

## RESEARCH ARTICLE

# The Frigging Kinship Between Prostate Carcinogenesis and the Genomic Landscape of Indian Males

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## Abstract

Prostate Cancer (PCa) is a major global health issue in men over 50 years of age, arising due to complex and often population-specific interactions between genes, environment, and lifestyle. According to GLOBOCAN, PCa incidence in India is on the rise, albeit at a slower rate than that of the global average. This review delves deep into the nuanced relationship between PCa and the genomic landscape of Indian males. The study thoroughly reviews the epidemiology of PCa and examines the contribution of the genetic determinants like polymorphisms, mutations, and methylation patterns; microbial infections as well as the influence of lifestyle habits like diet, smoking, and drinking on the progress and manifestation of cancer among Indian males, thus intending to provide a holistic understanding of the complex interplay driving the malady. This knowledge would not only help us understand the disease mechanisms but also provide a basis for personalized diagnostic, therapeutic, and preventive strategies tailored to India's unique genetic and environmental landscape.

**Key Words:** Prostate Cancer (PCa); Epidemiology; Polymorphisms; Mutations; Methylation

## Abbreviations

PCa: Prostate cancer; SNP: Single Nucleotide Polymorphism; PSA: Prostate Specific Antigen; DRE: Digital Rectal Examination; EPI: ExoDx Prostate Intelliscore; PET: Positron Emission Tomography; ICMR: Indian Council of Medical Research; CYP: Cytochrome P450; GST: Glutathione S-Transferase; SFRP: Secreted Frizzled-Related Protein; miR: MicroRNA; mEH: microsomal Epoxide Hydrolase; CCL: Chemokine (C-C motif) Ligand; DR: Death Receptor; IL: Interleukin; TNF: Tumor Necrosis Factor; TLR: Toll-Like Receptor; MMP: Matrix Metallo Proteinase; KLK: Kallikrein; CASP: Caspase; COX: Cyclooxygenase; ER: Estrogen Receptor;

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CCND: Cyclin D; NQO: NAD (P)H Quinone Oxidoreductase; VDR: Vitamin D Receptor; XP: Xeroderma Pigmentosum; XRCC: X-ray Repair Cross-Complementing protein; MDM2: Mouse Double Minute 2 homolog; TIMP: Metallo Peptidase Inhibitor; MMR: DNA Mismatch Repair; BPH: Benign Prostatic Hyperplasia; GJB6: Gap Junction Beta-6 protein; RNASEL: Ribonuclease L; MSR: Macrophage Scavenger Receptor; GCP: Glutamate Carboxy-Peptidase; PSMA: Prostate-Specific Membrane Antigen; Ec-SOD: Extracellular Superoxide Dismutase; RASSF: Ras-Association domain Family; BNIP: BCL2/adenovirus E1B 19-kDa Interacting Protein; ETS: Erythroblast Transformation Specific; SPINK1: Serine Protease Inhibitor Kazal-type 1; PTEN: Phosphatase and Tensin homologue; HPV: Human Papilloma Virus; HCMV: Human Cyto Megalo Virus; HSV: Human herpes Simplex Virus; HHV: Human Herpes Virus; EBV: Epstein-Barr Virus; XMREV: Xenotropic Murine leukemia virus-Related Virus; HBV: Hepatitis B; PBCR: The Bombay Population Based Cancer Registry; ROS: Reactive Oxygen Species; PAH: Polycyclic Aromatic Hydrocarbons; IPCF: The Indian Prostate Cancer Foundation

## 1. Introduction

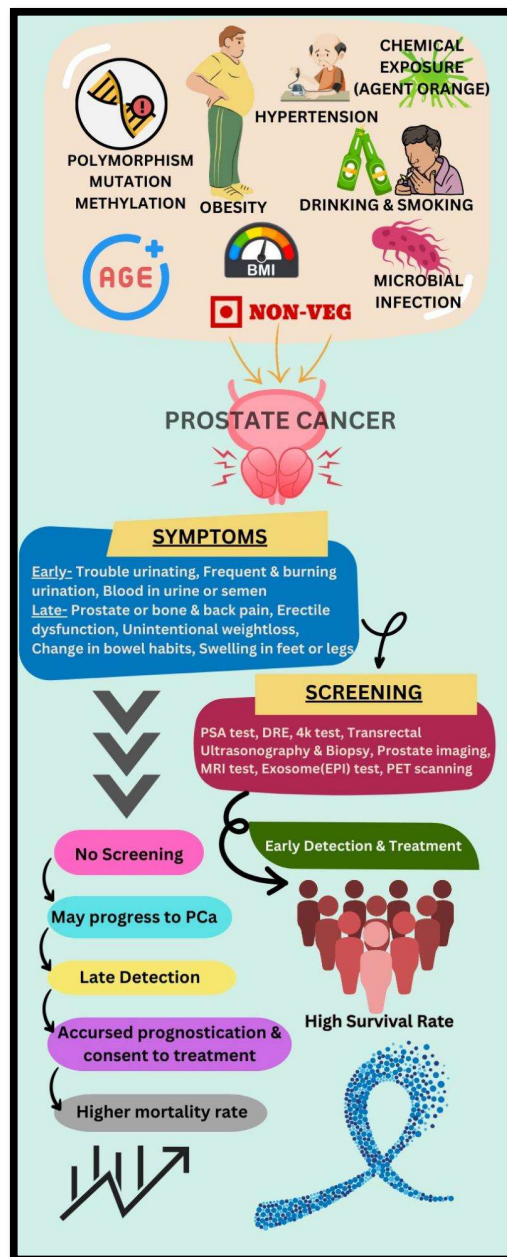
Prostate Cancer (PCa) is the most frequently diagnosed malignancy that primarily targets males above 50 years of age [1,2]. In fact, it is the 2<sup>nd</sup> most common cancer in men and ranks 5<sup>th</sup> in cancer-related fatalities globally [3]. Hence, early detection and timely management of PCa are crucial in improving the prognosis and survival rate of the affected individuals. The incidence rates of PCa exhibit geographical variations, with Asia showing comparatively lower incidence than Europe, Australia, and North America [1]. In 2020, the Global Cancer Observatory database reported PCa incidence of 3,71,225 cases in Asia, with an alarming mortality rate of 32.1% [4]. In the next two decades, the incidence rate is expected to reach up to 88.3%, while the mortality rate may rise to 92.8% worldwide [4]. These staggering figures highlight the immediate need to raise awareness about this debilitating ailment and the importance of early detection and effective treatment.

The likelihood of developing PCa is relatively less than 45 years of age; however, it drastically increases in men above 50 [5,6]. It is important to note that neoplastic changes in the prostate gland may begin during a male's adolescent years [7,8]. PCa risk is influenced by various factors that range from advancing age, socio-economic status, obesity, altered hormonal status, genetic makeup, and occupational hazards like exposure to insecticides and pesticides, shift-works, etc. [9-13]. It is thus essential to adopt preventive measures and monitor one's health closely, through effective screening of all the risk factors.

PCa ranks 5<sup>th</sup> in terms of cancer incidences in Indian men [14]. According to the Indian Council of Medical Research (ICMR), the incidence rate is 9-10 per 100,000 people, which is higher than that of other Asian and African countries but lower than that of North Americans and Europeans, in general. Recent records suggest that ~5.5% of Indian males are diagnosed with PCa during their lifetime, ~2.7% of which result in death, with about a 64% 5-year survival rate [15]. However, the survival rates of patients with PCa are greatly influenced by the precise stage of the disease at the time of diagnosis. According to a study conducted in a Mumbai-based hospital by Balasubramaniam *et al.* 2013, undergoing timely surgery may increase the 5-year survival rate to 91%. Radiation therapy could increase the rate to 88% while dipping down to only 57% for patients treated with hormone therapy [16]. India still lacks comprehensive pan-country reports on the epidemiology of the risk factors as well as cancer survivorship owing to inadequate patient follow-up and a flawed death registration system [17]. Implementing all-inclusive screening and diagnostic programs in India's densely

populated and rapidly developing regions is imperative to ensure early detection and timely treatment of PCa.

This work reviews and investigates, in detail, the available knowledge on the epidemiology of PCa in Indian men. It examines the risk factors, including their genetic makeup, encompassing polymorphisms, mutations, and methylation patterns. The study also reviews microbial infection, environmental factors, lifestyle dependencies, and their interaction with genetic susceptibility variants in shaping disease outcomes (Figure 1). Thus, by collating and analyzing this wealth of genetic and environmental/lifestyle datasets, this review aspires to provide a comprehensive understanding of the disease mechanisms that, in turn, may pave the way toward personalized diagnostic, therapeutic, and preventive strategies tailored to India's unique genetic and environmental landscape.



**Figure 1:** Prostate cancer: prognosis.

Prostate cancer is caused by the uncontrollable growth of cells in the prostate gland. Age, family history, and genetics may contribute to its development. Early detection is crucial for effective treatment, and regular screenings help identify potential issues before symptoms manifest. Symptoms typically appear in the later stages of the disease. They may include difficulty urinating, frequent urination, blood in the urine, discomfort in the pelvic area, and bone pain. Biopsy is the definitive method for confirming the presence of prostate cancer. Treatment options vary based on the cancer's stage, grade, and the patient's overall health. Early detection and advancements in treatment contribute to improved outcomes and reduced mortality rates in many cases.

## 2. Epidemiology of Prostate Cancer in India

Geographical variation in PCa incidence/year is quite significant, with European countries like France (66,070 cases), Sweden (10,949 cases), and Ireland (4,503 cases) etc. having higher incidence rates than that of India. This may be attributed to longer lifespans and differences in lifestyle as also due to widely conducted prostate-specific antigen (PSA) screening [18]. Various Indian studies have reported ~111 new cases of PCa annually and ~19 deaths per 100,000 men [19]. Compared to rural India, PCa incidence has been found to be higher in urban areas such as Bangalore, Barshi, Bhopal, Chennai, Delhi, Mumbai, Kamrup, Ahmedabad, Kolkata, Kollam, Nagpur, Pune, Trivandrum, and Wardha, with the incidence significantly higher in metropolitan cities like Kolkata and Bangalore compared to smaller towns like Kollam and Bhopal [20]. This may be attributed to a more cosmopolitan population base in the metropolitan cities [21] with different genetic backgrounds and lifestyle habits [22]. It is the 3rd most common male cancer in Delhi, followed by Mumbai (4th), Bangalore (5th) and Chennai (9th) [23]. The cancer registry data indicated that the occurrence of PCa in Kolkata was relatively low between 1998 and 1999, accounting for only ~4.2% of all reported cases of malignancy [24]. However, since 2003, there has been a steady rise in the occurrence rate, which gained momentum in 2007 (17.76%) and peaked in 2010 (28.97%) [25]. Gujarat and Madhya Pradesh have also been noted to have relatively lower occurrences of this type of cancer [26,27]. The mean annual percentage change of crude incidence rates ranged from 0.14 to 8.6, varying from West to South India [28,29].

Interestingly, the prevalence of PCa is lowest in the country's northeastern region [27]. Manipur has been found to have a relatively low case rate of 0.8% per year compared to Delhi (10.9%). The lack of urology services in most Northeast Indian states may contribute to the low diagnosis rate [30]. Notably, PCa diagnosis has become more prevalent after the age of 65 [31]. According to a study conducted between the years 1983 and 2002, it was found that men between the ages of 55 to 64 residing in Chennai, Bangalore, and Mumbai showed a rising trend in the incidence of PCa. Conversely, the men in Delhi were more prone to developing PCa at a younger age, i.e., between 35 to 44 years [32]. Kamrup has the highest age-adjusted incidence rate of PCa in northeast India (10.9 per 100,000 men), followed by Aizawl (4.8 per 100,000 men) and Mizoram (3.8 per 100,000 men) [33].

## 3. Exploring the Risk Factors of Prostate Cancer in India

Research conducted in India so far has revealed that a combination of genetic and various other factors like lifestyle dependencies, e.g., smoking, tobacco consumption, diet, as well as obesity, can influence the likelihood of developing PCa.

## 3.1 Genetic factors

### 3.1.1. Single nucleotide polymorphisms

Single Nucleotide Polymorphisms (SNPs) have long been identified as significant risk factors in PCa pathogenesis. These variations may reside within genes that are critical for cellular processes such as DNA repair, hormone metabolism, and cell cycle regulation, thereby influencing prostate cancer risk.

Genes related to metabolic and detoxification processes of xenobiotics, such as cytochrome P450 (CYP) and glutathione S-transferase (GST) families of genes, play an important role in maintaining cellular homeostasis and protecting against carcinogenic insults. Genetic alterations in these genes can thus affect enzymatic activity, substrate specificity and impact hormone metabolism and detoxification pathways, increasing an individual's susceptibility to prostate cancer. For a downstream transcript variant rs4646903 (CYP1A1\*2A; c.3801T>C) in cytochrome p4501A1 gene, Vijayalakshmi *et al.* 2005 reported from Chennai, that heterozygous TC genotype conferred increased PCa risk (P value <0.01, OR=4.64, 95%CI=1.51–14.86) [34]. For another 5' UTR variant rs743572 (CYP17; c.1931T>C; MspA1), Sobti *et al.* from Chandigarh reported the homozygous CC genotype to significantly increase PCa susceptibility (P value=0.03, OR=2.77, 95%CI=1.05–7.32) [35–37]. The variant genotypes of missense variants CYP1B1\*3 (c.4326C>G; Leu432Val) rs1056836 (P value=0.02, OR=3.37, 95%CI=1.12–10.06) and CYP19A1\*4 (C>T; Arg264Cys) rs700519 (P value=0.01, OR=2.35, 95%CI=1.23–4.49) have been studied in Chandigarh population and found to increase PCa risk [35,38]. Several association studies have established a correlation between SNPs in the Glutathione S-transferase (GST) superfamily genes and an elevated risk of PCa. Among different studies conducted independently in the North Indian population, Kesarwani *et al.* 2009 studied the intronic 3bp-AGG deletion variant, rs1799735 of GSTM3 and found the combined variant genotype to be associated with almost 2.5-fold increased PCa risk (P value=0.028, OR=2.51, 95%CI=1.11–5.68) [39]. Null genotypes of GSTM1 and GSTT1 deletion polymorphisms were reported to be associated with increased PCa risk by Srivastava *et al.* 2005, Mittal *et al.* 2004, Mittal *et al.* 2006 and Thakur *et al.* 2010 [40–43]. While Qadri *et al.* 2011 did not find any genotypic association for GSTP1 non-synonymous coding variant rs1695 (c.313A>G, Ile105Val) in the Kashmiri population, the heterozygous AG genotype was found to be associated with increased PCa risk in North Indian population by Mittal *et al.* 2006 and Srivastava *et al.* 2005, and with decreased PCa risk in South Indian population by Vijayalakshmi K *et al.* 2005 [40,42,44,45]. Furthermore, Roy *et al.* 2023 found positive association results for these polymorphisms of GSTM1, GSTT1, and GSTP1 populations in the East India, Kolkata population [46].

There is a growing recognition of how genes involved in immunoregulatory and inflammatory pathways can impact tumor development in the prostate microenvironment. SNPs within these genes can regulate immune responses and inflammatory signaling cascades, affecting tumor initiation, progression, and response to therapy. A report by Mandal *et al.* in 2015 from the Urologic Clinics of Sanjay Gandhi Postgraduate Institute of Medical Sciences in Lucknow suggested that the intronic In/Del variant rs3917887 of the pro-inflammatory gene CCL2 (also referred to as the monocyte chemoattractant protein-1, MCP-1) to be a valuable genetic marker for predicting susceptibility towards PCa, as the heterozygous ID genotype (P value=0.010, OR=1.71, 95%CI=1.13–2.59) and the variant allele D (P value=0.040, OR=1.53, 95%CI=1.01–1.78) showed statistically significant association with increased PCa risk [47]. Bandil *et al.* 2017 demonstrated significant contribution of variant alleles of two anti-inflammatory IL-10 UTR SNPs [rs1800896; c.-1082A>G and rs1800872; c.-



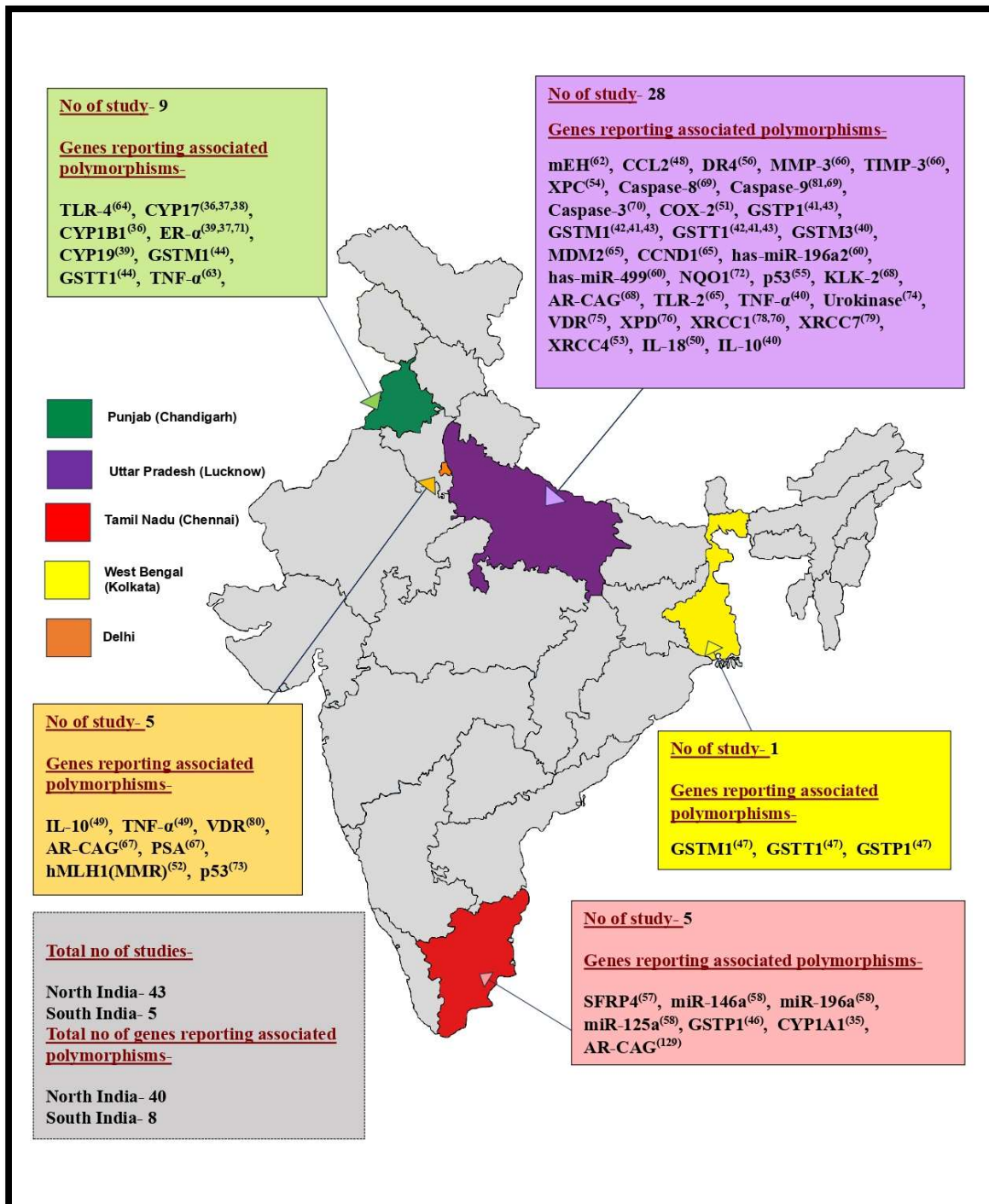
592C>A] {P value<0.0001, OR(95%CI)=2.41(1.60-3.61) and P value=0.0491, OR(95%CI)=0.66(0.45-0.98)}, respectively, the heterozygous CT genotype of c.-819C>T variant, rs1800871 (P value=0.0007, OR(95%CI)=2.98(1.62-5.50)) as well as variant alleles of two pro-inflammatory TNF- $\alpha$  UTR SNPs [rs361525; c.-238G>A and rs1800629; c.-308G>A]; {P value=0.0027; OR (95%CI)=1.81(1.24-2.65), and P value=0.003; OR(95%CI)=0.37(0.20-0.71), respectively} towards the progression of PCa [48]. Homozygous variant genotypes and dominant model of pro-inflammatory cytokine IL-18 UTR variants c.-137G>C; rs187238 and c.-607C>A, rs1946518 showed significant association in Lucknow population-based study by Dwivedi et al. 2015 [49]. In a Lucknow hospital based case/control study Mandal et al. 2011 reported for two COX-2 3'UTR variants, allele C carriers of c.-765G>C, rs20417 and c.8473T>C, rs5275 were associated with higher risk for PCa (P value=0.016; OR (95%CI)=1.74(1.10-2.75) and P value=0.045; OR(95%CI)=1.82(1.01-3.28) respectively) [50].

DNA repair pathways are essential for maintaining genomic integrity, and preventing mutations that drive carcinogenesis. In a study by Soni *et al.* 2011, for a novel UTR promoter SNP rs1800734 (c.-93G>A) of hMLH1 gene, a significant positive correlation was observed through both the codominant (P value=0.013, OR=1.40, 95%CI=0.63-3.08) and dominant model of inheritance (P value=0.01, OR=2.11, 95% CI=1.18-3.79), in a representative New Delhi population [51]. Mandal *et al.* 2011 studied 2 intronic variants of XRCC4 in Lucknow population and reported the homozygous variant genotypes of both intron-3 rs28360071 (P value=0.023, OR(95%CI)=2.99(1.25-7.12)) and intron-7 rs28360317 (P value=0.007, OR(95%CI)=2.05(1.21-3.47)) were associated with PCa susceptibility [52]. The team also reported association for XPC homozygous ins/ins variant rs77907221 (P value=0.012, OR(95%CI)=2.55(1.22-5.33)) and missense c.33512A>C variant rs2228001 (Lys939Gln) (P value=0.026, OR(95%CI)=2.15(1.09-4.23)) [53].

Genes regulating cell cycle and apoptosis are crucial for cellular proliferation and survival. SNPs affecting these pathways may cause abnormal cell proliferation and evasion of apoptotic mechanisms, which are hallmarks of cancer progression. Significant association was reported for two SNPs of tumor suppressor gene P53 by Mittal *et al.* 2011; with the heterozygous GA genotype of intron-6 polymorphism rs1625895, c.13494G>A (P value=0.051, OR=1.48, 95%CI=0.999-2.220) and heterozygous GC genotype of exon-4 non-synonymous polymorphism rs1042522 (c.215G>C; Arg72Pro) (P value=0.050, OR=1.5, 95%CI=1-2.199) showed an increased risk of PCa [54]. The team also reported 2 missense variants of DR4, rs6557634 (G>A; His141Arg) and rs4871857 (C>G; Thr209Arg) whose homozygous variant genotypes conferred higher PCa risk (P value=0.007, OR(95%CI)=2.54(1.29-5.00) and P value=0.003, OR(95%CI)=2.58(1.38-4.81), respectively) [55].

Compared to other regions, most of the hospital-based case-control studies have been conducted on males from northern India. Lucknow, the capital city of Uttar Pradesh alone, reports 28 independent studies on polymorphisms in 32 different genes (Figure 2).

Numerous case-control studies have been conducted across different regions in India to investigate genetic associations with Prostate Cancer (PCa). Studies conducted between 2004 and 2022 focused on the five highlighted states. A total of 43 studies were identified from the North Indian population, which collectively reported 40 individual gene polymorphisms, with Lucknow alone contributing 28 studies. In the South, 5 studies from Chennai alone reported genetic polymorphisms in 8 genes. Meanwhile, a single study conducted in Kolkata, West Bengal, reported three associated GST superfamily genes. The most frequently reported genes showing polymorphisms were TNF- $\alpha$ , cytochrome-P family and GST superfamily genes. These findings provide valuable insights into the genetic susceptibility of PCa in different regions of India.



**Figure 2:** State-wise summary results of genetic polymorphisms and case-control studies of PCa in India.

Among many other Indian reports, in a Chennai population-based study, Natarajan *et al.* 2020 reported a significant preponderance of the heterozygous GA genotype for a non-synonymous variant in the SFRP4 gene, rs1802074 (c.1019G>A; Arg340Lys) in PCa cases when compared to controls (P value=0.0005, OR=4.708, 95%CI=2.04-11.03) [56]. Again, Damodaran *et al.* 2020 revealed an increased risk for PCa for the carriers of heterozygous CT genotype of the miR-196a2 non-coding transcript variant rs11614913 (C>T) (P value=0.02, OR=1.88, 95%CI=1.06-3.35) and the homozygous CC genotype of the miR-125a upstream transcript

variant rs12976445 (T>C) (P value=0.03, OR=2.55, 95%CI=1.15-4.65) [57]. According to a study conducted at a Mumbai hospital by Chavan *et al.* 2010, the heterozygous genotypes of two intronic variants in the prostate-specific antigen (PSA) gene viz. rs2569733, (c.-5429T/G: P value=0.021, OR=3.59, 95%CI=1.16-11.09) and rs2739448, (c.-5412T/C: P value=0.021, OR=3.26, 95%CI=1.04-10.22), after age adjustment, showed an increased risk towards advanced PCa, while heterozygous genotypes of rs925013 (c.-4643A/G: P value=0.086, OR=2.46, 95%CI=0.86-7.04) showed marginal significance [58].

Table 1 provides a complete list of gene polymorphisms found to increase susceptibility to Prostate cancer. These SNPs have been identified and reported in studies conducted on Prostate cancer cases from diverse populations across India, as evidenced by available research publications from PUBMED and Google Scholar.

**Table 1:** Genetic polymorphisms associated with prostate cancer risk in diverse Indian population.

Sl. No.	Genetic Variant Details	RSID	The Risk Factor Association	Geographical Location	Study Reference
1	SFRP4 gene (1019 G>A; Arg340Lys)	rs1802074	The heterozygous GA genotype and dominant model (GA+AA). The T allele, heterozygous CT genotype and combined	Chennai	[56]
2	miR-196a (C>T)	rs11614913	(CT+TT) genotype. The heterozygous CT genotype.	Lucknow	[59]
3	miR-125a (T>C)	rs12976445	The homozygous CC genotype and recessive model (TT+TC) genotype.	Chennai	[57]
4	hsa-mir499 (C>T)	rs3746444	The C allele and heterozygous CT genotype.	Lucknow	[59]
5	CYP1A1 (CYP1A1*2A; Msp1; T3801C)	rs4646903	The heterozygous TC genotype. Dominant model (TC+CC).	Chennai	[34]
6	CYP1A1 (A>G)	rs1048943	Dominant model (AG+GG).	Lucknow	[60]
7	CYP17 (1931T>C; MspA1)	rs743572	The C allele and homozygous CC genotype.	Chandigarh	[35-37]
8	CYP1B1 (CYP1B1*3; 4326C>G; Leu432Val)	rs1056836	The homozygous GG genotype.	Chandigarh	[35]
9	CYP19 (CYP19A1*4; C>T; Arg264Cys)	rs700519	The T allele (coding for 264Cys), the heterozygous CT genotype and homozygous TT genotype.	Chandigarh	[38]
10	mEH gene (T>C; Tyr113His)	rs1051740	The heterozygous TC genotype and homozygous CC genotype.	Lucknow	[61]



11	CCL2 (Ins/Del)	rs3917887	The D allele (deletion), heterozygous ID genotype and dominant model (ID+DD).	Lucknow	[47]
12	DR4 (G>A; His141Arg)	rs6557634	The A allele (coding for 141His) and homozygous AA genotype.	Lucknow	[55]
13	DR4 (C>G; Thr209Arg)	rs4871857	The G allele (coding for 209Arg) and homozygous GG genotype.	Lucknow	[55]
14	IL-10 (-1082A>G)	rs1800896	The G allele, heterozygous AG genotype and homozygous GG genotype.	New Delhi	[48]
15	IL-10 (-819 C>T)	rs1800871	The A allele, the heterozygous GA genotype and homozygous AA genotype.	Lucknow	[62]
16	IL-10 (-592 C>A)	rs1800872	The T allele and heterozygous CT genotype.	New Delhi	[48]
17	IL-18 (-137G>C)	rs187238	The A allele and homozygous AA genotype.	New Delhi	[48]
18	IL-18 (-607C>A)	rs1946518	The heterozygous GC genotype, homozygous CC genotype and combined (GC+CC) genotype.	Lucknow	[49]
19	TNF-a (-308 G>A)	rs1800629	The homozygous AA genotype and combined (CA+AA) genotype.	Lucknow	[49]
20	TNF-a (-238 G>A)	rs361525	The A allele and combined (GA+AA) genotype.	New Delhi, Chandigarh	[48,61]
21	TNF-a (-1031 T>C)	rs1799964	The A allele, heterozygous GA genotype, and homozygous AA genotype.	New Delhi	[48]
22	TLR-4 (896A>G; Asp299Gly)	rs4986790	The C allele, homozygous CC genotype and (TC+CC) genotype.	Lucknow	[63]
23	-196 to -174 deletion of TLR-2	NA	The heterozygous AG genotype.	Chandigarh	[61]
24	GSTM1 deletion	NA	The D allele (deletion) and combined (Ins/Del+Del/Del) genotype.	Lucknow	[64]
25	GSTT1 deletion	NA	The null genotype.	Kolkata, Lucknow, Chandigarh	[40-43,46]
			The null genotype.	Kolkata, Lucknow, Chandigarh	[40-43,46]

26	GSTP1 (313A>G; Ile105Val)	rs1695	The heterozygous AG genotype.	Kolkata, Lucknow, Chandigarh	[40,46]
27	GSTM3 (intron-6; 3bp AGG deletion)	rs1799735	The heterozygous AG genotype and homozygous GG genotype.	Lucknow	[42]
28	MMP-3 (1171 5A>6A Ins/Del)	rs35068180	The homozygous 5A/5A genotype.	Lucknow	[65]
29	PSA (-158G>A)	rs266882	The A allele, the heterozygous GA genotype, and homozygous AA genotype.	New Delhi	[66]
30	KLK-2 (748C>T; Arg250Trp)	rs198977	The homozygous CC genotype.	Lucknow	[67]
31	Caspase-8 (IVS12-19 G>A)	rs3769818	The A allele, the heterozygous GA genotype, and homozygous AA genotype.	Lucknow	[68]
32	Caspase-3 (G>A)	rs4647603	The G allele, the heterozygous GA genotype, and homozygous GG genotype.	Lucknow	[69]
33	COX-2 (-765G>C)	rs20417	The C allele, the heterozygous GC genotype and homozygous CC genotype.	Lucknow	[50]
34	COX-2 (+8473T>C)	rs5275	The C allele, the heterozygous TC genotype, and the homozygous CC genotype.	Lucknow	[50]
35	ER- $\alpha$ (C>T; PvuII)	rs2234693	The T allele, the heterozygous CT genotype, and the homozygous TT genotype.	Chandigarh	[36,38,70]
36	hMLH1 (-93G>A)	rs1800734	The heterozygous GA genotype.	New Delhi	[51]
37	CCND1 (870 G>A; 242Pro=)	rs134556	The A allele and the homozygous AA genotype.	Lucknow	[64]
38	NQO1 (139C>T; Arg139Trp)	rs4986998	The T allele, the heterozygous CT genotype and combined (CT+TT) genotype.	Lucknow	[71]
39	NQO1 (609C>T; Pro187Ser)	rs1800566	The T allele, the heterozygous CT genotype and combined (CT+TT) genotype.	Lucknow	[71]
40	P53 (Intron-6; 13494G>A)	rs1625895	The heterozygous GA genotype.	Lucknow	[54]

41	P53 (c.215G>C; Arg72Pro)	rs1042522	The heterozygous GC genotype. The homozygous CC genotype.	Lucknow New Delhi	[54] [72]
42	CAG repeats in exon-1 of Androgen Receptor gene	NA	Short AR-CAG repeats.	New Delhi, Lucknow, Chennai	[67,68,73]
43	Urokinase (4065 T>C; ApaL1)	rs4065	The T allele, the heterozygous CT genotype and homozygous TT genotype.	Lucknow	[74]
44	VDR (C>T; Thr>Met; Fok-I)	rs2228570	The T allele (coding for Met) and homozygous TT genotype.	Lucknow	[75]
45	XPC PAT (Ins/del)	rs77907221	The Insertion allele and homozygous Ins/Ins genotype.	Lucknow	[53]
46	XPC (33512A>C; Lys939Gln)	rs2228001	The C allele (coding for 939Gln) and homozygous CC genotype.	Lucknow	[53]
47	XPD (G23592A; Asp312Asn)	rs1799793	The homozygous AA genotype.	Lucknow	[76]
48	XPG (G3507C; Asp1104His)	rs17655	The homozygous CC genotype.	Chandigarh	[77]
49	XRCC1 (G23591A; Arg399Gln)	rs25487	The homozygous AA genotype.	Chandigarh	[77]
50	XRCC1 (G>A; Arg280His)	rs25489	The heterozygous GA genotype.	Lucknow	[78]
51	XRCC7 (6721 T>G)	rs7003908	The G allele, the homozygous GG genotype and the combined (TG+GG) genotype.	Lucknow	[79]
52	XRCC4 (Intron-3 Ins/Del)	rs28360071	The homozygous Del/Del genotype.	Lucknow	[52]
53	XRCC4 (Intron-7 Ins/Del)	rs28360317	The homozygous Del/Del genotype.	Lucknow	[52]

It is worth noting that some genetic variants have been found to offer protection against the development of PCa, too. For instance, a study on Chennai population by Vijayalakshmi *et al.* 2005a reported that having variant G allele or heterozygous AG genotype of Cytochrome family CYP1A1 non-synonymous polymorphism rs1048943 (c.4889A>G, Ile462Val) can decrease the risk of PCa (P Value=0.03, OR=0.17, 95%CI=0.02-0.89) [34].

In another study, Damodaran *et al.* 2020 reported that the heterozygous AG genotype of miR-146a upstream transcript variant rs57095329 (c.-386A>G) was significantly decreased in the cases (P value=0.02, OR=0.45, 95%CI=0.24-0.85) compared to the controls, suggesting a probable protective role of the G allele towards PCa [57].

Similarly, in a representative New Delhi population, Kambale *et al.* 2017 found that two VDR polymorphisms, intron-9 variant rs7975232 C>A (heterozygous AC genotype; P value=0.043, OR=0.336; 95%CI=0.120-0.941) and synonymous exon-9 variant rs731236 c.1056T>C (Ile=)

(heterozygous TC genotype: P value=0.016, OR=0.286; 95%CI=0.108-0.758) show a reduced risk of PCa development [80].

Other polymorphisms reported from North Indian cohort as associated with reduced risk towards PCa include TIMP-3 c.1298C>T (CT genotype; P<0.001; OR=0.31, 95%CI=0.18-0.52; variant T allele, P value=0.001, OR=0.49, 95%CI=0.32- 0.75), Caspase-9 UTR variant rs4645978 (c.-1263A>G; AG genotype: P value=0.002, OR=0.45, 95%CI=0.278-0.758) and MDM2 intronic variant rs2279744; (c.309T>G; GG genotype: P value=0.041, OR=0.59, 95%CI=0.35-0.97) [64,65,68].

Table 2 provides a comprehensive list of protective factors that decrease susceptibility to Prostate cancer. These SNPs have also been identified and reported from diverse populations pan India.

**Table 2:** Genetic factors associated with protection against prostate cancer in India.

Sl. No.	Genetic Variant Details	RSID	The Risk Factor Association	Geographical Location	Study Reference
1	miR-146a (-386 A>G)	rs57095329	The G allele and heterozygous AG genotype.	Chennai	[57]
2	GSTP1 gene (313 A>G; Ile105Val)	rs1695	The heterozygous AG genotype.	Chennai	[45]
3	CYP1A1 (4889A>G; Ile462Val)	rs1048943	The heterozygous AG genotype.	Chennai	[34]
4	VDR (T1056C; Taq1; Ile=)	rs731236	The heterozygous TC genotype.	New Delhi	[80]
5	VDR (C>A; Apa1)	rs7975232	The heterozygous CA genotype.	New Delhi	[80]
6	TLR-4 (896A>G; Asp299Gly)	rs4986790	The homozygous AA genotype.	Chandigarh	[61]
7	Caspase-9 (-1263A>G)	rs4645978	The G allele and heterozygous AG genotype.	Lucknow	[68,81]
8	MDM2 (309T>G)	rs2279744	The G allele and homozygous GG genotype.	Lucknow	[64]
9	XRCC1 (G27466A; Arg280His)	rs25489	The heterozygous GA genotype.	Lucknow	[76]
10	XRCC4 (-1394 G>T)	rs6869366	The homozygous GG genotype.	Lucknow	[52]
11	TIMP-3 (1298C>T)	rs11547635	The heterozygous CT genotype	Lucknow	[65]
12	Caspase-9 (-1263A>G)	rs4645978	The heterozygous AG genotype	Lucknow	[68]
13	MDM2 (309T>G)	rs2279744	The homozygous GG genotype	Lucknow	[64]

### 3.1.2. Mutations

Mutations, including epigenetic alterations like DNA methylation and histone modifications, can cause prostate cancer. Changes in gene transcription have also been linked to the disease, affecting diagnosis, prognosis, and treatment. Identifying specific mutations can be challenging for researchers.

DNA mismatch repair (MMR) is a crucial mechanism that ensures genetic stability by identifying and correcting these errors. Preventing recombination between non-identical DNA sequences and responding to DNA damage are additional roles that MMR plays. Although the exact relationship between MMR and PCa development is still not fully understood, it has been suggested that MMR deficiency in PCa may have important clinical implications. A transcriptional analysis of PCa tissue in the Indian population revealed the downregulation of three essential MMR genes: hMLH1, hMLH2, and hMLH3. The study conducted a comprehensive analysis of six MMR genes (hMLH1, hMSH2, hPMS1, hPMS2, hMSH3, and hMSH6) in carefully selected cases of PCa and benign prostatic hyperplasia (BPH). One of the key findings was the discovery of a novel variant rs1800734 (c.-93G>A) in the promoter region of hMLH1. The study also revealed that MMR deficiency could significantly increase the risk of developing cancer due to an elevated spontaneous mutation rate [51]. Furthermore, the downregulation of MMR genes in the Indian PCa cases was associated with a low incidence of PCa. The study results also suggested that the loss of hPMS2 gene expression could be a marker for progression in PCa. Interestingly, mutations in MMR have been reported to cause Lynch syndrome, a hereditary cancer syndrome associated with various carcinogenesis such as prostate, urinary tract, stomach, brain, etc. [82,83]. Men with Lynch syndrome are approximately five times more likely to develop PCa [84]. However, cases of Lynch syndrome and PCa progression have not yet been reported in India. Through a whole exome sequencing on individuals with prostate cancer as cases and benign prostatic hyperplasia (BPH) as controls, representing the northwest region of India, Gupta *et al.* 2020 aimed to uncover potential cancer genes that are yet to be functionally characterized as biomarkers. Though most mutations were found in the DNA repair gene family, viz. helicases, TP53, and BRCA (including rs276174889, rs80358600, rs80359171, rs771203198, and rs145988146), several other mutations in GJB6, KRIT1, GNPTAB, ANG, MCM8, NF1 genes, significant in high-grade PCa, including variants of unknown significance that could potentially cause harm (TNNI3 gene-rs730881069/ chr19:55154172C/ TR136Q) were also reported [3].

In a study conducted on the Asian-Indian population (samples collected from North India), Rennert *et al.* 2008 investigated the role of protein-coding genes RNASEL and MSR1 in the progression toward advanced PCa. The study identified 8 variants for the RNASEL gene, of which 7 variants were novel, and 1 was a known variant, D541E, in the 3' UTR region. For MSR1, 4 novel variants (2 intronic, 2 exonic) and 2 known variants (exonic P275A and c.14637A>G in 5'UTR promoter region) were observed. However, the study failed to establish any role for RNASEL or MSR1 mutations in advanced Asian-Indian PCa [85].

### 3.1.3. Epigenetic alteration: methylation

The possibility for Glutamate carboxypeptidase II (GCPII) haplotypes to impact the likelihood of developing prostate cancer was studied by Divyya *et al.* 2013 in Hyderabad. It had been previously demonstrated that GCPII haplotypes influence circulating folate levels and PSMA expression (Prostate-specific membrane antigen) to affect PCa susceptibility. This case-control



study with 146 participants (48 PCa cases, 10 benign prostate hyperplasia cases, and 88 healthy individuals) hypothesized alterations in the DNA methylation of the genes PSMA, BNIP3 (BCL2/adenovirus E1B 19-kDa interacting protein 3), GSTP1 (glutathione-S-transferase P1), Ec-SOD (extracellular superoxide dismutase) and RASSF1 (Ras-association domain family 1A) may raise the risk of cancer by causing genome instability, mutagenicity, and enhanced oxidative stress. The RT-PCR and gene expression analysis showed that PCa cases had increased expression for PSMA and BNIP3 (P value=0.03) and reduced expression for Ec-SOD (P value=0.03) and RASSF1A (P value< 0.005) as compared with controls. In addition, hypomethylation of BNIP3 (P value <0.0001), hypermethylation of Ec-SOD (P value <0.0001), and RASSF1 (P value=0.008) were also noted in PCa cases. Among the different variants of GCPII, the D191V variation was positively associated with oxidative stress and inversely associated with Ec-SOD expression. In contrast, the H475Y variation was positively associated with Ec-SOD expression and inversely associated with oxidative stress. The R190W variation was found to reduce oxidative stress by increasing glutathione levels. These findings highlighted the role of GCPII genetic variations in increasing oxidative stress and the risk of prostate cancer by modulating CpG island methylation of Ec-SOD [86].

A recent study by Ateeq *et al.* 2015 investigated the prevalence of ETS or RAF gene rearrangements, SPINK1 over-expression patterns, and PTEN deletion status in 94 Indian PCa cases from North India. The findings revealed that 12 patients (12.5%) exhibited SPINK1 over-expression, while PTEN deletion was found in 21.52% of all PCa cases. Interestingly, PTEN deletion was observed in 30% of the ERG-positive cases (P=0.017), but only one case showed over-expression of SPINK1 (P=0.67). Additionally, the study detected BRAF and RAF1 gene rearrangements in approximately 1% and 4.5% of the PCa cases, respectively. The author notes that due to inadequate health/medical awareness and patients' socioeconomic status in India, follow-up information on patients and evaluations of associations with clinical outcomes are limited. However, this study offers valuable molecular stratification of PCa in this patient population, which could guide healthcare professionals in making informed decisions regarding surgical, targeted therapy, hormonal and chemo, and radiation therapy [87].

Studies have demonstrated that DNA methylation patterns can effectively differentiate between benign and malignant tumors in various cancers, including PCa, indicating its potential role in oncogenesis. After studying the Kashmiri population and found that 58.0% of PCa cases displayed methylated GSTP1 through methylation-specific PCR (MSP) analysis, while the RASSF1A gene was methylated in 34.0% of PCa samples. The findings suggest that the epigenetic regulation of GSTP1 and RASSF1A genes via promoter hypermethylation could be crucial in the development of PCa and the progression of benign prostatic hyperplasia into prostate cancer. These results underscore the significant role of RASSF1A and GSTP1 in fundamental molecular pathways of carcinogenesis, such as DNA repair, cell cycle regulation, and signaling. However, it is essential to note that the development of PCA is not solely attributed to RASSF1A or GSTP1-methylation [88].

### 3.2. Microbial infections

The prostate gland is vulnerable to infections caused by microbial pathogens such as bacteria, fungi, and viruses. While these infections can be asymptomatic, they can also result in serious complications such as prostate cancer (PCa). Additionally, these pathogens can exacerbate existing PCa symptoms, making it crucial for individuals to seek prompt medical attention if they suspect they have an infection. A range of herpesviruses, for instance, human cytomegalovirus (HCMV), human herpes simplex virus type 2 (HSV2), human herpesvirus

type 8 (HHV8), Epstein-Barr virus (EBV), BKV, and xenotropic murine leukemia virus-related virus (XMRV), have been found to be involved in causing PCa globally [89-91]. Recent studies have identified human papillomavirus (HPV) infection as a contributing factor in the development or progression of prostate carcinogenesis. In the North Indian population, a case-control study was conducted involving five different types of HPV virus - L1, HPV 16, HPV 18, HPV 6, and HPV 11. The results confirmed that HPV 16 and 18 are more commonly associated with PCA than the other types. In fact, HPV 16 infection alone accounts for 60% of PCA cases [92]. These findings suggest that HPV testing may be valuable in diagnosing and managing PCA. Research by Sarkar *et al.* 2022 on prostate tissue samples of patients from Kolkata also revealed some startling findings. The 16s rRNA sequencing followed by qPCR analyses reported high levels of harmful Gram-positive bacteria, of which *Prevotella copri*, *Cupriavidus campinensis*, and *Propionibacterium acnes* were found to be prominent. The samples also contained several human tumor viruses, including hepatitis B (HBV), Epstein-Barr (EBV), and HPV-16 and HPV-18, which have been linked to PCA carcinogenesis [93].

### 3.3. Other determinants: age, lifestyle, and diet

Aside from genetic factors and microbial infections, several other factors like diet, lifestyle, obesity, age, and hypertension contribute to prostate cancer (PCA) development. Ganesh *et al.* 2011 in a Mumbai hospital-based case-control study, suggested individuals over 55 years of age had about 18-fold increased PCA risk compared to those below 55 years, while a medical history of hypertension had a 2.8-fold increased risk over non-hypertensive controls [94]. Also, individuals with a BMI over 24.9, considered obese, had a 2-fold increased risk compared with less than 25 BMI individuals. North Indian males revealed a significant association of PCA with higher ionized serum calcium level (P value  $\leq 0.001$ ) and total serum calcium level (P value=0.020), with 22.5% of PCA patients having hypercalcemia compared to 2.5% controls [95].

The use of chemical pesticides has been associated with disturbances in the normal functioning of hormones and an increased risk of hormone-mediated cancers. They were considering that prostate cancer (PCA) is a malignancy that depends on hormones. A study in the Lucknow representative population aimed to investigate the link between different types of pesticides and PCA. The study selected ten pesticides commonly used in northern India because of their persistent nature and high consumption rates. Although the concentrations of these pesticides were low, they were detected in the blood of PCA patients and in both benign prostatic hyperplasia (BPH) groups. The study found that the median levels of five and seven pesticides were significantly higher in the PCA group than in the two BPH groups. PCA patients had a higher reported exposure to pesticides (80.4%) compared to controls (45.7%). This resulted in a significant 3 to 4-fold increase in risk (P value=0.001, OR=4.86, 95%CI=2.47-9.59) for PCA [60]. Additionally, the research found a significant association between GSTP1 gene promoter hypermethylation in PCA patients from Kashmir who had been exposed to pesticides (P value=0.02, OR=0.23, 95%CI=0.07-0.80), suggesting its potential role in the development and progression of PCA [88].

The Bombay Population Based Cancer Registry (PBCR) observed that vasectomy could be a contributing factor to prostate cancer. The study revealed men who underwent the procedure before the age of 45 had a 2.1-fold higher risk (95%CI=1.2-3.9; P value=0.01), while those who had it at a later age had a 1.8-fold higher risk (95%CI=1.1-2.9; P value=0.01) of developing PCA compared to those who did not undergo vasectomy. This highlights the importance of considering all possible risk factors when assessing one's risk for prostate cancer [96]. Evidence from an in vivo model study indicates that a diet rich in fat can lead to inflammation

and oxidative stress in the prostate gland. Findings revealed that high-fat diet intake enhances the generation of ROS through elevated expression of NADPH oxidase subunits, which causes activation of NF- $\kappa$ B and induction of NF- $\kappa$ B regulated genes COX-2 and iNOS. These results demonstrate that NF- $\kappa$ B is an essential downstream effector of both oxidative stress and inflammatory pathways, and it can be activated by consuming a high-fat diet. This study strengthens the link between the 'Western-style' high-fat diet and the increased risk of prostatic diseases, including BPH and prostate cancer [97].

From a study conducted by Tyagi *et al.* 2010 in Delhi found fish consumption was deemed to be a determinant factor for PCa (P value=0.046; OR=1.45, 95%CI=1.01-2.09). Among the other dietary determinants, tea (P value=0.043; OR=0.45, 95%CI=0.21-0.97), sunflower oil (P value=0.031; OR=1.63, 95%CI=1.05-2.55), vitamins (P value=0.012; OR=1.75, 95%CI=1.13-2.7) and egg (P value=0.013; OR=1.49, 95%CI=1.09-2.04) consumption was marginally associated with increased risk of PCa. However, consuming citrus fruits (P value=0.028, OR=0.17, 95%CI=0.03-0.83) and melon (P value=0.010, OR=0.48, 95%CI=0.27-0.84) was observed to decrease the risk of developing PCa [22]. Further, a study from Mumbai analyzed the effects of a low-fat diet on the risk of developing PCa. The results showed a statistically significant protective effect for PCa in cases consuming 2-3 kg of fruits and vegetables (OR=0.5, 95%CI=0.3-0.8) and more than 3 kg (OR=0.4, 95%CI=0.3-0.6) per week compared to cases consuming less than 2 kg per week. The protective effect increased significantly with the consumption of fruits and vegetables (P value=0.001) [98]. Numerous studies have been conducted to explore the influence of covariate or confounding factors, including tobacco smoking, alcohol consumption, education, physical activity, and income, on the susceptibility to prostate cancer (PCa). These factors have been examined to determine their impact on the development and progression of the disease [99].

Table 3 highlights the various environmental factors that have been reported in diverse Indian population to increase susceptibility towards PCa.

### 3.4. Gene-environment/lifestyle interplay

Many Indian researchers have widely studied smoking and alcohol intake as risk factors for PCa.

The development and functionality of the prostate gland relies heavily on androgens. These hormones have also been linked to the development of prostate cancer. An elevated level of testosterone and estrogen in the bloodstream has been linked to a higher likelihood of developing prostate cancer. Testosterone is produced from cholesterol through several enzymatic reactions that involve cytochrome P450 enzymes, including CYP17. CYP17 is a marker for prostate cancer susceptibility as it produces the cytochrome P450c17 enzyme, which plays a crucial role in the biosynthesis of steroid hormones. This enzyme is responsible for the 17 $\alpha$ -hydroxylation of pregnenolone and progesterone and the 17,20-lysis of 17 $\alpha$ -hydroxypregnenolone and 17 $\alpha$ -hydroxyprogesterone. A study from Chandigarh examined the effect of 5' UTR polymorphism rs743572 (c.1931T>C) of the CYP17 gene on the risk of developing PCa and indicated a notable increased risk for smoker cases with homozygous mutant CC genotype (P value=0.02, OR=3.90, 95% CI=1.19-12.81) and combined heterozygous and mutant (TC+CC) genotype (P value=0.019, OR=2.15, 95% CI=1.13-4.09) [37]. Furthermore, GSTM3 is an enzyme that belongs to the phase II group of metabolic enzymes. This enzyme may have a significant role in the conjugation and detoxification of various carcinogenic agents present in the environment and workplace. The inability of the body to detoxify certain drugs and environmental toxins due to a lack of acetylation could be a significant mechanism

in the development of prostate cancer. In the North Indian population, Kesarwani *et al.* 2009 reported that in the dominant model of intronic polymorphism of GSTM3 rs1799735 (3bp AGG deletion), smoker patients exhibited a 4-fold increased risk compared to smoker controls (P value=0.044, OR=4.11, 95%CI=1.04-16.23). Individuals carrying the variant allele who consume alcohol are at a 4.3-fold greater risk of developing prostate cancer. This increased risk is attributed to the higher production of reactive oxygen species (ROS) during ethanol metabolism in alcoholics, which contributes to the development of prostate cancer (P value=0.027, OR=4.38, 95%CI=1.18-17.05) [39].

**Table 3:** Environmental factors associated with prostate cancer risk in diverse Indian population.

Sl. No.	Environmental Factors	Association Type	Geographical Location	Study Reference
1	Citrus fruits (orange, melon)	Protective association	Delhi	[22]
2	Low-fat diet (fruits and vegetables)	Protective association	Mumbai	[98]
3	Tea consumption	Protective association	Delhi	[22]
4	Dietary calcium intake	Increases PCa risk	Lucknow	[95]
5	Non-vegetarian food habit (egg, fish)	Increases PCa risk	Punjab, Delhi	[22,48,100]
6	Non-vegetarian food habit (high intake of red meat)	Increases PCa risk	Kashmir	[101]
7	Sunflower oil and other oil	Increases PCa risk	Delhi	[22]
8	Vitamins	Increases PCa risk	Delhi	[22]
9	Age	Increases PCa risk	Mumbai, Lucknow	[60,94]
10	Hypertension	Increases PCa risk	Mumbai	[94]
11	BMI, Obesity	Increases PCa risk	Mumbai, Lucknow, Kashmir	[94,101,102]
12	Lack of physical activity	Increases PCa risk	Kashmir	[103]
13	Diabetes mellitus	Increases PCa risk	Kashmir	[103]
14	Vasectomy	Increases PCa risk	Mumbai	[96]
15	Urban dwelling	Increases PCa risk	Kashmir	[101]
16	Exposure to pesticides	Increases PCa risk	Lucknow	[60]

The role of IL-10 polymorphisms in cancer development is a controversial topic due to its complex involvement in immune regulation and angiogenesis. Some studies suggest that IL-10 may promote tumor development through its immune-suppressive properties, while others propose its anti-angiogenic effects may hinder tumor progression [103]. Bandil *et al.*

2017 in the New Delhi population, revealed that smokers with variant genotypes of the anti-inflammatory IL-10 UTR polymorphism rs1800872 (c.-592A>C) displayed a statistically significant correlation with PCa (P value=0.03, OR=3.28, 95%CI=1.19-9.01), while alcohol users carrying the heterozygous AG genotype for IL-10 UTR polymorphism rs1800896 (c.-1082A>G) polymorphism were shown to have a higher susceptibility towards PCa (P value=0.008, OR=0.20, 95%CI=0.06-0.61) [48]. Interestingly, a significant correlation is recorded between the methylation of the RASSF1A promoter and the smoking habits of PCa patients within the Kashmiri population (P value=0.03, OR=5.07, 95%CI=1.22-21.06) [88]. Mittal *et al.* 2007b showed significant correlations between tobacco use and some specific genetic markers. Tobacco users with the heterozygous TC genotype of CYP1A1 rs4646903 (c.3801T>C) (P< 0.001, OR=5.40, 95%CI=2.37-12.26), or with the heterozygous TC genotype (P value=0.001, OR=2.66, 95%CI=1.49-4.73) or homozygous variant CC genotype (P< 0.000, OR=4.90, 95%CI=2.372-10.130) of exonic mEH variant rs1051740 (T>C, Tyr113His) had a higher likelihood of developing PCa. Additionally, tobacco users with the wild-type AA genotype (P value=0.003, OR=2.89, 95%CI=1.43-5.85) for exonic mEH variant rs2234922 (A>G; His139Arg) were more likely to develop PCa [61].

Research conducted by Qadri *et al.* 2011 in Kashmir on 50 male populations from rural and urban areas to study the potential impact of occupational pesticide exposure on PCa risk revealed that rural men have a higher disease occurrence rate than urban men (P value=0.24). [44] Also, in the North Indian population, the study revealed a notable disparity in non-vegetarian consumption between PCa patients (42%) and controls (14%), with non-vegetarians exhibiting a significantly higher percentage (OR=4.46, 95%CI=2.32-8.59) and a strong correlation (P value <0.0001) with PCa. [48] About 4.3-fold increased risk (95% CI=1.27-14.53; P value=0.02) and 2.5 fold increased risk (95% CI=1.30-4.63; P value=0.005) was noted respectively in non-vegetarians carrying mutant genotype and mutant allele carriers of CYP17 5' UTR variant rs743572 (c.1931T>C) polymorphism [37].

Table 4 provides a list of gene polymorphisms which, on interaction with environmental factors, are found to increase susceptibility to Prostate cancer.

**Table 4:** List of genetic factors which upon interaction with environmental factors, associate with prostate cancer in India.

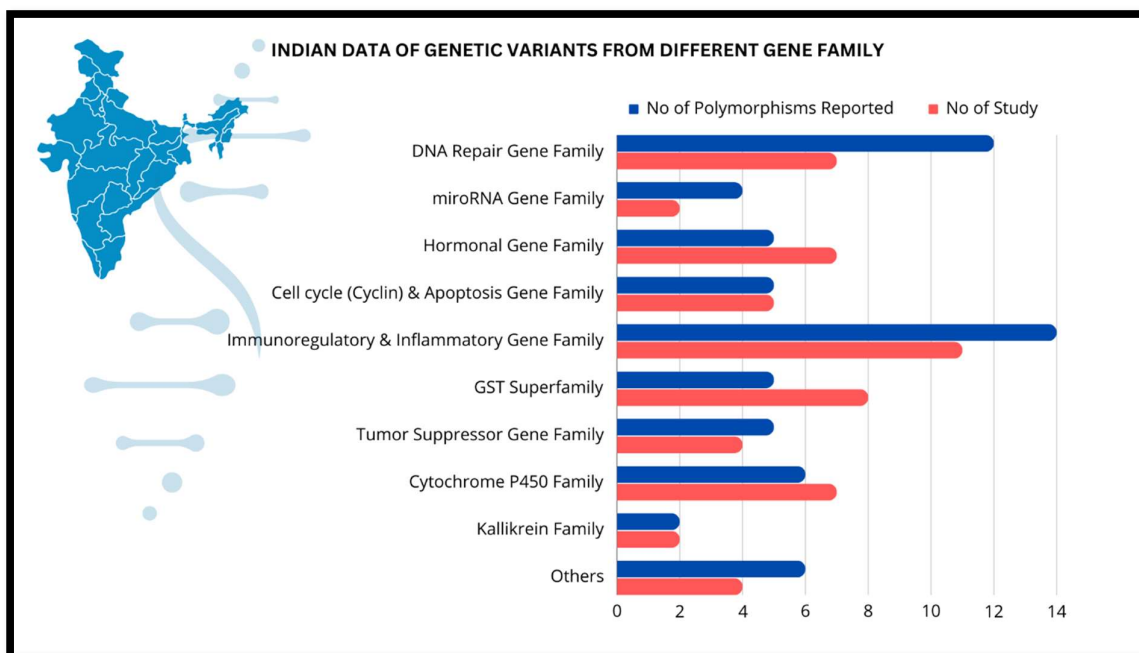
Sl. No.	Genetic Variant Details	RSID	The Associated Risk Factor	Geographical Location	Study Reference
1	CYP1A1 (CYP1A1*2A; Msp1; T3801C)	rs4646903	The heterozygous TC genotype in cases with low age of onset.	Chennai	[34]
			The heterozygous TC genotype in tobacco user cases.	Lucknow	[61]
			The combined (TC+CC) genotype in smoker cases	Lucknow	[60]
			The combined (TC+CC) genotype in cases exposed to pesticides.		
2	CYP1A1 (A4889G; Ile462Val)	rs1048943	The combined (TC+CC) genotype in smoker cases	Lucknow	[60]
			The combined (TC+CC) genotype in cases exposed to pesticides.		



3	CYP17 (1931T>C; MspA1)	rs743572	The homozygous CC genotype, heterozygous CT genotype and combined (CT+CC) genotype in cases with smoking habit and non-vegetarian food habit.	Chandigarh	[37]
4	mEH gene (T>C; Tyr113His)	rs1051740	The (heterozygous TC genotype and homozygous CC) genotype in tobacco user cases.	Lucknow	[61]
5	mEH gene (A>G; His139Arg)	rs2234922	The heterozygous AG genotype in tobacco user cases.	Lucknow	[61]
6	IL-10 (- 1082A>G)	rs1800896	The combined (AG+GG) genotype in alcoholic cases, or cases with vegetarian food habit.	New Delhi	[48]
7	IL-10 (-819 C>T)	rs1800871	The combined (CT+TT) genotype in cases with vegetarian food habit.	New Delhi	[48]
			The combined (CA+AA) genotype in cases with smoking habit, or vegetarian food habit.	New Delhi	[48]
8	IL-10 (-592 C>A)	rs1800872	The homozygous CC genotype and the combined (CC+AC) genotype in smokeless tobacco users, and in tobacco smokers.	Lucknow	[49]
9	IL-18 (-137G>C)	rs187238	The heterozygous GC genotype, homozygous CC genotype and the combined (GC+CC) genotype in tobacco smokers.	Lucknow	[49]
10	IL-18 (-607C>A)	rs1946518	The heterozygous CA genotype, homozygous AA genotype, and combined (CA+AA) genotype in smokeless tobacco users, and in tobacco smokers.	Lucknow	[49]
11	TNF- $\alpha$ (-308 G>A)	rs1800629	The combined (GA+AA) genotype in cases with vegetarian food habits.	New Delhi	[48]
12	TNF- $\alpha$ (-238 G>A)	rs361525	The combined (GA+AA) genotype in cases with smoking, alcohol, vegetarian food habits, or non-vegetarian food habit.	New Delhi	[48]
13	GSTP1 (313A>G; Ile105Val)	rs1695	The heterozygous GG genotype and cases with advanced age group.	Kashmir	[44]
14	GSTM3 (intron- 6; 3bp AGG deletion)	rs1799735	The combined (AB+BB) genotype in cases with smoking and/or alcohol habits.	Lucknow	[39]
15	Caspase-8 (IVS12-19 G>A)	rs3769818	The heterozygous GA genotype in cases with tobacco habit.	Lucknow	[68]
16	ER- $\alpha$ (C>T; PvuII)	rs2234693	The homozygous TT genotype in cases with smoking habit.	Chandigarh	[70]
17	Urokinase (4065 T>C; ApaI1)	rs4065	The heterozygous CT genotype in tobacco user cases.	Lucknow	[74]

## 4. Discussion

In view of the information mentioned above, it can well be said that PCa is a complex ailment that is influenced by a variety of factors, including genetics, environment, and lifestyle. Interestingly, from North India, a total of 42 independent studies that report 40 associated genes have been recognized, as opposed to only 5 independent studies on South Indian men, which report 8 associated genes. East India reports a single study with 3 associated genes, while no association study has yet been reported from Western India. The most identified and reported polymorphisms throughout India include the GST superfamily gene SNPs, GSTM1 and GSTT1 deletion polymorphisms, and GSTP1 missense variant rs1695, followed by Cytochrome-P450 family genes, CYP1A1 variant rs4646903, and CYP17 variant rs743572. Figure 3 represents a comparison of gene families that have been studied in Indian men.



**Figure 3:** Rate of associated genetic polymorphism reported from Indian case-control studies.

Genes are grouped broadly accordingly to gene family and the total number of reported polymorphisms with total number of studies for each gene family is graphically represented. DNA Repair Gene Family (XPC, XPD, XRCC1, XPG, XRCC4, XPG, XRCC7, hMLH1), miRNA Gene Family (mir-196a, mir-125a, has-mir499, mir146a), Hormonal Gene Family (VDR, ER- $\alpha$ , AR), Cell cycle (Cyclin) & Apoptosis Gene Family (CCND1, CASP), Immunoregulatory & Inflammatory Gene Family (CCL2, IL-10, IL-18, TNF- $\alpha$ , TLR-2, TLR-4, COX), GST Superfamily (GSTM1, GSTT1, GSTP1, GSTM3), Tumor Suppressor Gene Family (P53, SFRP4, DR4), Cytochrome P450 Family (CYP1A1, CYP17, CYP19, CYP1B1), Kallikrein Family (PSA, KLK2), Others (mEH, MMP3, Urokinase, NQO1).

For the formation of DNA adducts, chemical carcinogens must be activated into electrophilic reactive forms, and this process is catalyzed by phase I enzymes (cytochrome-P450 family). Conversely, phase II enzymes (glutathione-S transferases family) couple metabolic intermediates into water-soluble forms, allowing rapid elimination [34]. Consequently, it may be inferred that individuals with lower detoxification activity and higher metabolic activity

are more susceptible to acquiring prostate cancer. Thus, variations in metabolic activity are predicted to have an impact on cancer susceptibility.

Other SNPs reported from India include SFRP4 (rs1802074), miR-196a2 (rs11614913), and prostate-specific antigen (PSA) variants (rs2569733, rs2739448, rs925013), that are associated with an increased risk of PCa. Elevated SFRP4 expression links to aggressiveness and non-canonical Wnt pathway and epithelial-to-mesenchymal transition (NCWP-EMT) markers, making it a potential cancer biomarker [56,104-106]. While miR-146a acts as a tumor suppressor by down-regulating genes like Rac1 and modulating HA/ROCK1-mediated tumorigenicity, PSA contributes to PCa progression through protease activity, epithelial-mesenchymal transition, and cell migration. PSA levels correlate with PCa stage and grade, aiding post-treatment monitoring [4,36,58,107-10].

Conversely, SNPs in genes such as CYP1A1 (rs1048943), miR-146a (rs57095329), and VDR (rs7975232, rs731236) have demonstrated a protective effect by reducing PCa risk. Vitamin D impacts cell growth and differentiation, primarily via the active form 1,25-dihydroxyvitamin D<sub>3</sub>, synthesized by prostatic epithelial cells. Changes in VDR's ability to bind 1,25(OH)<sub>2</sub>D<sub>3</sub> or activate VDRE genes can alter regulatory gene expression, like CDKv [80,111].

Moreover, evidence suggests that among the majority of identified environmental factors, PCa is most prevalent among tobacco smokers and alcohol drinkers. More than 7000 compounds, including polycyclic aromatic hydrocarbons (PAHs) and cadmium, can be produced when cigarettes are burned (Centers for Disease Control and Prevention (US), 2010) [112]. Genes involved in PAH metabolism and detoxification may have mutations or functional polymorphisms that increase the risk of PCa [113]. Additionally, GSTs are capable of detoxifying PAHs, and GSTM has been linked to a higher risk of PCa in smokers. Researchers have associated alcohol consumption with an increased risk of PCa, as the formation of reactive oxygen species (ROS) during ethanol metabolism in alcoholics is recognized [39].

Further research is necessary to uncover additional genetic factors and environmental determinants to understand PCa pathogenesis fully.

## 5. Screening of Prostate Cancer

Despite decades of research, there is no credible way by which prostate cancer can be cured once it has become malignant. Thus, PCa screening is necessary because the tumors present a high risk of dissemination if not detected early and treated in time [114]. At present, there are few routine screening procedures for prostate cancer - PSA (Prostate Specific Antigen) test and DRE (Digital Rectal Examination), Transrectal ultrasonography and biopsies, Ultrasound-guided trans-perineal and template-guided biopsies [93]. According to an article published in John Hopkins, the average normal median PSA for 40-50 years old adults ranges between 0.6 and 0.7 ng/ml. In contrast, a more than 2.5 ng/ml value is considered abnormal. For males aged 60 and older, the range is between 1.0 and 1.5 ng/ml; greater than 4.0 ng/ml is considered abnormal [114]. Based on a study conducted by Gupta *et al.* 2014 on the Indian population, a reference range for serum PSA levels in healthy males of varying ages was established. The study revealed a strong correlation between age and PSA levels, with higher levels observed in older age groups. The reference range for serum PSA levels was found to be highly reliable with values of 0.71 ng/ml for those under 40 years, 0.85 ng/ml for those aged between 40 and 49, 1.13 ng/ml for those between 50 and 59, 1.45 ng/ml for those between 60 and 69, 1.84 ng/ml for those between 70 and 79, and 2.35 ng/ml for those over 80 years old. [115] However, the PSA test is often regarded as controversial due to frequent false positive

or negative results. A false-negative result increases the risk of PCA because appropriate treatment is initially ignored, and a false-positive result leads to unnecessary further investigations; therefore, MRI is sometimes offered before the biopsy [116]. Currently, according to ICMR, the traditional PSA test has been replaced by the 4k test, considering it provides more information about the risk for aggressive prostate cancer [117]. Patients are advised to get a complete physical check, including a DRE, bone scan, imaging test, and CT scan for early detection of prostate cancer. In India, it is recommended that men undergo PSA testing after a consultation with a urologist if they are experiencing urinary symptoms or are undergoing executive health checks. Thanks to the rise in executive health check-ups, more cases of prostate cancer are being detected at an early stage. A recent study examined the PSA levels of 4702 men aged 50 to 75 initially screened with DRE and PSA. Of those men, 70.9% had PSA levels under 4 ng/ml, while 11.8% had PSA levels between 4.1-10 ng/ml, 5.4% had levels between 10.1-20 ng/ml, and 11.8% had levels above 20 ng/ml. Although the PSA positivity rate was 29.1%, the PPV of PSA in symptomatic men was low, indicating that many PSA-positive men may undergo unnecessary biopsies. To reduce the number of unnecessary biopsies, the author suggests raising the PSA threshold to 5.4 ng in symptomatic men with regular rectal examinations [118]. Another study conducted in Gurgaon, India, for two years, from January 2010 to January 2012, analyzed 1300 Indian adult males who underwent the executive health check-up package. Of the subjects, 1060 were healthy and belonged to a specific religion, A, and 193 were from another religious group, B, without prostate disease between the ages of 19 and 97. The study revealed that the age-specific reference range of serum PSA in healthy Group A males is lower than in Group B males, with 0.69 ng/ml for those under 40, 0.83 ng/ml for those aged 40-49, 1.13 ng/ml for those aged 50-59, 1.46 ng/ml for those aged 60-69, and 1.83 ng/ml for those over 70. For healthy Group B males, the reference range is 0.86 ng/ml for those under 40, 1.01 ng/ml for those aged 40-49, 1.41 ng/ml for those aged 50-59, 1.70 ng/ml for those aged 60-69, and 2.92 ng/ml for those over 70. The data also suggests that PSA levels increase with age [119].

## 6. Summary

Prostate Cancer (PCa) is a prevalent malignancy that becomes more prevalent after age 50. The incidence of PCa varies globally, with lower rates in Asia compared to Europe, Australia, and North America, as reported by sources like the Cancer Registry and Globocan 2020. Unfortunately, there seems to be a disturbing upward trend in mortality rates, which could be attributed to various factors, including inadequate diagnosis, limited awareness, and insufficient education on the topic. Projections show that this trend will continue until 2040. Multiple factors influence PCa risk, including age, socio-economic status, obesity, hormonal changes, genetics, and occupational hazards. In India, PCa ranks fifth in cancer incidence among men, higher than in many Asian and African countries. Urban areas like Bangalore, Delhi, and Mumbai also have higher rates, possibly due to lifestyle and genetic diversity. Notably, cities such as Kolkata, Delhi, and Pune have recorded the highest age-adjusted rates of this disease per 100,000 males. However, regions like Northeast India report lower PCa prevalence, partly due to a lack of urology services.

Research has shown that certain genetic variations, like single nucleotide polymorphisms (SNPs), can significantly impact the risk of developing Prostate Cancer (PCa). Specifically, specific SNPs in genes SFRP4, miR-196a2, and PSA have been linked to an increased risk of PCa, while some variants in genes CYP1A1, miR-146a, and VDR have been associated with a reduced risk. GST superfamily gene variants and SNPs in genes like CCL2 and hMLH1 also contribute to PCa susceptibility. Additionally, mutations and epigenetic alterations, such as

DNA methylation, can contribute to the development of PCa, with some studies finding an association with the downregulation of MMR genes.

Infections caused by various pathogens, including Human papillomavirus (HPV), herpes virus, bacteria like *Prevotella copri*, *Cupriavidus campinensis*, and *Propionibacterium acnes*, certain fungi, and parasites, can also impact prostate health. In addition, various case-control studies from different regions in India have revealed that the incidence of PCa is more prevalent in men who engage in smoking, drinking, tobacco chewing, or have been exposed to hazardous environments in occupation. Other determinants like a non-vegetarian diet, consumption of sunflower oil or vitamins, obesity, hypertension, and vasectomy increase PCa risk, while consuming citrus fruits and melon can reduce it. The interplay between genes and lifestyle factors like smoking and alcohol consumption can further increase PCa risk.

It is of utmost importance to spread awareness and educate people about the risks associated with these infections. It is recommended to undergo a comprehensive physical examination to detect any potential abnormalities in the prostate and avoid cancer development. Ensuring early detection and timely treatment of prostate cancer is of utmost importance. PCa screening methods include PSA testing, digital rectal examination, and biopsies. Accurate screening necessitates establishing reference ranges for PSA levels across different age groups. Health education workshops are a practical way to promote public awareness and encourage individuals to seek appropriate care and preventative measures. In India, the Prostate Cancer Awareness Program (BCAP) and the Breast Cancer Awareness Program were launched in November 2018 to raise awareness of sexual organ malignancies in men and women. The Indian Prostate Cancer Foundation (IPCF) is dedicated to organizing multiple awareness programs each year, including a recent group meeting held on September 14, 2022, to discuss various treatments, therapies, and robotic surgeries related to prostate cancer. This provided an opportunity for individuals to address their concerns and receive expert guidance.

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## Author Contributions

Souradeep Banerjee: Conceptualization, Writing - Original draft, Writing - Review & Editing, Data curation; Bratati Dutta: Writing - Original draft, Writing - Review & Editing, Data curation; Soumili Biswas: Writing - Original draft, Data curation, Mainak Sengupta: Conceptualization, Supervision, Writing - Original draft, Writing - Review & Editing.

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