Revisiting Prostate Cancer in India: A Genomic View

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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
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 different health care systems
and more importantly the diet (Whitemore 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).

![Diagram showing PCa incidence by region]

**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,
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 PCs (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.](image)

The incidence of PCs is relatively low in some states like Gujarat (Ahmedabad and Wardha PBRCs) and Madhya Pradesh (Bhopal PBCR) with the lowest being north east region of India [12]. PCs is the second leading cancer among males in large Indian cities like Delhi, Kolkata, Pune and Thrivananthapuram, 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 PCs (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*, *NKK3-1* (Barbieri et al. 2017) and *CDKN1B* (Shen and Abate-Shen...
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.
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-
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
miR-375 have been the most frequently investigated in urine from PCa patients (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 (Busse-makers 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 IncRNA (Wang et al. 2014), and FR0348383, a PCa-associated IncRNA (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. IncRNAs 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 (Mikhaillenko 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
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.
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.
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 and TP53I3). (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 upring, one question still remains elusive: Is there an end to the problems of early detection of PCa?
Conflict of interest: none

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