Revisiting Prostate Cancer in India

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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 causation 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 discuss 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 [1] as it accounts to the second most common cancer worldwide (GLOBOCON 2012, 2018)[2] and third most prevalent cancer in India [3]. 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(PSA) based screening policies [4]. In 2012,

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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%) [5]. Reported PCa incidence rates varied over 25-fold worldwide [6], where awareness about PCa is lacking as men may not come forward for the diagnoses itself. On the other hand, the PSA screening serves as one of the most common non-invasive biomarkers to detect PCa [7]. 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) [6]. 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 diverse health care systems and importantly the diet [8]. Conversely, 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[9].

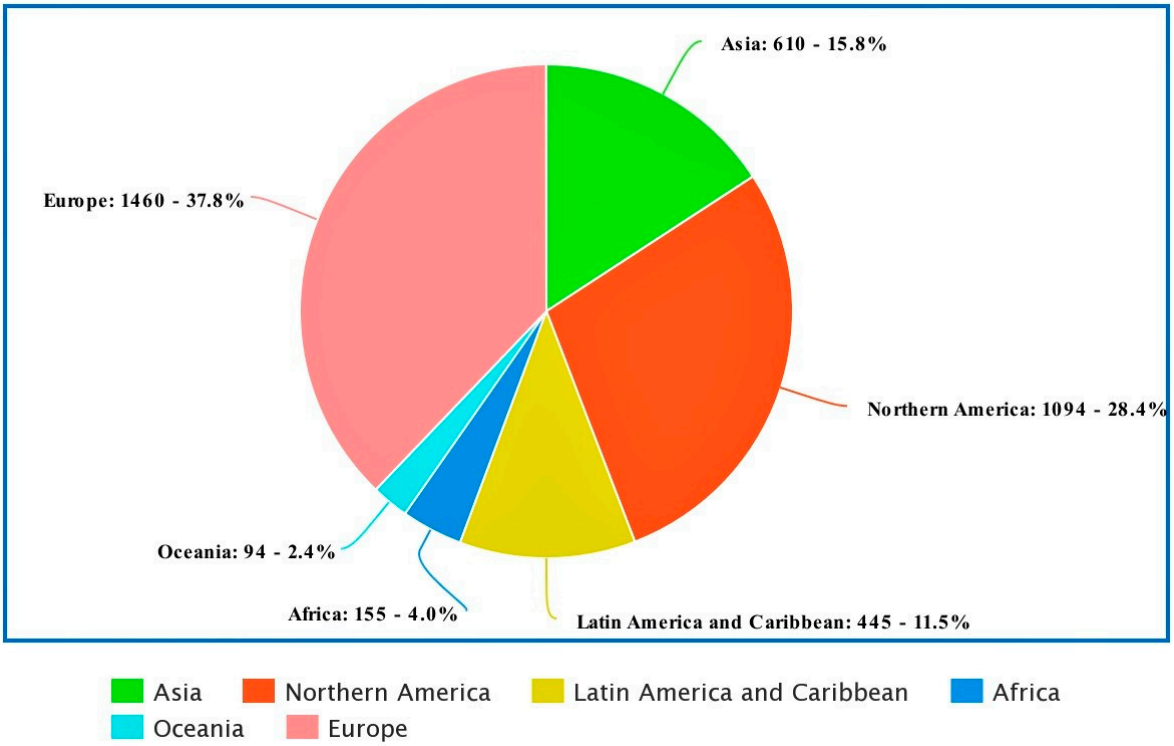

Figure Error! No sequence specified. **:** Estimated five year prevalence of PCa cases (*1000), adult population. Source: *GLOBOCAN*, 2012.

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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[10]. 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 in India (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 [11]. In south Asians, there is higher prevalence of polymorphisms in XRCC1 and XPD genes responsible for DNA repair.

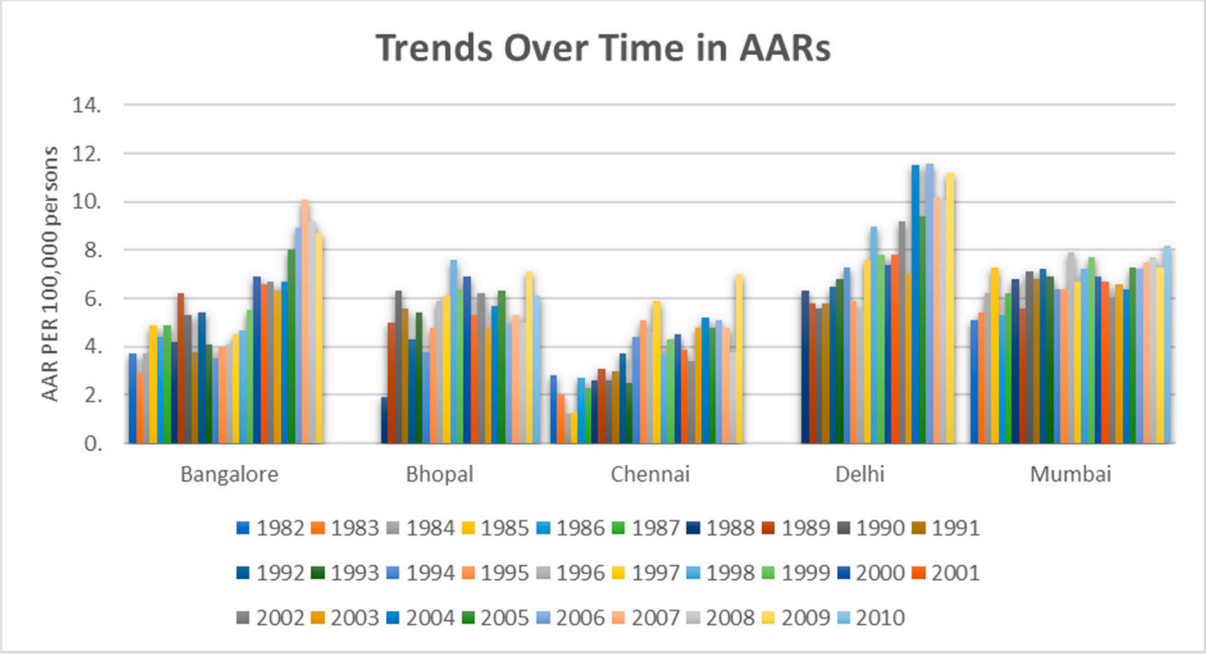

Figure 2: Graph showing trends over time in age adjusted rates for five population-based cancer registries. Image adapted from Jain, Saxena and Kumar, 2014.The incidence of PCa is relatively low in some states like Gujrat (Ahmedabad and Wardha PBRCs) and Madhya Pradesh (Bhopal PBCR) with the lowest being 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.

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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 [13]screening a large number of genes with greater sensitivity, precision and cost effectiveness [14]. With NGS studies branched towards understanding the cancer genome of several tumor types [15], an attempt is made to perform diagnostic, prognostic, predictive biomarkers and biomarker-designed clinical trials[14]. Furthermore, NGS has led towards easier identification of the PCa variants by exposing hidden information through genomic and transcriptomic landscape. A large focus is through understanding 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 [16]. 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[17] due to deletion of tumor suppressors such as *PTEN, TP53, NKX3-1*[18] and *CDKN1B*[19] and BRCA mutations identified in patients with PCa were found to be somatic with ca. 15% of patients to be metastatic CRPC (mCRPC) [16]. 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 [20]. As somatic copy number alterations (SCNA) could be helpful for ascertaining novel mutational hotspots, identifying them have caught an immense interest to the research community [21]. 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 is 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 [24]. Based on the ChIP-Seq, Chen *et al.*, 2013showed 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 [26]. 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 [27]. Various DNA methylation markers have been found in PCa, *viz.* CpG island

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hypermethylation of *glutathione-S-transferase P* (*GSTP1*) promoter DNA, resulting in the loss of *GSTP1* expression [28]. A number of methylation profiles have been developed and are being evaluated as potential markers for early diagnosis and risk assessment [25]. In the recent-past, iCLIP-Seq methods to infer RNA-Protein interactions at a higher resolution is made available [29].

1.3. Screening PCa using PSA

The PSA is a glycoprotein (serine protease) of approximately 33 kDa in size, with enzymatic protease activity secreted by prostatic epithelium [30]. 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 increased PSA [31].After the first discovery of (PSA) in late 1970s, it has been widely used as a tumor marker for PCa detection [32]. 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 [33] even as PSA does not differentiate between different stages of PCa [34]. 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 [35]. However, the most widely accepted method is the Gleason grading system[36].

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 [37]. 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 [38].

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 [39]. However, association of diabetes with decreased risk of PCa has been reported from several studies [39,40]. There are several mechanisms to describe the protective effect of diabetes on PCa where protection against the PCa is due to the hormonal alterations, insulin and testosterone (T) in diabetes patients [41]. Initially insulin level of diabetic patients seems to be higher, thereafter, it decreases 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 [42]. Numerous human and animal studies have shown that both androgens [43] and insulin [44] have an effect on prostate

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cell growth and malignant transformation. Therefore, it is believed the 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 [42]. Baradaran *et al.*, 2009 demonstrated that a small, although significant drop of PCa risk for increasing level of T/SHBG ratio is seen and further Will, Vinicor and Calle, in 1999 observed PCa risk to have doubled more than 5 years of diabetes diagnosis. Nevertheless, steroids are not only the key factors for protective effect on PCa in diabetes patients but there could be an influence of hormonal environment apart from testosterone, insulin like growth factors (IGF) and leptin showing effect on this inverse relationship [40]. 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. Progressive insulin resistance and B-cell failure along with insulin depletion arising with long-standing diabetes may limit insulin actions and reduce the PCa risk. 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 [46]. In addition, genetic variation in peroxisome proliferator-activated receptor-gamma (PPARG) has association with a higher incidence of diabetes mellitus [47] showing expression in human prostate adenocarcinomas. Inhibition of PCa cell growth is expected to show the activation of this receptor with specific ligands [48]. As described by Hsing, Sakoda and Chua Jr., 2007, long term diabetes condition results in insulin resistance. However, declined androgen levels in severe diabetics is probably due to a toxic effect of hyperglycemia on the Leydig cells of the testis [50].

The PCa incidence and mortality rates around the world highly demonstrate correlation with average level of fat consumption. It is speculated that, western diet associated 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. Some reports revealed that men who consume higher levels of Calcium via food intake or as supplement may prone to develop advanced PCa [51]. 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 [10] even as fresh vegetables, fruits, pulses and whole grains resulting in a low intake of fiber and phytonutrients may protect against PCa [51]. 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 is known to block the activity of nuclear factor kappa-B (NF-kB), responsible for cancer cell growth in many cell types [10].

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3. Genetic Biomarkers for PCa

Urine, a waste product of kidney, has become one of the most attractive bio-fluids in clinical proteomics [52]. Urine is non-invasive, harmless and can be collected in large quantities without any significant proteolytic degradation [53,54]. Since prostate cells can be detected in urine [55], different biomarkers specific to PCa have been identified through urine and used as serological marker in diagnostic tests.

3.1 Non-coding RNA as biomarkers

MicroRNAs (miRNAs) are naturally-occurring, small (18-22 nucleotides) non-coding RNAs [56] that control the expression of more than 60% of protein-coding genes. They have regulatory function on various molecular signaling pathways in the cell and therefore serve as potential prognostic indicators for tumor formation and metastasis[57]. 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 [58]. Currently, over 10000 human miRNAs have been reported out of which more than 200 have been analyzed from urine exosomes. There are large number of studies proving the usefulness of urinary miRNAs in combination with clinical parameters for enhancing the accuracy of classification of PCa, for example *miR-141, miR-21, miR-200b, miR221, miR-106b* and *miR-375*[59,60]. 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 which significantly improves 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 [61]. The PCA3 score is calculated as the ratio of PCA3 to PSA mRNA (PCA3 mRNA/PSA mRNA x 1000) [62]. 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 [63,64]. The limiting factor with PCA3 is that it does not corelate with Gleason score and clinical tumor staging which restricts its use in the medical field. On the other hand, long non-coding RNAs (lncRNA) in plasma do not exist in their full-length form, although few stable fragments can be highly expressed and detectable in human plasma [68]. Recent studies, however has enabled identification of urinary lncRNA such as metastasis-associated lung adenocarcinoma transcript 1 (*MALAT-1*) a multiple cancer-associated lncRNA [65], and *FR0348383*, a PCa-associated lncRNA [66]. Whereas *MALAT-1* has a great potential as independent predictors of PCa, a large multi-center study has validated the clinical utility of a 3 protein-coding gene panels

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(*HOXC6, TDRD1,* and *DLX1*) in urine [67]. 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.

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 [69]. 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 [70]. The diagnostic accuracy of combining *TMPRSS2-ERG* and *PCA3* into a urine test is significantly higher than that of the PSA test [71]. 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 [72].A different approach was carried out by Liong *et al.,* which can differentiate between PCa from normal samples using blood-based microarray analysis [73]. Through quantitative RT-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 [74–76].

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 [77]. 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 losses observed underlining its involvement in early carcinogenesis [78]. On the other hand, 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 [79].

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3.4.Protein based biomarkers

Through proteomics studies, thousands of peptides can be analyzed simultaneously which leads to identification of new biomarkers. Using MALDI-TOF, a group identified two markers; uromodulin and semenogelin that shows high sensitivity and specificity and could distinguish PCa from 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 [80]. Human kallikrein 2 (KLK2), a protease localized to prostatic epithelium, when used in combination with PSA, PCa diagnosis is significantly improved [81]. 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 [82,83].

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 [84,85]. B7-H3 (or CD276), an antigen-specific inhibitor of T-cell mediated anti-tumoral immunity has been observed in high pathological stages of PCa [86,87]. Early prostate cancer antigen (EPCA), a nuclear matrix protein, have recently been shown to be involved in PCa which needs further evaluation [88].

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 [89]. The initial diagnosis date has been risen up approximately 5 years with the use of PSA testing [90]. Onset in familial PCa is usually reported in men under 55 years old, however, sporadic PCa is rarely diagnosed at this age [91]. An approximate 10% have been reported as familial PCa with 40% of patients under 55 years old accounting for familial PCa even as shared environmental factors and genetic susceptibility may result in the familial predisposition to PCa. Specific mutations in two genes; *BRCA1* and *BRCA2*which are responsible for breast cancer patterns have shown to be greater risk with PCa with mutations in *BRCA2* consistently associated with risk of PCa and relative risk higher in men under 65 years old [92].

The marker PSA is specific to the prostate gland and not for PCa while PSA elevation is also seen with the disease condition of BPH and Prostatitis. Discoveries on different molecular forms of PSA represent the potential means of diagnostic specificity by differentiating PSA elevations seen with PCa and BPH. For example, serum PSA level associate with PCa is at least 10 times higher per gram of tissue when compared with BPH due to the variable amounts and weight of the latter further

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causing difficulty in interpreting PSA value [30]. 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 correlation with patient's race, age and prostate volume (Table 1) [30]. 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 [93]. Due to the heterogeneity of the disease, no single biomarker will be diagnostic and prognostic for every patient [94]. 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 (Figure 4; supplementary table 1) across Caucasians, American and Asian (Chinese) [95–97] and tried to predict the common genes across these varied NGS datasets. 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.*

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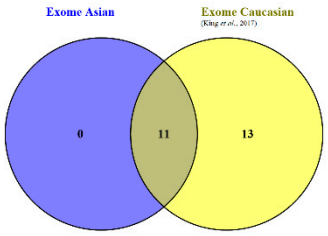

Figure.4a

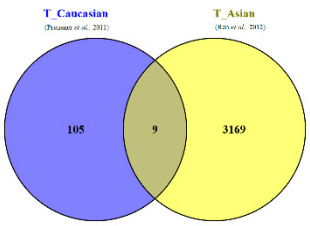

Figure.4b

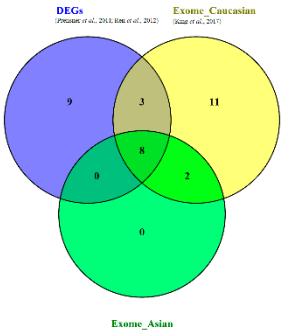

Figure.4c

Figure 4(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. 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. 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 [98,99]. Early PCa, however, does not usually cause extreme symptoms such as having an erection; pain with ejaculation; and blood in the urine or semen with several options for treating PCa including surgery, radiation therapy and hormone therapy in use[100,101]. The survival, however for post-palliative care is assumed to be nine to twelve months.With the NGS datasets rising, one question still remains ethereal: Is there an end to the problems of early detection of PCa?

Authors' contributions: PP, AG, MN AND NS contributed equally. MN, AG and PS have written sections on NGS and ncRNAs, MS, SM, VSS, MKV, PM contributed towards sections on clinical

correlation, markers, and diagnoses. KMM, DS and PS proofread the manuscript. All authors agreed and checked the manuscript before submission.

Competing interests: none

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