* were identified that could distinguish between aggressive PCa and healthy patients with a high sensitivity and specificity rate. All these significant genes have been shown to be involved in the immune response, chemotaxis and gene transcription regulation in carcinogenesis (Roth et al. 2000; Pasquier 2004; Yeh et al. 2008).

3.3. *Gene methylation markers*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

Gene methylation, a process by which methyl groups are added to DNA, represents an epigenetic alteration in PCa that has been well characterized in tissues and is a promising area for urine biomarker development (Kulis and Esteller 2010). In urine as well as tissue specimens, aberrant DNA methylation can be detected by a number of methods, *viz.* including methylation-specific polymerase chain reaction (MSP), methylation-sensitive single-nucleotide primer extension (MS-SNuPE), bisulfite sequencing, and combined bisulfite restriction analysis (COBRA). One well-known DNA methylation target is glutathione-S-transferase P1 (*GSTP1*), a gene involved in phase II metabolism playing an important role in cell-cycle regulation. Expression of *GSTP1* is high in the basal cell layer and luminal cells of benign prostate glands, with progressive loses observed in PIN with only the basal cell layer staining and is absent in PCa glands which underlines its involvement in early carcinogenesis (Martignano et al. 2016). Several studies have reported that measurement of *GSTP1* promoter methylation may complement PSA screening for PCa diagnosis. Along with *GSTP1*, some other gene methylation markers (for e.g. *APC*, *CRIP3*, *HOXD8*) have also been tested which needs further evaluation to be used as a biomarker for PCa detection (Zhao et al. 2017).

3.4. *Protein based biomarkers*

Through proteomics studies, thousands of peptides can be analyzed simultaneously which leads to identification of new biomarkers. By using MALDI-TOF, a group identified two markers; uromodulin and semenogelin that shows high sensitivity and specificity and could distinguish PCa versus BPH. Engrailed -2 (EN2), a protein found in the urine of patients with PCa, proved to be a potential biomarker for the diagnosis of PCa compared to ELISA (Morgan et al. 2011). Human kallikrein 2 (KLK2), a protease localized to prostatic epithelium, when used in combination with PSA, PCa diagnosis is significantly improved (Saedi et al. 2001). In addition, an olfactory Prostate-specific G-protein-coupled receptor (PSGR) is known to activate major cell-survival signaling cascades causing an inhibition in PCa cell proliferation and might form a new subset of potential biomarker for the detection of PCa (Xu et al. 2000, 2006).

3.5. *Immunological biomarkers*

One of the most widely used immunological biomarkers is alpha-methyl acyl-CoA Racemase (AMACR) which is highly expressed in prostate adenocarcinomas and can be detected in blood and urine with a high sensitivity and specificity (Jiang et al. 2003; Sreekumar et al. 2004). B7-H3 (or CD276), an antigen-specific inhibitor of T-cell mediated anti-tumoral immunity has been observed in high pathological stages of PCa (Mahnke et al. 2007; Roth et al. 2007). Early prostate cancer antigen (EPCA), a nuclear matrix protein, have recently been shown to be involved in PCa which needs further evaluation (Zhao et al. 2010).

4. Current challenges for diagnosis of PCa

Factors that related with significant PCa are PSA level, Gleason score, smaller prostate volume, abnormal DRE findings, age besides ethnicity (National Collaborating Centre for Cancer (UK), 2008). Four third of all PCa patients are above 65 years old and it is rarely diagnosed in men under 50 (Parkin et al. 2005). The initial diagnosis date has been risen up approximately 5 years with the use of PSA testing (Kessler and Albertsen 2003). Onset in familial PCa is usually reported in men under 55 years old however, sporadic PCa rarely diagnose at this age (Carter et al. 1993). From all cases approximately 10% have been reported as familial PCa

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

whereas approximately 40% of patients under 55 years old account for familial PCa. Shared environmental factors and genetic susceptibility may result the familial predisposition to PCa. Specific mutations in two genes; *BRCA1* and *BRCA2* which are responsible for breast cancer patterns, even have greater risk with PCa. Mutations in *BRCA2* consistently associate with risk of PCa and relative risk is higher in men under 65 years old (Liede et al. 2004).

The marker PSA is specific to the prostate gland and not for PCa, PSA elevation are also seen with the disease condition BPH and Prostatitis. Under mention several PSA derivatives and concepts have been studied in effort to reduce the number of unnecessary biopsies and identify clinically significant tumors. Discoveries on different molecular forms of PSA represent the potential means of diagnostic specificity by differentiating PSA elevations seen with PCa and BPH. Serum PSA level associate with PCa are at least 10 times higher per gram of tissue than with BPH but due to the variable amounts and weight of BPH tissue in the gland cause difficulty in interpreting PSA value (Held-Warmkessel 2006). Current recommended normal reference range for PSA is 0-4.0 ng/ml. However efforts to increase the sensitivity of cancer detection in younger men and decrease the number of unnecessary biopsies in older men (improve specificity) led to establishing age and race specific PSA range suggested recommendations have been developed based of the results of several researches that demonstrated the PSA levels correlation with patient's race, age and prostate volume (Table 1) (Held-Warmkessel 2006). Since the use of PSA is limited and controversial, the search for novel PCa-specific biomarkers, especially from non-invasive bio-fluids is an important task (Wu et al. 2017). Due to the heterogeneity of the disease, no single biomarker will be diagnostic and prognostic for every patient (Velonas et al. 2013). Based on this, it can be concluded that the next diagnosis or PSA test will most likely be an assay comprising multiple biomarkers that are differentially expressed in PCa. Also, success of these biomarkers will depend on their validation in large cohort of patients and translation of these findings to clinical practice.

5. Comparative NGS analyses of PCa datasets:

There has been a consistent need to understand the genetics behind PCa although a large number of cohort studies have been instrumental in identifying the causal genes and differentially expressed genes (DEG). From our pilot analyses, we surveyed four datasets (supplementary table 1) across Caucasians, American and Asian (Chinese) (Prensner et al. 2011; Ren et al. 2012; King et al. 2017) and tried to predict the common genes across them (figure 3). This gives a subtle reason to demonstrate the effect of DEGs and the nature of the genes observed from transcriptome and whole exome sequencing (WES) respectively (supplementary information). While comparing exomes between Caucasian and Asian population, we observed eleven common genes between them, *viz. ITGA7, ZNF691, ZSWIM5, NRG4, KRBA2, ECT2, FAM91A1, PDZD8, PYGL, EDN2 and TP53I3.* On the other hand, *CRISP, CSRP3, COL2A1, UGT1A6, UGT1A1, LRRN1, UGT1A3, B4GALNT4* and *KCNC2,* a total of nine genes were common between transcriptomes of Caucasian and Asians, and we observed eight common genes in between "DEGs", "Exome Caucasian" and "Exome Asian" in the form of *ITGA7, ZNF691, ZSWIM5, NRG4, KRBA2, FAM91A1, PDZD8, PYGL* and three common between the DEGs and exome Caucasian, *IGDCC4, LIG4* and *EZH2.*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 April 2019 doi:10.20944/preprints201811.0571.v2

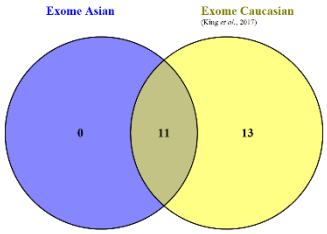

Figure.3a

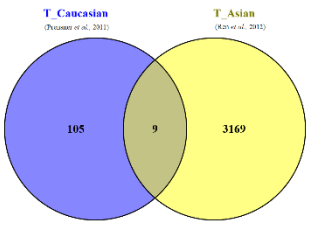

Figure.3b

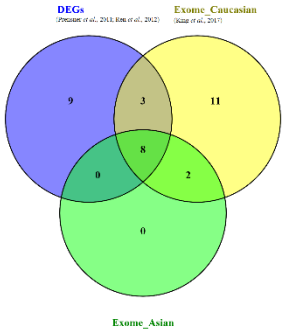

Figure.3c

Figure 3 (a) The Venn diagram shows eleven common genes across Caucasian and Asian exome datasets (*ITGA7*, *ZNF691*, *ZSWIM5*, *NRG4*, *KRBA2*, *ECT2*, *FAM91A1*, *PDZD8*, *PYGL EDN2 andTP53I3*). (b) Nine common genes in Caucasian and Asian transcriptomes (*CRISP3*, *CSRP3*, *COL2A1*, *UGT1A6*, *UGT1A1*, *LRRN1*, *UGT1A3*, *B4GALNT4*, *KCNC2)* out of total 3169 genes from Asian dataset and 105 genes from the Caucasian dataset and (c) Eight common genes (*ITGA7*, *ZNF691*, *ZSWIM5*, *NRG4*, *KRBA2*, *FAM91A1*, *PDZD8*, *PYGL*) across Asian exome, Caucasian exome and DEGs were found. However, three common genes (*IGDCC4*, *EZH2*, *LIG4*) were found across DEGs and Caucasian exome.

6. Palliative Care

Palliative care is specialized medical care that is catered for serious illness. While it focuses on providing relief from the symptoms, pain and stress, several attempts have been made to improve quality of life for the patient and family members (Lutz et al. 2007; Thompson et al. 2007a). PCa leads to various problems such as interrupted flow of urine, difficulty starting or stopping urination and painful or burning sensation during urination. Other symptoms might include pain in bones, lower back, hips or upper thighs; difficulty having an erection; pain with ejaculation; and blood in the urine or semen. Early PCa, however, does not usually cause such extreme symptoms. Several options for treating PCa include surgery, radiation therapy and hormone therapy (Thompson et al. 2007b). Abiraterone acetate is a type of hormone therapy given to patients with metastatic PCa when they stop responding to other types of hormone therapy as the drug stops the testosterone production as the PCa cells that cannot proliferate in its absence (Zobniw et al. 2014). The survival, however for post-palliative care is assumed to be nine to twelve months.

7. Conclusions

We have attempted to discuss the reasons pertaining to the lack of PCa diagnoses in Indian population while reviewing the challenges, methods and histopathological aspects of PCa. However, one definitive need for post treatment regimen is palliative care which is certainly lacking with PCa diagnoses. With the NGS datasets uprising, one question still remains elusive: Is there an end to the problems of early detection of PCa?

Conflict of interest: none

References

Baradaran N, Ahmadi H, Salem S, et al (2009) The protective effect of diabetes mellitus against prostate cancer: Role of sex hormones. Prostate 69:1744–1750. doi: 10.1002/pros.21023

Barbieri CE, Baca SC, Lawrence MS, et al (2012) Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 44:685–689. doi: 10.1038/ng.2279

Barbieri CE, Bangma CH, Bjartell A, et al (2013) The mutational landscape of prostate cancer. Eur Urol 64:567–576. doi: 10.1016/j.eururo.2013.05.029

Barbieri CE, Chinnaiyan AM, Lerner SP, et al (2017) The Emergence of Precision Urologic Oncology: A Collaborative Review on Biomarker-driven Therapeutics. Eur Urol 71:237–246. doi: 10.1016/j.eururo.2016.08.024

Barratt J (2018) Collaborative communication: learning from advanced clinical practice patient consultations. Nurs Stand 33:27–32. doi: 10.1038/sj.bjc.6601857

Bartel DP (2009) MicroRNAs: Target Recognition and Regulatory Functions. Cell 136:215–233

Bashir MN (2015) Epidemiology of prostate cancer_1. Asian Pacific J Cancer Prev 16:5137–5141. doi: 10.7314/APJCP.2015.16.13.5137

Berger MF, Lawrence MS, Demichelis F, et al (2011) The genomic complexity of primary human prostate cancer. Nature 470:214–220. doi: 10.1038/nature09744

Bryant RJ, Pawlowski T, Catto JWF, et al (2012) Changes in circulating microRNA levels associated with prostate cancer. Br J Cancer 106:768–774. doi: 10.1038/bjc.2011.595

Bussemakers MJG, Van Bokhoven A, Verhaegh GW, et al (1999) DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Res 59:5975–5979. doi: 10.1038/ncb2161

Camacho N, Van Loo P, Edwards S, et al (2017) Appraising the relevance of DNA copy number loss and gain in prostate cancer using whole genome DNA sequence data. PLoS Genet 13:1–28. doi: 10.1371/journal.pgen.1007001

Carter BS, Bova GS, Beaty TH, et al (1993) Hereditary prostate cancer: Epidemiologic and clinical features. J Urol 150:797–802. doi: 10.1016/S0022-5347(17)35617-3

Catalona WJ, Loeb S (2010) Prostate cancer screening and determining the appropriate prostate-specific antigen cutoff values. J Natl Compr Canc Netw 8:265–270. doi: 10.6004/jnccn.2010.0017

Catalona WJ, Partin AW, Slawin KM, et al (1998) Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: A prospective multicenter clinical

trial. J Am Med Assoc 279:1542–1547. doi: 10.1001/jama.279.19.1542

Catto JWF, Alcaraz A, Bjartell AS, et al (2011) MicroRNA in prostate, bladder, and kidney cancer: A systematic review. Eur. Urol. 59:671–681

Chen R, Ren S, Meng T, et al (2013) Impact of glutathione-S-transferases (GST) polymorphisms and hypermethylation of relevant genes on risk of prostate cancer biochemical recurrence: a meta-analysis. PLoS One 8:e74775. doi: 10.1371/journal.pone.0074775

Chen SL, Wang SC, Ho CJ, et al (2017) Prostate cancer mortality-to-incidence ratios are associated with cancer care disparities in 35 countries. Sci Rep 7:1–6. doi: 10.1038/srep40003

De Kok JB, Verhaegh GW, Roelofs RW, et al (2002) DD3PCA3, a very sensitive and specific marker to detect prostate tumors. Cancer Res 62:2695–2698. doi: 10.1016/s0022-5347(01)65160-7

Eckersberger E, Finkelstein J, Sadri H, et al (2009) Screening for Prostate Cancer: A Review of the ERSPC and PLCO Trials. Rev Urol 11:127–33. doi: 10.3909/riu0474

Eric Thomas C, Sexton W, Benson K, et al (2010) Urine collection and processing for protein biomarker discovery and quantification. Cancer Epidemiol. Biomarkers Prev. 19:953–959

Ferlay J, Soerjomataram I, Dikshit R, et al (2015) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386. doi: 10.1002/ijc.29210

Fernandez-Serra A, Casanova-Salas I, Rubio L, et al (2015) [Update on the diagnosis of PCa in urine. The current role of urine markers]. Arch Esp Urol 68:240–9

Fujita K, Pavlovich CP, Netto GJ, et al (2009) Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology. Hum Pathol 40:924–933. doi: 10.1016/j.humpath.2009.01.004

Giunta CJ (2013) Historical Chemists in Fiction. In: Biomedical Engineering and Computational Biology. pp 129–142

Gleason DF (1981) Histologic Grading and Staging of Prostatic Carcinoma. Am J Surg Pathol 5:193–208. doi: 10.1108/RPJ-07-2011-0067

Gou X, Huang P, Mou C, Luo Y (2014) The PCA3 test for guiding repeat biopsy of prostate cancer and its cut-off score: a systematic review and meta-analysis. Asian J Androl 16:487. doi: 10.4103/1008-682X.125390

Haas GP, Delongchamps N, Brawley OW, et al (2008) The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. Can J Urol 15:3866–3871. doi: 10.3892/ol.2015.3556

Håheim LL (2007) Metabolic syndrome and prostate cancer. Expert Rev Endocrinol Metab 2:633–640. doi: 10.1586/17446651.2.5.633

Hegele RA, Cao H, Harris SB, et al (2000) Peroxisome proliferator-activated receptor-γ2 P12A and type 2 diabetes in Canadian Oji-Cree. J Clin Endocrinol Metab 85:2014–2019. doi: 10.1210/jc.85.5.2014

Heitzer E, Ulz P, Belic J, et al (2013) Tumor-associated copy number changes in the circulation of patients with prostate cancer identified through whole-genome sequencing. Genome Med 5:30. doi: 10.1186/gm434

Held-Warmkessel J (2006) Contemporary issues in Prostate cancer: A Nursing perspective, 2nd edn. Jones and Bartlett, Philadelphia

Hernández J, Thompson IM (2004) Prostate-specific antigen: A review of the validation of the most commonly used cancer biomarker. Cancer 101:894–904. doi: 10.1002/cncr.20480

Hessels D, Schalken JA (2013) Urinary biomarkers for prostate cancer: A review. Asian J Androl 15:333–339. doi: 10.1038/aja.2013.6

Hsing AW (2001) Hormones and Prostate Cancer: What's Next? [Miscellaneous Article]. Public Health 23:42–58

Huppertz I, Attig J, D'Ambrogio A, et al (2014) iCLIP: Protein-RNA interactions at nucleotide resolution. Methods 65:274–287. doi: 10.1016/j.ymeth.2013.10.011

Hwang YW, Kim SY, Jee SH, et al (2009) Soy food consumption and risk of prostate cancer: A meta-analysis of observational studies. Nutr Cancer 61:598–606. doi: 10.1080/01635580902825639

Jackson BL, Grabowska A, Ratan HL (2014) MicroRNA in prostate cancer: functional importance and potential as circulating biomarkers. BMC Cancer 14:930. doi: 10.1186/1471-2407-14-930

Jain S, Saxena S, Kumar A (2014) Epidemiology of prostate cancer in India. Meta Gene 2:596–605. doi: 10.1016/j.mgene.2014.07.007

Jansson MD, Lund AH (2012) MicroRNA and cancer. Mol Oncol 6:590–610. doi: 10.1016/j.molonc.2012.09.006

Jiang Z, Fanger GR, Woda BA, et al (2003) Expression of α-methylacyl-CoA racemase (P504S) in various malignant neoplasms and normal tissues: A study of 761 cases. Hum Pathol 34:792–796. doi: 10.1016/S0046-8177(03)00268-5

Kessler B, Albertsen P (2003) The natural history of prostate cancer. Urol Clin North Am 30:219–226. doi: 10.1016/S0094-0143(02)00182-9

King CJ, Woodward J, Schwartzman J, et al (2017) Integrative molecular network analysis identifies emergent enzalutamide resistance mechanisms in prostate cancer. Oncotarget 8:111084–111095. doi: 10.18632/oncotarget.22560

Kovács G, Hoskin P (2013) Interstitial Prostate Brachytherapy. Springer Berlin Heidelberg, Berlin, Heidelberg

Kulis M, Esteller M (2010) DNA Methylation and Cancer. In: Advances in Genetics. pp 27–56

Leyten GHJM, Hessels D, Smit FP, et al (2015) Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clin Cancer Res 21:3061–3070. doi: 10.1158/1078-0432.CCR-14-3334

Li LC, Carroll PR, Dahiya R (2005) Epigenetic changes in prostate cancer: Implication for diagnosis and treatment. J Natl Cancer Inst 97:103–115. doi: 10.1093/jnci/dji010

Liede A, Karlan BY, Narod SA (2004) Cancer Risks for Male Carriers of Germline Mutations in BRCA1 or BRCA2 : A Review of the Literature. J Clin Oncol 22:735–742. doi: 10.1200/JCO.2004.05.055

Lilja H, Ulmert D, Vickers AJ (2008) Prostate-specific antigen and prostate cancer: Prediction, detection and monitoring. Nat Rev Cancer 8:268–278. doi: 10.1038/nrc2351

Lin P-C, Giannopoulou EG, Park K, et al (2013) Epigenomic Alterations in Localized and Advanced Prostate Cancer. Neoplasia 15:373-IN5. doi: 10.1593/neo.122146

Lin X, Tascilar M, Lee WH, et al (2001) GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. Am J Pathol 159:1815–1826. doi: 10.1016/S0002-9440(10)63028-3

Liong ML, Lim CR, Yang H, et al (2012) Blood-based biomarkers of aggressive prostate cancer. PLoS One 7:e45802. doi: 10.1371/journal.pone.0045802

Liu Y, Hegde P, Zhang F, et al (2012) Prostate cancer - a biomarker perspective. Front Endocrinol (Lausanne) 3:72. doi: 10.3389/fendo.2012.00072

Lutz ST, Chow EL, Hartsell WF, Konski AA (2007) A review of hypofractionated palliative radiotherapy. Cancer 109:1462–1470

MacConaill LE, Garraway LA (2010) Clinical implications of the cancer genome. J Clin Oncol 28:5219–5228. doi: 10.1200/JCO.2009.27.4944

Mahnke K, Ring S, Johnson TS, et al (2007) Induction of immunosuppressive functions of dendritic cellsin vivo by CD4+CD25+ regulatory T cells: Role of B7-H3 expression and antigen presentation. Eur J Immunol 37:2117–2126. doi: 10.1002/eji.200636841

Mantzoros CS, Tzonou A, Signorello LB, et al (1997) Insulin like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br J Cancer 76:1115–1118. doi: 10.1038/bjc.1997.520

Martignano F, Gurioli G, Salvi S, et al (2016) GSTP1 Methylation and Protein Expression in Prostate Cancer: Diagnostic Implications. Dis Markers 2016:1–6. doi: 10.1155/2016/4358292

Merdan S, Tomlins SA, Barnett CL, et al (2015) Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy. Cancer 121:4071–4079. doi: 10.1002/cncr.29611

Meyer P, Zuern C, Hermanns N, Haak T (2007) The association between paternal prostate cancer and type 2 diabetes. J Carcinog 6:1–5. doi: 10.1186/1477-3163-6-14

Mikhaĭlenko DS, Perepechin D V, Apolikhin OI, et al (2014) Markers for non-invasive molecular genetic

diagnosis of oncourological diseases. Urologiia 116–120

Morgan R, Boxall A, Bhatt A, et al (2011) Engrailed-2 (EN2): A tumor specific urinary biomarker for the early diagnosis of prostate cancer. Clin Cancer Res 17:1090–1098. doi: 10.1158/1078-0432.CCR-10-2410

Mueller E, Smith M, Sarraf P, et al (2000) Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. Proc Natl Acad Sci 97:10990–10995. doi: 10.1073/pnas.180329197

Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global Cancer Statistics, 2002. CA Cancer J Clin 55:74–108. doi: 10.3322/canjclin.55.2.74

Pasquier L Du (2004) Innate immunity in early chordates and the appearance of adaptive immunity. Comptes Rendus - Biol 327:591–601. doi: 10.1016/j.crvi.2004.04.004

Pitteloud N, Mootha VK, Dwyer AA, et al (2005) Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 28:1636–1642. doi: 10.2337/diacare.28.7.1636

Ploussard G, De La Taille A (2010) Urine biomarkers in prostate cancer. Nat. Rev. Urol. 7:101–109

Prensner JR, Iyer MK, Balbin OA, et al (2011) Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. Nat Biotechnol 29:742–749. doi: 10.1038/nbt.1914

Ren S, Peng Z, Mao JH, et al (2012) RNA-seq analysis of prostate cancer in the Chinese population identifies recurrent gene fusions, cancer-associated long noncoding RNAs and aberrant alternative splicings. Cell Res 22:806–821. doi: 10.1038/cr.2012.30

Ren S, Wang F, Shen J, et al (2013) Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for diagnosing prostate cancer. Eur J Cancer 49:2949–2959. doi: 10.1016/j.ejca.2013.04.026

Ren S, Wei GH, Liu D, et al (2018) Whole-genome and Transcriptome Sequencing of Prostate Cancer Identify New Genetic Alterations Driving Disease Progression [Figure presented]. Eur Urol 73:322–339. doi: 10.1016/j.eururo.2017.08.027

Robinson D, Van Allen EM, Wu YM, et al (2015) Integrative clinical genomics of advanced prostate cancer. Cell 161:1215–1228. doi: 10.1016/j.cell.2015.05.001

Roth C, Schuierer M, Günther K, Buettner R (2000) Genomic structure and DNA binding properties of the human zinc finger transcriptional repressor AP-2rep (KLF12). Genomics 63:384–390. doi: 10.1006/geno.1999.6084

Roth TJ, Sheinin Y, Lohse CM, et al (2007) B7-H3 ligand expression by prostate cancer: A novel marker of prognosis and potential target for therapy. Cancer Res 67:7893–7900. doi: 10.1158/0008-5472.CAN-07-1068

Saedi MS, Zhu Z, Marker K, et al (2001) Human kallikrein 2 (HK2), but not prostate-specific antigen (PSA), rapidly complexes with protease inhibitor 6 (PI-6) released from prostate carcinoma cells. Int J Cancer 94:558–563. doi: 10.1002/ijc.1501

Shaneyfelt T, Husein R, Bubley G, Mantzoros CS (2000) Hormonal Predictors of Prostate Cancer: A Meta-Analysis. J Clin Oncol 18:847–847. doi: 10.1200/JCO.2000.18.4.847

Shen M, Abate-Shen C (2010) Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev 1967–2000. doi: 10.1101/gad.1965810.GENES

Sinha R, Anderson DE, McDonald SS, Greenwald P (2003) Cancer risk and diet in India. J Postgrad Med 49:222–228

Sreekumar A, Laxman B, Rhodes DR, et al (2004) Humoral immune response to alpha-methylacyl-CoA racemase and prostate cancer. JNCI J Natl Cancer Inst 96:834–843. doi: Doi 10.1093/Jnci/Djh145

St. John J, Powell K, Katie Conley-LaComb M, Chinni SR (2012) TMPRSS2-ERG fusion gene expression in prostate tumor cells and its clinical and biological significance in prostate cancer progression. J. Cancer Sci. Ther. 4:94–101

Stratton MR (2011) Exploring the genomes of cancer cells: Progress and promise. Science (80-) 331:1553–1558. doi: 10.1126/science.1204040

Thompson JC, Wood J, Feuer D (2007a) Prostate cancer: Palliative care and pain relief. Br Med Bull 83:341–354. doi: 10.1093/bmb/ldm018

Thompson JC, Wood J, Feuer D (2007b) Prostate cancer: Palliative care and pain relief. Br Med Bull 83:341–354. doi: 10.1093/bmb/ldm018

Thu KL, Vucic EA, Kennett JY, et al (2009) Methylated DNA Immunoprecipitation. J Vis Exp 23–26. doi: 10.3791/935

Tinzl M, Marberger M, Horvath S, Chypre C (2004) DD3PCA3 RNA analysis in urine - A new perspective for detecting prostate cancer. Eur Urol 46:182–186. doi: 10.1016/j.eururo.2004.06.004

Tomlins SA (2005) Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer. Science (80-) 310:644–648. doi: 10.1126/science.1117679

Tran HN, Udaltsova N, Li Y, Klatsky AL (2018) Low Cancer Risk of South Asians: A Brief Report. Perm J 22:17-095. doi: 10.7812/TPP/17-095

Travis RC, Key TJ, Allen NE, et al (2007) Serum androgens and prostate cancer among 643 cases and 643 controls in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 121:1331–1338. doi: 10.1002/ijc.22814

Velonas VM, Woo HH, dos Remedios CG, Assinder SJ (2013) Current status of biomarkers for prostate cancer.

Int J Mol Sci 14:11034–11060. doi: 10.3390/ijms140611034

Wang F, Ren S, Chen R, et al (2014) Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. Oncotarget 5:11091–11102. doi: 10.18632/oncotarget.2691

Whittemore AS, Kolonel LN, Wu AH, et al (1995) Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 87:652–661. doi: 10.1093/jnci/87.9.652

Will JC, Vinicor F, Calle EE (1999) Is diabetes mellitus associated with prostate cancer incidence and survival? Epidemiology 10:313–318. doi: 10.1097/00001648-199905000-00021

Wong MCS, Goggins WB, Wang HHX, et al (2016) Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries. Eur Urol 70:862–874. doi: 10.1016/j.eururo.2016.05.043

Wu D, Ni J, Beretov J, et al (2017) Urinary biomarkers in prostate cancer detection and monitoring progression. Crit Rev Oncol Hematol 118:15–26. doi: 10.1016/j.critrevonc.2017.08.002

Xu LL, Stackhouse BG, Florence K, et al (2000) PSGR, a novel prostate-specific gene with homology to a G protein-coupled receptor, is overexpressed in prostate cancer. Cancer Res 60:6568–6572

Xu LL, Sun C, Petrovics G, et al (2006) Quantitative expression profile of PSGR in prostate cancer. Prostate Cancer Prostatic Dis 9:56–61. doi: 10.1038/sj.pcan.4500836

Yeh JH, Sidhu SS, Chan AC (2008) Regulation of a Late Phase of T Cell Polarity and Effector Functions by Crtam. Cell 132:846–859. doi: 10.1016/j.cell.2008.01.013

Zhang W, Ren SC, Shi XL, et al (2015) A novel urinary long non-coding RNA transcript improves diagnostic accuracy in patients undergoing prostate biopsy. Prostate 75:653–661. doi: 10.1002/pros.22949

Zhao F, Olkhov-Mitsel E, van der Kwast T, et al (2017) Urinary DNA Methylation Biomarkers for Noninvasive Prediction of Aggressive Disease in Patients with Prostate Cancer on Active Surveillance. J Urol 197:335–341. doi: 10.1016/j.juro.2016.08.081

Zhao Z, Zeng G, Zhong W (2010) Serum early prostate cancer antigen (EPCA) as a significant predictor of incidental prostate cancer in patients undergoing transurethral resection of the prostate for benign prostatic hyperplasia. Prostate 70:1788–98. doi: 10.1002/pros.21215

Zobniw CM, Causebrook A, Fong MK (2014) Clinical use of abiraterone in the treatment of metastatic castration-resistant prostate cancer. Res Reports Urol 6:97–105. doi: 10.2147/RRU.S29003

(2012) GLOBOCAN. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 6 Sep 2018