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UNDERSTANDING PROSTATE CANCER: A COMPREHENSIVE REVIEW OF ITS MECHANISMS, TREATMENTS, AND THE EMERGING ROLE OF NATURAL COMPOUNDS

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ABSTRACT: Prostate cancer is among the most frequently diagnosed malignancies in men and remains a major contributor to cancer-related morbidity worldwide, particularly in ageing populations. Despite advances in screening and therapeutic strategies, challenges related to disease progression, therapeutic resistance, and treatment-associated adverse effects persist. This review critically examines the aetiology, risk factors, clinical manifestations, and underlying pathophysiological mechanisms involved in prostate cancer development and progression. Established treatment modalities, including surgery, radiotherapy, androgen-deprivation therapy, and chemotherapy, are discussed with emphasis on their clinical utility and limitations. In addition, emerging evidence on biologically active natural compounds is evaluated as a complementary area of research. Natural agents such as curcumin, quercetin, and red sea moss-derived constituents have demonstrated anti-inflammatory, antiproliferative, and pro-apoptotic activities in experimental models of prostate cancer. However, the majority of supporting data remains preclinical, with limited and inconsistent clinical validation. This review highlights the importance of distinguishing evidence-based therapies from investigational and supportive approaches. It further emphasises the need for well-designed translational and clinical studies to assess the safety, efficacy, and therapeutic relevance of integrating natural compounds with conventional treatment regimens. This synthesis provides a focused framework to guide future research priorities and optimise evidence-based prostate cancer management strategies worldwide clinically.

INTRODUCTION: Prostate cancer is one of the most prevalent malignancies affecting men worldwide and represents a growing public health concern, particularly in ageing populations. More than 1.4 million new cases are reported annually, with substantial geographic variation driven by differences in genetic background, screening practices, environmental exposures, and lifestyle factors.

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Although most diagnoses occur after the age of 50, the disease exhibits marked clinical heterogeneity, ranging from indolent localised tumours to aggressive, treatment-resistant metastatic forms. The pathogenesis of prostate cancer is multifactorial, involving complex interactions among hormonal regulation, genetic susceptibility, metabolic alterations, and environmental influences.

Central to disease initiation and progression is dysregulation of androgen receptor (AR) signalling, which enables sustained tumour proliferation and survival, particularly under therapeutic pressure. As the disease advances, adaptive mechanisms such as AR amplification, mutations, splice variants, and

ligand-independent activation contribute to resistance against androgen-deprivation therapy. In parallel, aberrant activation of oncogenic pathways, including PI3K/AKT/mTOR signalling often associated with PTEN loss—along with MAPK, Wnt/β-catenin, and TGF-β pathways, promotes cell survival, epithelial–mesenchymal transition, and metastatic dissemination. Oxidative stress and chronic inflammation further exacerbate genomic instability and sustain a tumour-promoting microenvironment.

Management strategies are largely guided by disease stage and risk stratification. Localised prostate cancer is commonly treated with surgery or radiotherapy, while androgen-deprivation therapy remains central for advanced disease. However, progression to castration-resistant prostate cancer, along with treatment-related morbidity, limits long-term outcomes. Although recent advances in molecular profiling, imaging, and systemic therapies have improved disease control in selected patients, recurrence and resistance remain common. In this context, increasing attention has been directed toward biologically active natural compounds as potential adjuncts, though current evidence is predominantly preclinical and requires rigorous clinical validation. This review integrates epidemiological trends, key molecular mechanisms, and established therapeutic approaches to identify critical gaps and inform future research directions in prostate cancer management.

Development of the Prostate Gland: The prostate gland develops during early fetal life through tightly regulated epithelial–mesenchymal interactions originating from the urogenital sinus. Prostatic epithelial buds arise from the ventral urogenital sinus and undergo coordinated branching morphogenesis, stromal differentiation, and lobar organisation, establishing the structural framework required for normal prostate function [1].

By mid-gestation, reciprocal signalling between epithelial and mesenchymal compartments drives the formation of distinct prostatic regions and an encapsulated glandular structure. Classical descriptions of prostate development and lobar organisation, including the lobe-based classification proposed by Lowsley, have historically informed anatomical and developmental understanding of the gland [2]. Although contemporary concepts increasingly emphasise zonal anatomy, these foundational models remain relevant for interpreting early morphogenetic patterning. Despite advances in developmental biology, several early regulatory mechanisms and aspects of regional specialisation remain incompletely defined, underscoring the relevance of developmental processes to prostate disease susceptibility later in life.

Gross Anatomy Features: The prostate gland is a fibro-glandular organ situated inferior to the urinary bladder, surrounding the proximal urethra at the bladder neck, and positioned anterior to the rectum and posterior to the symphysis pubis. The anterior surface lies behind the pubic arch, while the posterior surface is traversed at its base by the ejaculatory ducts, which open into the prostatic urethra near the seminal colliculus (verumontanum). A fibrous connective tissue layer, known as Denonvilliers' fascia, separates the prostate and seminal vesicles from the rectum, providing an important anatomical and surgical plane. In adult males, the prostate typically weighs approximately 20 g and demonstrates a compact conical configuration. Standard anatomical dimensions are described in transverse, vertical, and anteroposterior axes, reflecting its compact morphology within the pelvic cavity. Anatomically, the prostate is located within the pelvis, inferior to the bladder and superior to the urogenital diaphragm, where it plays a central role in male reproductive and urinary function.

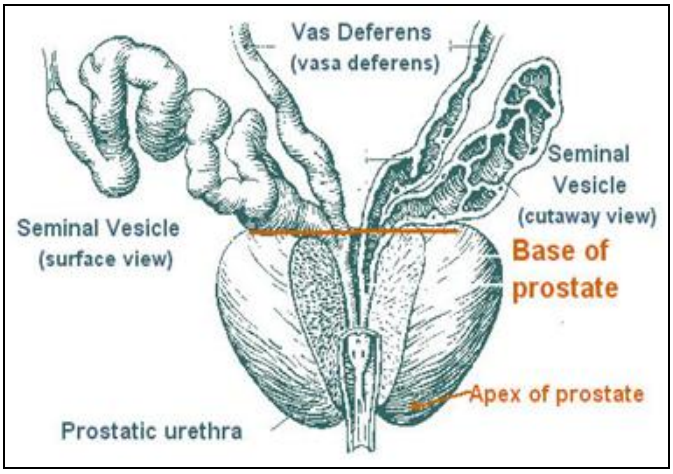

FIG. 1: PROSTATE GLAND

Composition of the Prostate Gland at the Molecular Level:

Luminal or Secretory Cells: Secretory cells (SCs) constitute the predominant epithelial cell population of the prostate, lining the luminal surface of acini and ducts. These columnar epithelial cells are functionally specialised for secretion and are characterised by a basally positioned nucleus and cytoplasmic organisation that supports high metabolic and secretory activity. The basal cytoplasm is enriched in organelles involved in protein synthesis and energy metabolism, whereas the apical region contains secretory vesicles and lysosomal structures, reflecting their role in glandular secretion. SCs are essential for male reproductive function, synthesising and releasing key components of seminal fluid that support sperm viability and motility. They produce clinically relevant biomarkers, including prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), which are secreted into the prostatic lumen. These cells exhibit strong androgen dependence, expressing nuclear androgen receptors and characteristic epithelial markers such as cytokeratin8 and 18. Consequently, their survival and function are markedly reduced during androgen-deprivation therapy.

Despite high metabolic activity, SCs display limited proliferative capacity, with epithelial integrity maintained by an underlying basal cell layer. Their androgen sensitivity and secretory function underscore their central role in prostate physiology and their clinical relevance in prostate cancer, particularly in the context of hormone-targeted therapies.

Basal Cells: Basal cells, first described by McNeal as a key component of the bilayer prostatic epithelium, are located between luminal secretory cells and the basement membrane, where they maintain epithelial structure and integrity. These non-secretory, polygonal cells are defined by the expression of cytokeratin 5 and 14 and the surface marker CD44 and exhibit lower androgen receptor expression than luminal cells, accounting for their relative resistance to hormonal regulation. Although traditionally viewed as less likely to initiate prostate cancer, emerging evidence indicates that basal cells possess stem-like and regenerative properties, enabling cellular plasticity under specific molecular conditions [6]. Differences in androgen sensitivity, proliferative capacity, and lineage potential between basal and luminal epithelial compartments influence tumour initiation, progression, and therapeutic response. This epithelial interplay provides a critical framework for understanding prostate cancer heterogeneity, disease aggressiveness, and resistance to hormone-targeted therapies.

Stem Cells: Stem cells are undifferentiated cells characterised by their capacity for self-renewal and multilineage differentiation and are present in both embryonic and adult tissues. While embryonic stem cells arise from the inner cell mass of the blastocyst, adult (somatic) stem cells reside within specialised tissue niches and contribute to tissue maintenance and regeneration. In the prostate, epithelial homeostasis is sustained by a stem-like cell population located primarily within the basal cell layer. These cells occupy the apex of the epithelial hierarchy and generate intermediate progenitor cells that subsequently differentiate into basal, luminal/secretory, and neuroendocrine cell lineages.

Prostatic stem cells maintain their pool through symmetric self-renewing divisions while also supporting epithelial turnover and repair. Their identification has been supported by the expression of characteristic stem cell-associated markers, including CD133, CD44, α2β1 integrin, breast cancer resistance protein-1 (BCRP-1), ATP-binding cassette subfamily G member 2 (ABCG2), telomerase reverse transcriptase (TERT), and basal cytokeratin CK5 and CK14. The presence of this stem-like population has important implications for prostate development, epithelial plasticity, and disease pathogenesis, particularly in the context of tumour initiation, progression, and therapeutic resistance.

Intermediate or Amplifying Cells: Amplifying cells are a short-term population of cells that originate from stem cells and divide instantly for a short amount of time before becoming fully specialised (distinct). They serve as an intermediary between stem and mature cells. Intermediate cells are proliferating cells that carry characteristics found in both basal and secretory

cells. In the basal layer, these cells exhibit luminal marker cytoplasmic keratins 8 and 18, while certain layers in the luminal layer express basal cell cytokeratins 5 and 14.

Neuroendocrine Cells: Neuroendocrine cells represent a highly specialised epithelial cell population within the prostate that exhibits features of both neuronal and endocrine lineages. These cells are androgen-independent, sparsely distributed along the basal epithelial compartment, and play a regulatory role in maintaining epithelial growth, differentiation, and secretory homeostasis through paracrine signalling. Neuroendocrine cells may be classified into open and closed subtypes based on their contact with the glandular lumen, reflecting functional heterogeneity.

In prostate cancer, neuroendocrine differentiation becomes increasingly prominent in advanced and hormone-resistant disease. Tumour progression toward neuroendocrine prostate cancer or small cell carcinoma is associated with aggressive clinical behaviour, reduced responsiveness to androgen-deprivation therapy, and poor prognosis. Neuroendocrine cells are characterised by the expression of specific markers, including chromogranin A, serotonin, bombesin, neuron-specific enolase, and calcitonin, which are commonly used for diagnostic and prognostic assessment. The emergence of neuroendocrine differentiation highlights the role of cellular plasticity in disease progression and therapeutic resistance.

Regulation of Prostatic Function:

Androgens: Androgens are the principal hormonal regulators of prostate development, differentiation, and function and play a central role in prostate cancer pathogenesis. Their biological effects are mediated through the androgen receptor (AR), a ligand-activated transcription factor that regulates gene expression essential for epithelial growth and survival. Under physiological conditions, androgen–AR signalling maintains normal prostate homeostasis; however, in prostate cancer, this pathway becomes dysregulated and drives tumour initiation and progression. Testosterone, produced primarily by the testes, is converted intracellularly to the more potent androgen dihydrotestosterone (DHT) by 5α-reductase. In the absence of ligand, AR remains inactive in the cytoplasm, associated with heat shock proteins. Upon DHT binding, AR undergoes conformational change, translocates to the nucleus, and interacts with transcriptional co-activators such as NCOA1–3 (Nuclear Receptor Coactivator) and TIP60 (Tat-interacting protein) to activate genes involved in proliferation and survival. This activity is modulated by transcriptional repressors, including SMRT (Silencing Mediator for Retinoid & Thyroid hormone) and NCOR (Nuclear Receptor CoRepressor), which fine-tune androgen-responsive gene expression.

The dependence of prostate cancer cells on androgen signalling underlies the clinical effectiveness of androgen-deprivation therapy in advanced disease. However, adaptive mechanisms enabling AR reactivation or bypass signalling ultimately lead to treatment resistance and disease progression. In addition to classical secretory proteins such as prostate-specific antigen and prostatic acid phosphatase, androgen-regulated genes involved in cell cycle control and survival include CDK8 (Cyclin-dependent kinase 8), PIK3R1 (Phosphoinositide-3-kinase Regulatory Subunit 1), and RAB4A (RAS-related protein Rab-4a), reflecting the broad regulatory scope of AR signalling in prostate cancer.

Estrogen: Estrogens exert dual regulatory effects on prostate biology through both endocrine and local paracrine mechanisms. Systemically, Estrogens suppress luteinizing hormone secretion *via* modulation of the hypothalamic–pituitary–gonadal axis, indirectly reducing testicular androgen production and androgen-dependent prostate activity. At the tissue level, estrogenic effects are mediated through two receptor subtypes, Estrogen receptor alpha (ER-α) and Estrogen receptor beta (ER-β), which display distinct and compartment-specific expression patterns within the prostate.

ER-β is widely regarded as tumour suppressive, regulating epithelial homeostasis by promoting cell cycle arrest, limiting oxidative stress, and restraining proliferative signalling. In contrast, ER-α activation is associated with pro-inflammatory signalling, increased reactive oxygen species production, and aberrant epithelial proliferation,

processes implicated in the initiation of prostatic intraepithelial neoplasia. The relative balance between ER-α and ER-β signalling is therefore critical in determining disease trajectory.

During ageing and prostate cancer progression, ER-β expression is frequently diminished, while ER-α signalling becomes dominant, creating a microenvironment permissive to disease progression and castration-resistant growth through activation of alternative pathways such as MAPK and PI3K. Emerging evidence supports the therapeutic potential of selectively targeting Estrogen receptor signalling, particularly through ER-β agonists or ER-α antagonists. However, challenges remain in achieving tissue-specific modulation and defining Estrogen-mediated interactions within the prostate tumour microenvironment.

Prolactin: Prolactin (PRL) contributes to prostate physiology through autocrine and paracrine signalling, as the gland functions both as a target tissue and a local source of this pleiotropic hormone. Prolactin receptors are widely expressed in prostatic epithelial and stromal compartments, where PRL signalling regulates ductal morphogenesis, epithelial differentiation, and maintenance of secretory architecture. In normal prostate tissue, PRL also influences metabolic function, particularly citrate production, through modulation of mitochondrial enzyme activity and protein kinase C–dependent pathways.

Beyond its physiological role, PRL acts as a survival and growth factor for prostatic epithelium, primarily through activation of the PRLR–JAK2–STAT5 (Prolactin receptor-Janus Kinase 2- Signal Transducer& Activator of Transcription 5) signalling axis, which promotes proliferation and suppresses apoptosis. Dysregulation of this pathway has been implicated in prostate cancer progression, including enhancement of androgen receptor signalling in castration-resistant disease, induction of epithelial–mesenchymal transition, and metabolic reprogramming. These oncogenic effects have prompted interest in targeting PRL signalling, with preclinical studies demonstrating that inhibition of PRLR or STAT5 can induce apoptotic responses in prostate cancer cells. However, challenges remain in achieving tissue-specific targeting and fully defining PRL's role within the tumour microenvironment. Collectively, current evidence supports the PRL/PRLR axis as a biologically relevant but complex contributor to prostate cancer progression.

Oxytocin: Oxytocin (OXT), a neurohypophysial nonapeptide structurally related to vasopressin, exhibits biologically relevant activity within the prostate gland through an established autocrine and paracrine signalling system. Both epithelial and stromal compartments express OXT and its cognate receptor (OXTR), with local hormone levels regulated in part by circulating sex steroids, including androgens and Estrogens. This regulatory framework suggests a physiological role for OXT in maintaining prostate tissue homeostasis.

Functionally, OXT has been shown to exert growth-inhibitory effects on prostatic epithelial and stromal cells, indicating a modulatory role in controlling glandular proliferation. In addition to its direct anti-proliferative actions, OXT influences local androgen metabolism by regulating 5α-reductase activity, thereby modulating dihydrotestosterone availability within prostate tissue. Through these combined mechanisms, OXT may contribute to the fine regulation of androgen-dependent growth.

Although interest has emerged regarding the potential involvement of OXT signalling in prostate pathology, including hormone-responsive disease states, current evidence remains largely experimental. Ongoing research aims to clarify the molecular pathways underlying OXT-mediated effects and to evaluate the therapeutic feasibility of targeting OXTR. Challenges related to tissue-specific modulation and defining OXT's role within the prostate tumour microenvironment remain key areas for future investigation.

Thyroid Hormone: Thyroid hormones have emerged as potential modulators of prostate cancer risk, with epidemiological studies reporting an inverse association between hypothyroidism and prostate cancer incidence. Mechanistic support for this observation is provided by experimental evidence demonstrating that triiodothyronine (T3) enhances prostate-specific antigen (PSA) expression at both transcriptional and protein levels

in androgen-responsive prostate cells. Importantly, this effect is dependent on intact androgen signalling, as T3-mediated PSA induction is minimal under androgen-deprived conditions, indicating functional crosstalk between thyroid hormone and androgen receptor pathways.

The molecular basis of this interaction remains incompletely defined. Proposed mechanisms include competitive or cooperative interactions between androgen receptor–response element complexes and thyroid hormone receptor–response element complexes, as well as indirect regulation through intermediary transcription factors. These interactions suggest that thyroid hormone signaling may influence androgen-driven transcriptional programs rather than acting independently.

Clinically, it remains unclear whether the reduced prostate cancer risk associated with hypothyroid states reflects direct hormonal effects or secondary metabolic alterations. Additionally, the potential impact of thyroid hormone status on PSA interpretation and responsiveness to androgen-deprivation therapy warrants further investigation. Elucidating thyroid–androgen signaling interactions may provide novel insights into endocrine regulation of prostate carcinogenesis and inform future preventive or therapeutic strategies, particularly in patients with concurrent thyroid dysfunction.

Growth Factor: The maintenance of prostate architecture and function depends on tightly coordinated signaling mediated by multiple growth factors that regulate communication between epithelial and stromal compartments. These signals are highly context dependent, and their balanced activity is essential for preserving normal glandular homeostasis. Among these regulators, insulin-like growth factors (IGFs) are produced by both epithelial and stromal cells in an androgen-responsive manner and act as strong drivers of cellular proliferation. Epidermal growth factor (EGF) also promotes prostate cell growth, and aberrant elevation of EGF and its related ligand transforming growth factor-alpha (TGF-α) has been repeatedly linked to malignant transformation through disruption of normal growth restraints. Counterbalancing these proliferative signals, members of the transforming growth factor-beta (TGF-β) family play a dominant inhibitory role in normal prostate development. Although TGF-β isoforms are expressed by both epithelial and stromal cells, their signaling activity is largely mediated through stromal receptors, underscoring the importance of paracrine regulation. Fibroblast growth factors (FGFs) similarly participate in epithelial–stromal signaling, whereas keratinocyte growth factor (KGF) represents a distinct stromal-derived factor that selectively acts on epithelial targets.

During prostate carcinogenesis, this regulatory equilibrium becomes progressively disrupted. Notably, TGF-β signaling may undergo a functional shift from growth suppression to facilitation of invasion and metastasis in advanced disease, driven by changes in receptor expression and downstream signaling. Elucidating the mechanisms governing growth factor imbalance and receptor crosstalk remains critical for identifying therapeutic strategies capable of limiting disease progression and overcoming treatment resistance.

Bone Morphogenetic Proteins: Bone morphogenetic proteins (BMPs) constitute a functionally diverse subgroup of the transforming growth factor-β superfamily and play a central role in regulating tissue architecture by coordinating cell growth, lineage commitment, and apoptosis. Although originally characterized for their role in bone formation, BMPs are now recognized as critical regulators of epithelial development. In the prostate, several BMP isoforms including BMP-2, BMP-3, BMP-4, BMP-6, and BMP-7 participate in developmental patterning by restricting excessive epithelial expansion and shaping glandular organization. Experimental evidence indicates that BMP-4 and BMP-7 act as negative modulators of ductal branching during prostate organogenesis, ensuring controlled morphogenesis and proper spatial arrangement of the ductal system.

BMP signaling operates through ligand-dependent activation of type I and type II serine/threonine kinase receptors, leading to downstream Smad-mediated transcriptional responses. These signaling events influence genes involved in extracellular matrix regulation, epithelial cohesion, and cellular positioning, thereby governing ductal elongation

and epithelial stability. Importantly, BMP activity appears to be integrated with androgen-dependent developmental cues, suggesting coordinated hormonal and growth factor control of prostate formation.

In disease states, BMP signaling demonstrates context-dependent behaviour. While intact BMP activity may limit early neoplastic transformation, alterations in receptor expression or downstream signaling components can repurpose this pathway to support invasion and metastatic progression in advanced prostate cancer. The determinants governing this functional switch remain incompletely understood but are likely influenced by inflammatory signaling and microenvironmental changes. Continued investigation into BMP pathway regulation may provide new opportunities for therapeutic intervention in prostate disorders.

Components of Prostatic Fluid:

Prostatic-specific Antigen: Prostate-specific antigen (PSA) is a prostate-derived serine protease with central importance in both reproductive physiology and clinical oncology. It is synthesized and secreted by luminal epithelial cells of the prostate, where its expression is tightly regulated under physiological conditions. In normal prostatic secretions, PSA is present at high concentrations, reflecting its role in maintaining seminal fluid dynamics and reproductive function.

PSA is initially produced as an inactive zymogen and undergoes post-secretory processing within seminal fluid. Only a limited proportion of the molecule acquires enzymatic activity, while a smaller fraction forms complexes with endogenous protease inhibitors. The majority of PSA remains enzymatically inactive, ensuring controlled proteolytic function and preventing excessive tissue degradation.

Upon entry into the circulation, PSA exists in distinct molecular forms that underpin its diagnostic utility. Most circulating PSA rapidly forms stable complexes with serine protease inhibitors, particularly α1-antitrypsin, whereas a smaller fraction remains unbound. The relative distribution of complexed and free PSA differs between benign and malignant prostatic conditions, providing clinically useful information beyond total PSA levels alone. Although PSA remains an indispensable biomarker in prostate cancer detection and monitoring, its biological behaviour reflects a nuanced regulatory system that extends beyond a simple disease indicator.

Prostatic Acid Phosphatise: Prostatic acid phosphatase (PAP) is a prostate-derived enzyme that historically played a pivotal role in the biochemical characterization of prostatic function and disease. It is a dimeric glycoprotein that exists in two principal forms: a cellular isoform localized within prostatic epithelial cells and a secretory isoform released into seminal fluid and the circulation. Although its clinical prominence has declined with the advent of prostate-specific antigen, PAP remains biologically and pathophysiological relevant.

Within the male reproductive tract, PAP contributes to seminal fluid biochemistry by catalysing the hydrolysis of phosphorylated substrates, including phosphorylcholine and phosphocreatine. Through this activity, PAP participates in regulating the availability of metabolic substrates that support sperm motility and post-ejaculatory function. This enzymatic role underscores its importance in maintaining an optimal biochemical environment for male fertility.

Clinically, circulating PAP levels are low in healthy individuals but increase during early stages of prostate malignancy, a feature that established PAP as one of the earliest prostate cancer biomarkers. However, in advanced and metastatic disease, serum PAP concentrations may decline, reflecting alterations in tumour differentiation and secretory capacity. This non-linear relationship between PAP levels and disease stage, together with the superior sensitivity of PSA-based testing, has limited its routine diagnostic use. Nevertheless, PAP continues to provide insight into prostate tumour biology and remains of interest in understanding disease progression and cellular differentiation.

Zinc: The prostate is distinguished by its exceptional capacity to accumulate zinc, a feature that is central to its metabolic specialisation and reproductive function. Under physiological conditions, prostatic epithelial cells actively

regulate zinc uptake and secretion, maintaining elevated concentrations within prostatic fluid that are optimal for sperm stability, motility, and post-ejaculatory function. This tightly controlled zinc homeostasis reflects a unique metabolic adaptation of the gland.

During malignant transformation, this regulatory capacity is markedly disrupted. Prostate cancer cells exhibit a profound reduction in intracellular zinc accumulation, accompanied by a parallel decline in citrate production. This metabolic shift represents a defining biochemical hallmark of prostate cancer and reflects altered mitochondrial function and energy metabolism. Loss of zinc removes a critical inhibitory influence on cellular respiration, thereby facilitating increased energy production and supporting uncontrolled cellular proliferation.

Beyond its metabolic role, zinc is increasingly recognised as a multifunctional modulator of cellular processes, including regulation of gene expression, signal transduction, and immune responses. Its depletion in prostate cancer has been associated with enhanced tumour growth and progression, supporting the concept of zinc as an intrinsic suppressive factor within normal prostate tissue. Continued investigation into zinc-regulated pathways may provide valuable insights into prostate cancer biology and identify novel avenues for prevention and therapeutic intervention.

Spermine and Spermidine: The prostate is a major site of polyamine biosynthesis, producing high concentrations of the polycations spermine and spermidine that contribute to the unique biochemical composition of prostatic fluid. These small, nitrogen-rich molecules accumulate at millimolar levels and support male reproductive function by stabilising nucleic acids, modulating phospholipid membrane dynamics, and interacting with negatively charged cellular constituents. Through these properties, polyamines play a critical role in preserving sperm structure, viability, and functional competence during transit within the reproductive tract. Polyamine metabolism within the prostate is highly regulated and includes enzymatic interconversion and degradation pathways. Oxidative breakdown of spermine, mediated by enzymes such as diamine oxidase, generates bioactive by products that contribute to local signalling and microenvironmental regulation. These reactions illustrate the dual structural and signalling roles of polyamines in prostate physiology.

Increasing evidence links altered polyamine homeostasis to prostate pathology. Changes in spermine-to-spermidine ratios have been associated with shifts in epithelial proliferative activity, and dysregulation of polyamine metabolic pathways has been observed during prostate cancer progression. In addition, oxidative metabolites generated during polyamine catabolism may influence redox balance and cellular behaviour within the tumour microenvironment. Collectively, these findings position polyamines as important metabolic regulators in prostate biology, with emerging relevance to disease development and progression.

Prostatic Inhibin: Prostatic inhibin, also referred to as β-microseminoprotein, is a low–molecular–weight protein abundantly expressed in normal prostate tissue and increasingly recognised for its tumour-suppressive potential. This 94–amino acid protein is markedly reduced in prostate cancer, a pattern observed consistently across tissue, serum, and seminal fluid, suggesting a physiologically relevant protective role in maintaining epithelial homeostasis.

Experimental evidence indicates that prostatic inhibin negatively regulates prostate cancer cell proliferation, although the precise molecular mechanisms remain incompletely defined. Notably, its expression is inversely associated with enhancer of zeste homolog 2 (EZH2), a key epigenetic regulator implicated in aggressive tumour behaviour. Epigenetic silencing of the prostatic inhibin gene through promoter methylation has been proposed as a mechanism underlying its loss during malignant transformation, thereby disabling an intrinsic growth-restraining pathway.

Despite the widespread clinical use of prostate-specific antigen, prostatic inhibin offers distinct advantages as a biomarker candidate. Its consistent depletion across multiple biological compartments, coupled with its epigenetic regulation, highlights potential utility in early disease detection and risk

stratification. Furthermore, elucidation of its tumour-suppressive function may provide a foundation for developing novel therapeutic strategies aimed at restoring endogenous anticancer mechanisms within the prostate.

Pre-Cancer Condition of the Prostate:

Prostatic Intraepithelial Neoplasia (PIN): Prostatic intraepithelial neoplasia (PIN) represents a well-recognised precursor lesion in prostate carcinogenesis, characterised by cytological atypia of epithelial cells while preserving the underlying basement membrane. This pre-invasive state reflects early molecular reprogramming that predisposes prostatic epithelium to malignant transformation without overt stromal invasion. Dysregulated androgen receptor signalling, loss of tumour suppressive control, epigenetic alterations, inflammatory stress, and impaired cell–cell adhesion collectively create a permissive microenvironment that supports neoplastic evolution.

Progression from low-grade to high-grade PIN is marked by increasing architectural disruption, nuclear atypia, nucleolar prominence, and attenuation of the basal cell layer. At the molecular level, high-grade PIN exhibits genomic and transcriptional alterations that closely resemble early-stage prostate cancer, including activation of oncogenic drivers, suppression of differentiation-associated genes, metabolic disturbances, and heightened inflammatory signalling. These similarities underscore the biological continuity between high-grade PIN and invasive carcinoma.

The transition from PIN to invasive disease requires additional pathway reprogramming, including acquisition of mesenchymal traits, induction of angiogenesis, metabolic adaptation, disruption of microRNA-mediated regulation, stabilisation of telomere maintenance mechanisms, and remodelling of the stromal microenvironment. These changes enable epithelial cells to breach tissue constraints and establish invasive growth patterns, positioning PIN as a critical intervention window for cancer prevention.

Advances in molecular profiling technologies have revealed substantial heterogeneity within PIN lesions, refining risk stratification beyond histopathology alone. Concurrently, investigational strategies targeting hormonal, metabolic, inflammatory, epigenetic, and immune pathways are being explored for chemoprevention in high-risk individuals. Effective clinical management of PIN, therefore, requires a balanced approach that integrates molecular risk assessment, patient-centred decision-making, and careful avoidance of overtreatment. Collectively, PIN serves not merely as a diagnostic entity but as a dynamic biological state offering valuable insight into the earliest stages of prostate cancer development.

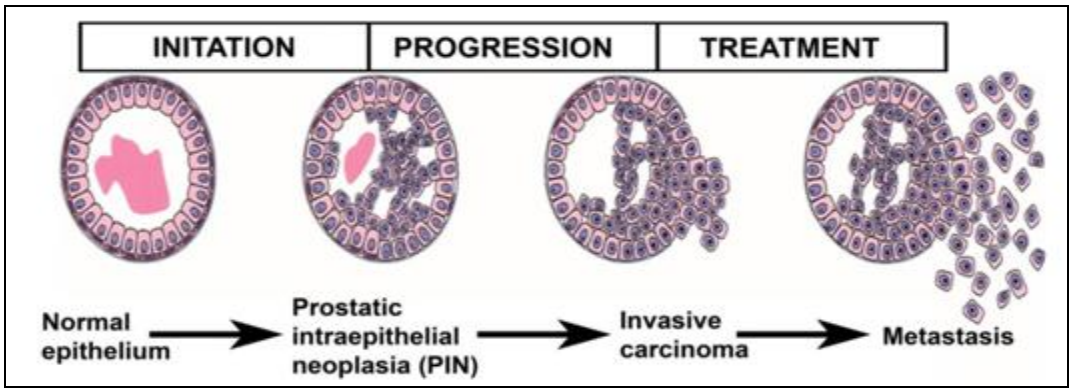

FIG. 2: PROSTATIC INTRAEPITHELIAL NEOPLASIA

Proliferative Inflammatory Atrophy (PIA): Proliferative inflammatory atrophy (PIA) reflects a chronic adaptive response of the prostate epithelium to sustained tissue injury and inflammation. Histologically, PIA is characterised by focal glandular atrophy accompanied by inflammatory infiltrates, predominantly lymphocytes, and regions of increased epithelial proliferation. This coexistence of epithelial loss and compensatory hyperproliferation creates a biologically unstable state that predisposes affected tissue to neoplastic transformation.

The development of PIA is closely linked to persistent inflammatory stimuli, including infection, chemical irritation, and urinary reflux, which collectively generate oxidative stress and DNA damage. Disruption of hormonal signalling further alters epithelial homeostasis, while constitutive activation of inflammatory pathways particularly nuclear factor kappa B (NF-κB) sustains the production of pro-inflammatory mediators. These processes establish a microenvironment that promotes genomic instability and explains the frequent spatial association of PIA with other premalignant lesions.

Progression from PIA toward malignancy is facilitated by cumulative molecular alterations arising from repeated cycles of epithelial injury and regeneration. Chronic inflammation drives angiogenic and tissue-remodelling programs, while progressive DNA damage, telomere shortening, and epigenetic silencing of protective genes such as glutathione S-transferase pi 1 (GSTP1) erode cellular safeguards. As a result, the molecular profile of PIA increasingly resembles that of early prostate cancer.

Clinically, PIA presents diagnostic challenges due to its subtle histological features, absence of specific biomarkers, and variable progression risk among patients. Ongoing research is exploring preventive strategies aimed at interrupting inflammatory signalling, eliminating senescent or damaged cells, and mitigating oxidative stress. Recognising PIA as both a reparative response and a potential precursor to malignancy is essential for refining risk assessment and guiding early intervention strategies in prostate cancer prevention.

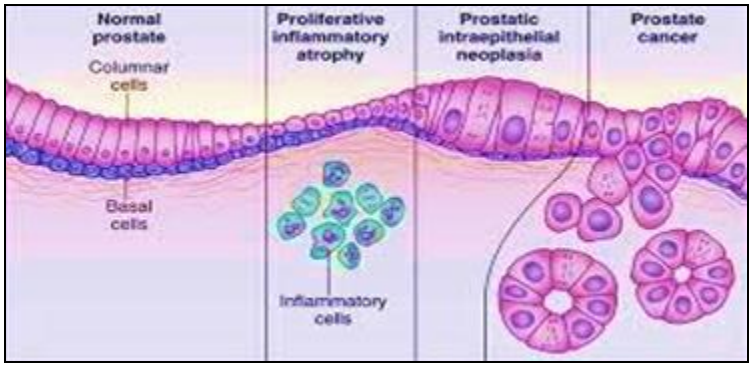

FIG. 3: PROLIFERATIVE INFLAMMATORY ATROPHY

Mutations that Cause Cancer or Inhibition Include: Prostate cancer arises through the coordinated disruption of hormonal control, metabolic regulation, and tissue homeostasis. A central driver of this process is dihydrotestosterone (DHT), a biologically active androgen that sustains prostate epithelial growth through prolonged activation of androgen receptor–dependent transcription. In normal physiology, this signalling is tightly regulated; however, malignant transformation is marked by persistent androgenic stimulation that promotes uncontrolled proliferation and survival.

The enzymatic conversion of testosterone to DHT by 5α-reductase represents a critical amplification step in androgen signalling. Therapeutic inhibition of this enzyme reduces intraprostatic androgenic drive and has been shown to modify disease risk and progression in selected clinical contexts. Alongside hormonal regulation, prostate-specific antigen (PSA) contributes to local tissue dynamics through its proteolytic function, influencing extracellular matrix turnover and cellular interactions within the prostate microenvironment. While primarily used as a diagnostic indicator, PSA activity may indirectly support conditions favourable to tumour expansion.

Metabolic reprogramming is another defining feature of prostate carcinogenesis. Healthy prostate epithelial cells uniquely accumulate high levels of intracellular zinc, which constrains mitochondrial respiration and limits cellular proliferation. Early loss of zinc retention removes this metabolic restraint, enabling increased energy production and tumour growth. Prostatic acid phosphatase (PAP), though largely replaced as a diagnostic marker, has gained renewed attention for its potential regulatory roles in tumour biology and immune interactions.

Additionally, transforming growth factor-beta (TGF-β) exhibits functional plasticity, acting as a suppressor of epithelial proliferation in normal tissue but frequently facilitating invasion and metastatic progression in advanced disease through altered stromal and immune signalling.

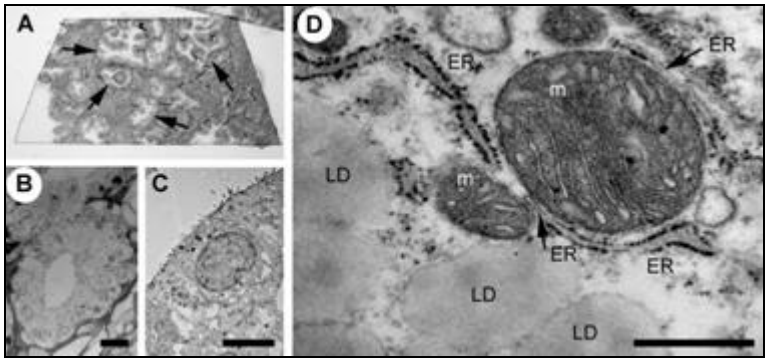

FIG. 4: ULTRASTRUCTURAL ANALYSIS OF PROSTATE CANCER TISSUE PROVIDES INSIGHTS INTO ANDROGEN-DEPENDENT ADAPTATIONS TO MEMBRANE CONTACT SITE ESTABLISHMENT

Pathophysiology of Prostate Cancer:

Initial Point: Prostate cancer most commonly arises within the peripheral zone of the gland, which accounts for approximately 70–80% of diagnosed cases. This regional predominance is attributed to distinct glandular architecture, hormonal responsiveness, and microenvironmental characteristics that favour neoplastic transformation. The earliest recognisable pathological alteration is prostatic intraepithelial neoplasia (PIN), a pre-invasive lesion characterised by cytological atypia of epithelial cells confined to the prostatic ducts and acini.

High-grade PIN is of particular clinical relevance, as it reflects advanced epithelial dysplasia with molecular features that overlap with early invasive carcinoma. Longitudinal studies have demonstrated that individuals with high-grade PIN carry a substantially increased risk of subsequent prostate cancer development over time, underscoring its role as a critical precursor lesion. Although the basement membrane remains intact at this stage, the presence of high-grade PIN signals underlying biological instability warrants close clinical surveillance. These early pathological events establish the foundation for disease progression and provide a window for early detection and preventive intervention.

Growth & Spread: Prostate cancer progression is characterised by a stepwise biological evolution that originates from molecular alterations within otherwise normal prostatic epithelial cells. These early genetic and epigenetic changes give rise to prostatic intraepithelial neoplasia, which may subsequently evolve into localised carcinoma confined to the gland. Disease progression reaches a clinically significant threshold when malignant cells breach epithelial boundaries and infiltrate the surrounding stromal tissue, with further extension into adjacent structures such as the seminal vesicles. This transition reflects a shift toward a more aggressive phenotype and is associated with increased metastatic potential. Advances in imaging modalities, particularly multiparametric magnetic resonance imaging, have improved the detection of local invasion and extraprostatic extension, enabling more accurate assessment of disease stage and progression risk.

Role of Zinc: The prostate exhibits a distinctive metabolic dependence on zinc that differentiates it from most other tissues. Under physiological conditions, prostatic epithelial cells accumulate exceptionally high intracellular zinc concentrations, a requirement for sustaining citrate synthesis and secretion into seminal fluid. This zinc-mediated metabolic state restricts mitochondrial oxidation and limits excessive cellular proliferation.

During malignant transformation, this specialised metabolic program is disrupted. Prostate cancer cells progressively lose the capacity to retain zinc, largely through downregulation of zinc influx transporters such as ZIP1. The resulting zinc depletion permits restoration of mitochondrial citrate oxidation, enabling enhanced energy production and supporting rapid cellular growth. This metabolic shift represents a critical adaptation

that facilitates tumour progression. Clinically, zinc-deficient prostate tumours are frequently associated with increased aggressiveness and unfavourable biological behaviour. The loss of zinc-dependent metabolic restraint underscores the importance of trace element homeostasis in prostate cancer pathophysiology and highlights zinc dysregulation as a defining feature of malignant metabolic reprogramming.

Androgen Receptor: The androgen receptor (AR) signalling axis remains the dominant driver of prostate cancer growth and a central determinant of therapeutic resistance. Sustained AR activation enables tumour cells to maintain proliferation and survival despite systemic androgen suppression, underscoring its role across multiple stages of disease progression. Consequently, modern treatment strategies increasingly focus on potent AR pathway inhibition through next-generation antiandrogens designed to block ligand binding, nuclear translocation, and transcriptional activity.

Despite initial efficacy, resistance to AR-targeted therapies commonly develops through adaptive molecular alterations. These include AR gene amplification, point mutations that expand ligand specificity, and the emergence of constitutively active splice variants lacking the ligand-binding domain. Additional mechanisms involve intratumoral androgen biosynthesis, increased recruitment of AR co-activators, and activation of alternative signalling pathways that bypass direct AR inhibition. Collectively, these adaptations sustain AR-driven transcriptional programs under therapeutic pressure, highlighting the need for improved strategies to overcome resistance and achieve durable disease control in advanced prostate cancer.

Prostatic-specific Membrane Antigen (PSMA): Prostate-specific membrane antigen (PSMA) has emerged as a key molecular target in contemporary prostate cancer diagnosis and treatment. This transmembrane glycoprotein is highly overexpressed in prostate cancer cells, particularly in advanced and metastatic disease, and is involved in folate metabolism that supports tumour growth and survival. Its consistent and elevated expression has enabled the development of highly sensitive molecular imaging modalities, most notably PSMA-based positron emission tomography, which allows precise localisation of primary tumours and metastatic lesions. Beyond diagnostics, PSMA also serves as an effective therapeutic target, facilitating the selective delivery of radionuclide therapies directly to malignant cells. This theranostic capability has significantly advanced precision medicine approaches in prostate cancer management.

Seminal Vessels: The seminal vesicles are paired accessory glands situated adjacent to the prostate and share close anatomical, vascular, and lymphatic connections with it. This proximity renders them particularly susceptible to direct tumour extension during prostate cancer progression. Involvement of the seminal vesicles reflects extra-prostatic spread and signifies a transition to locally advanced disease. Identification of seminal vesicle invasion through contemporary imaging modalities constitutes a critical staging determinant, as it is associated with a poorer prognosis and often necessitates modification of therapeutic strategies, including escalation of local or systemic treatment approaches.

Molecular Mechanism of Prostate Cancer:

Hormone-Dependent (Androgen-Dependent) Prostate Cancer: Prostate cancer is initially characterised by a marked dependence on male sex hormones for tumour initiation and growth. During these hormone-sensitive stages, malignant prostate cells require androgens primarily testosterone and its more potent derivative dihydrotestosterone (DHT) to sustain proliferation and survival. Circulating testosterone is produced predominantly by the testes and is converted intracellularly to DHT within prostate tissue through the enzymatic action of 5α-reductase, thereby amplifying androgenic signalling.

At the molecular level, DHT exerts its effects through high-affinity binding to the androgen receptor (AR), a ligand-activated transcription factor. Ligand engagement induces conformational changes in the AR, followed by receptor phosphorylation, dimerisation, and translocation to the nucleus. The activated AR complex binds to androgen response elements within target gene promoters, initiating transcriptional programs that promote cell cycle progression, suppress apoptotic

pathways, and support metabolic adaptations conducive to tumour growth.

Therapeutically, androgen deprivation therapy (ADT) remains the foundation of treatment for advanced prostate cancer. ADT reduces androgenic stimulation by suppressing testicular testosterone production, inhibiting peripheral androgen conversion, or directly antagonising AR signalling. Although these interventions are initially effective, most tumours eventually progress to a castration-resistant state. This transition is driven by adaptive mechanisms such as AR overexpression, emergence of constitutively active AR splice variants, intratumoral androgen synthesis, and activation of alternative growth and survival pathways. Ongoing research is therefore focused on developing next-generation AR pathway inhibitors and combination strategies aimed at overcoming resistance and achieving sustained disease control.

Hormone-Resistant (Androgen-Independent or CRPC) Prostate Cancer: Castration-resistant prostate cancer (CRPC) develops when tumour growth persists despite effective suppression of systemic androgen levels. A defining feature of this stage is continued androgen receptor (AR) activity maintained through adaptive molecular changes. Many tumours increase AR expression via gene copy number gains, enabling signalling under minimal ligand availability. Structural alterations within the AR, particularly mutations affecting the ligand-binding region, further expand receptor responsiveness to non-canonical steroids and therapeutic agents, thereby compromising treatment efficacy.

An important mechanism driving androgen independence is the emergence of truncated AR splice variants, most notably AR-V7 (Androgen Receptor splice variant 7). These isoforms lack the ligand-binding domain yet remain transcriptionally active, allowing continuous activation of AR-regulated genes without hormonal input. Their presence is strongly linked to resistance to AR-targeted therapies and unfavourable clinical outcomes.

When direct AR signalling is constrained, prostate cancer cells often rely on compensatory pathways to sustain survival and proliferation. Activation of PI3K/AKT/mTOR and MAPK (Mitogen-Activated Protein Kinase) signalling supports metabolic flexibility and growth, while inflammatory and developmental pathways, including JAK/STAT and Wnt/β-catenin, promote cellular plasticity. In a proportion of advanced cases, tumours undergo lineage reprogramming to a neuroendocrine phenotype characterised by AR independence, distinct epigenetic profiles, and aggressive metastatic behaviour. Ongoing research aims to define predictive biomarkers, clarify microenvironmental drivers, and develop effective therapeutic strategies for this highly treatment-resistant disease state.

TABLE 1: KEY GENETIC ALTERATIONS AND CORE SIGNALLING PATHWAYS IN PROSTATE CANCER

Gene / Pathway	Alteration or Dysregulation Type	Normal Biological Role	Pathological Role in Prostate Cancer	Therapeutic Relevance
TP53	Missense mutations, deletions	Cell-cycle arrest, DNA repair, apoptosis	Loss permits survival of genomically unstable cells	Prognostic marker; therapy resistance
BRCA1 / BRCA2	Frameshift, truncating mutations	Homologous recombination DNA repair	Genomic instability and aggressive tumour behaviour	PARP inhibitor sensitivity
ATM	Missense or loss-of-function	DNA damage sensing and checkpoint control	Defective repair and radio-/chemo-resistance	Predictive biomarker
PTEN / PI3K–AKT–mTOR	PTEN loss, pathway hyperactivation	Controls survival and metabolism	Uncontrolled growth and apoptosis resistance	PI3K/mTOR inhibitors (trials)
TMPRSS2–ERG	Androgen-driven gene fusion	AR-regulated transcription	Aberrant oncogenic transcriptional programs	Molecular subclassification
MYC	Gene amplification	Growth, metabolism, ribosome biogenesis	High proliferation and poor prognosis	Prognostic indicator
FOXA1	Missense mutations	AR chromatin binding	Alters AR	AR-pathway

		and lineage identity	transcriptional specificity	modulation
Androgen Receptor (AR)	Amplification, mutations, splice variants	Hormone-regulated growth	Sustained tumour growth and CRPC	ADT, enzalutamide, abiraterone
DNA Repair Pathway	Multigene defects	Maintains genomic integrity	Mutation accumulation and progression	PARP inhibitors
Wnt/β-catenin	Pathway activation	Stem-cell fate regulation	Invasion, metastasis, plasticity	Investigational
MAPK/ERK	Constitutive activation	Cell-cycle progression	Aggressive phenotype and resistance	Mult-kinase inhibitors
TGF-β / SMAD	Context-dependent switch	Growth suppression, immune balance	EMT, immune evasion in advanced disease	Experimental inhibitors
JAK/STAT (IL-6 axis)	Chronic activation	Inflammatory signalling	Survival signalling and resistance	STAT3 inhibitors (research)
Hippo–YAP/TAZ	Loss of growth restraint	Organ size control	Enhanced survival and therapy resistance	No approved therapy

TABLE 2: TUMOUR MICROENVIRONMENT MOLECULES AND THEIR FUNCTIONAL IMPACT IN PROSTATE CANCER

Molecule / Factor	Primary Cellular Source	Physiological Function	Contribution to Tumour Progression
PSA	Prostate epithelial cells	Semen liquefaction	Clinical biomarker reflecting tumour burden
VEGF	Stromal & endothelial cells	Angiogenesis	Promotes tumour vascularisation and growth
IL-6	Immune cells, tumour cells	Inflammatory signalling	Activates STAT3-mediated survival pathways
MMP-9	Fibroblasts, immune cells	Extracellular matrix remodelling	Facilitates invasion and metastasis
TGF-β	Tumour and stromal cells	Immune modulation	Drives EMT and immune escape in late-stage disease
CXCL12 (SDF-1)	Cancer-associated fibroblasts	Chemotactic signalling	Directs tumour cells toward bone niches
PD-L1	Tumour & immune cells	Immune checkpoint regulation	Suppresses cytotoxic T-cell responses
FGF-2	Stromal fibroblasts	Tissue repair, angiogenesis	Enhances tumour proliferation and remodelling
Zinc (↓)	Prostatic epithelial cells	Regulates citrate metabolism	Loss enables metabolic reprogramming
Citrate (↓)	Prostate epithelium	Seminal fluid energy source	Shift supports tumour bioenergetics

Other Symptoms Related To Prostate Cancer:

Benign Prostatic Hyperplasia (BPH): Benign prostatic hyperplasia (BPH) is an age-associated proliferative condition of the prostate characterised by non-malignant expansion of glandular and stromal elements. As the prostate enlarges, mechanical compression of the prostatic urethra may occur, leading to progressive lower urinary tract symptoms. Epidemiological data demonstrate a steady increase in symptom prevalence with advancing age, making BPH one of the most common urological conditions affecting older men. Despite its benign nature, the functional consequences of BPH can significantly impair daily activities and overall well-being.

Clinical assessment prioritises symptom burden rather than gland size alone. Standardised scoring systems, including the American Urological Association Symptom Index, allow structured quantification of urinary dysfunction and support evidence-based decision-making. A comprehensive clinical evaluation is essential to identify factors that may exacerbate symptoms, such as exposure to adrenergic medications, prior inflammatory prostate conditions, or recurrent urinary infections. Inflammatory disorders of the prostate may present with systemic manifestations and pelvic discomfort, necessitating differentiation from uncomplicated hyperplasia. Baseline diagnostic evaluation routinely includes urinalysis to exclude

infection, haematuria, or alternative urinary tract pathology. In patients with stable, mild symptoms and unremarkable clinical findings, additional laboratory investigations are often unnecessary at initial presentation. Pain involving the bladder, penile region, or pelvis should prompt consideration of non-BPH etiologies, including calculi, infectious processes, or neuropathic causes. Importantly, serum prostate-specific antigen levels lack discriminatory value between benign enlargement and malignancy, as elevations may occur in both conditions. The natural history of BPH is heterogeneous, with some individuals experiencing symptom progression, others remaining stable, and a subset demonstrating spontaneous improvement. Therapeutic intervention should therefore be individualised and guided primarily by symptom impact and patient preference. Decisions regarding treatment initiation must balance anticipated benefit against potential adverse effects, emphasising quality-of-life outcomes as the central determinant of care.

Prostatitis: Prostatitisrefers to a group of inflammatory conditions affecting the prostate gland and surrounding pelvic tissues and represents one of the most common urological disorders in men. It is particularly prevalent in younger males, where it accounts for a substantial proportion of urinary and pelvic complaints, and remains clinically relevant in older populations. Despite its frequency, prostatitis encompasses diverse disease mechanisms rather than a single pathological entity. The most prevalent subtype, chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS), occurs without detectable bacterial infection and is considered multifactorial in origin.

Proposed contributors include immune-mediated inflammation, pelvic floor neuromuscular dysfunction, prior urinary tract inflammation, chemical irritation from urinary reflux, and altered pain signalling. Persistent pelvic or perineal discomfort lasting longer than three months, often accompanied by urinary symptoms or ejaculatory pain, is a defining feature. Bacterial prostatitis represents an infectious form of the condition and may present acutely or chronically. Acute bacterial prostatitis is characterised by a rapid onset and systemic illness, whereas chronic bacterial prostatitis develops gradually and may persist despite therapy. Accurate diagnosis is essential due to symptom overlap with other pelvic disorders. Identified risk factors include advancing age, genetic susceptibility, obesity, smoking, sexually transmitted infections, prior prostatic inflammation, and environmental toxin exposure.

Emerging Role of Natural Compounds: Interest in natural compounds for prostate cancer management has expanded as molecular oncology has begun to clarify their biological effects beyond traditional empirical use. A growing body of evidence indicates that selected bioactive molecules can modulate pathways central to prostate carcinogenesis and treatment resistance. Compounds such as lycopene, sulforaphane, and γ-tocotrienol have been shown to influence androgen signalling, epigenetic regulation, and cancer stem cell maintenance, suggesting potential utility as adjunctive interventions rather than standalone therapies. Clinical and translational studies evaluating agents such as green tea catechins and pomegranate-derived polyphenols further support a role in slowing disease progression in defined patient populations, although findings remain context dependent. Current research efforts are primarily directed toward improving pharmacological limitations that have historically restricted clinical translation. Poor oral bioavailability and variability in botanical composition represent major barriers, prompting investigation into formulation strategies such as nanoencapsulation and synthetic analogue development. Equally important are efforts to standardise extracts, identify predictive biomarkers of response, and assess interactions with established therapies, particularly androgen-targeted agents. Marine-derived compounds, including sulphated polysaccharides, have attracted attention due to their combined immunomodulatory and anti-tumour properties. Future progress will depend on rigorous mechanistic validation and carefully designed clinical trials that position natural compounds as rational adjuvants within evidence-based treatment frameworks, particularly in early or treatment-sensitive disease settings.

Various Types of Treatment:

Modern Treatment Techniques: Contemporary management of prostate cancer encompasses a broad spectrum of therapeutic strategies that are

selected based on disease stage, risk category, molecular profile, patient age, comorbidities, and treatment intent. Hormone-based therapies form the backbone of treatment for advanced disease and include androgen-deprivation therapy achieved through gonadotropin-releasing hormone agonists or antagonists, androgen receptor antagonists, and inhibitors of androgen biosynthesis. These approaches aim to suppress androgen-driven tumour growth and are often combined with other modalities.

Chemotherapy is primarily used in metastatic and castration-resistant prostate cancer, with taxane-based regimens remaining the standard. Biologic and targeted therapies, including immunotherapeutic approaches, immune checkpoint inhibitors, PARP (PolyADP-Ribose Polymerase) inhibitors for DNA repair–deficient tumours, and radioligand therapies targeting prostate-specific membrane antigen, have expanded treatment options for molecularly defined patient subgroups.

Radiation therapy plays a central role in localised and locally advanced disease. External beam radiation techniques are complemented by brachytherapy, which may be delivered as low-dose-rate permanent seed implantation or high-dose-rate temporary catheter-based treatment. Advanced radiation modalities, such as stereotactic body radiation therapy and proton beam therapy, enable precise tumour targeting while minimising damage to surrounding tissues. Surgical intervention, most commonly radical prostatectomy, may be performed through open, laparoscopic, or robot-assisted approaches. Perineal prostatectomy remains an option in selected patients. In addition, focal and ablative therapies, including cryotherapy and high-intensity focused ultrasound, are utilised in carefully selected cases, particularly for localised or recurrent disease. Overall, modern prostate cancer treatment emphasises multimodal, individualised care aimed at optimising oncologic outcomes while reducing treatment-related morbidity and preserving quality of life.

Nutrition & Dietary Supplements: Nutritional patterns have been increasingly explored for their supportive role in prostate health, particularly through mechanisms related to oxidative balance and cellular stress regulation. Diets emphasising foods naturally rich in antioxidant compounds may help counteract reactive oxygen species that contribute to cellular damage within prostatic tissue. Fruits such as berries, watermelon, and tomatoes are notable in this context due to their high content of bioactive molecules involved in redox regulation.

Vegetable-derived phytochemicals also play an important role in modulating biological processes relevant to prostate disease. Regular consumption of vegetables, including squash, bell peppers, broccoli, cauliflower, cabbage, and Brussels sprouts, provides compounds that influence detoxification pathways, inflammatory signalling, and cellular homeostasis. These effects are considered supportive rather than therapeutic and are best viewed within a broader dietary framework.

Among specific dietary constituents, lycopene a carotenoid concentrated in tomatoes and watermelon has received attention for its potential interaction with growth factor signalling and oxidative pathways. In addition, certain vitamin E isoforms, particularly gamma-tocotrienol, have demonstrated biological activity in experimental models, including effects on proliferative and stem-like cell populations. However, current evidence remains largely preclinical, and supplementation should be approached cautiously.

Herbs: Several plant-derived agents have been explored as supportive interventions in prostate-related disorders, primarily for their antioxidant, anti-inflammatory, and hormone-modulating properties. Green tea (*Camellia sinensis*) has received considerable attention due to its catechin content, which has been shown in experimental and limited clinical settings to influence oxidative stress and cell-cycle regulation. Saw palmetto (*Serenoa repens*) is commonly used in prostate health formulations for its potential effects on androgen metabolism and lower urinary tract symptoms, although clinical outcomes remain variable. Botanicals such as milk thistle (*Silybum marianum*) and pomegranate (*Punica granatum*) are investigated mainly for cytoprotective and antioxidant activity, while garlic (*Allium sativum*)

has been associated with immunomodulatory and metabolic effects. Curcumin (*Curcuma longa*) has demonstrated broad anti-inflammatory and epigenetic activity in preclinical prostate cancer models, though its clinical utility is limited by bioavailability and formulation variability.

In addition to herbal agents, non-pharmacological complementary therapies are frequently used to address symptom burden and quality-of-life concerns. Acupuncture has been reported to reduce pelvic pain and urinary discomfort in selected patients. Massage and physical therapy, particularly pelvic floor–focused interventions, may alleviate musculoskeletal and neuromuscular contributors to chronic pelvic symptoms. Mind–body practices, including meditation and stress-reduction techniques, are increasingly recognised for their role in modulating neuroendocrine stress responses and improving overall well-being. Collectively, these approaches should be regarded as supportive measures, not substitutes for evidence-based medical treatment, and their use requires careful consideration of safety, standardisation, and clinical context.

Recent Research across the World: International collaboration has accelerated advances in prostate cancer management through coordinated late-phase clinical trials and translational research. Major oncology networks in North America and Europe, including the National Cancer Institute and the European Organisation for Research and Treatment of Cancer, have supported pivotal phase III studies evaluating agents such as enzalutamide, abiraterone, and cabazitaxel. These trials established survival benefits in metastatic castration-resistant prostate cancer and led to regulatory approvals, integrating next-generation androgen-receptor–targeted therapies into standard care. In parallel, targeted approaches continue to evolve, including PSMA (Prostate-Specific Membrane Antigen)-directed diagnostics and therapeutics, with ongoing phase II evaluations of antibody–drug conjugates and radioligand strategies. Asia-Pacific and Indian contributions have expanded notably, with institutions such as the Tata Memorial Centre and initiatives supported by the Indian Council of Medical Research advancing clinical trials, PSMA-based imaging, and optimised sequencing of systemic therapies. Collectively, these global efforts underscore a shift toward precision oncology and collaborative trial design to improve outcomes across diverse populations.

Survey in India: Indian observational research has provided insights into contextual factors associated with the early emergence of prostate-related pathological changes. Certain surveys have focused on socially and occupationally mobile groups, including individuals with frequent travel patterns, where delayed medical consultation, irregular health monitoring, and lifestyle instability may contribute to disease initiation. These early alterations are not malignant at presentation but may progress toward prostate cancer under sustained exposure to risk factors. Clinical investigations conducted within Indian healthcare settings have also highlighted methodological challenges, including heterogeneity in patient selection, follow-up duration, and outcome assessment, which can influence the interpretation of trial results. Nonetheless, such studies remain critical for generating population-relevant evidence. Two independent investigations carried out in Delhi identified lifestyle-related exposures as notable contributors to prostate cancer risk. Specifically, consistent associations were observed with tobacco use and alcohol intake, suggesting that behavioural factors may play a meaningful role in disease development within this population. These findings reinforce the importance of region-specific surveillance and preventive strategies tailored to local risk profiles, while emphasising the need for improved study design and long-term follow-up in future Indian prostate cancer research.

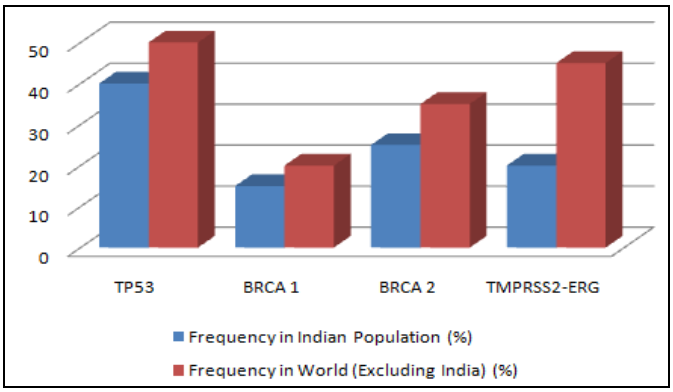

FIG. 5: CHART PLOTTED BETWEEN GENE MUTATION & AVERAGE POPULATION DISEASED BY SPECIFIC GENE IN INDIA AND AROUND THE WORLD

Most Frequent Prostate Cancer: Among the recurrent molecular abnormalities identified in prostate cancer, alterations involving the ERG (ETS [Erythroblast Transformation-specific] related gene) represent one of the most prevalent events. ERG is a proto-oncogene that encodes a transcription-regulating protein normally involved in cellular differentiation and nuclear signalling. In prostate cancer, aberrant ERG expression arises primarily from chromosomal rearrangements rather than point mutations, leading to inappropriate activation of oncogenic transcriptional programs.

The most extensively characterised rearrangement involves fusion of ERG with androgen-regulated promoter regions, resulting in androgen-driven overexpression of ERG in prostate epithelial cells. In addition to this dominant alteration, rearrangements involving SLC45A3 (Solute Carrier Family 45 Member 3), another androgen-responsive gene, have been identified as a frequent alternative mechanism contributing to dysregulated gene expression in prostate tumours. These fusion events highlight the central role of androgen signalling in shaping the prostate cancer genome. Collectively, ERG-associated rearrangements define a major molecular subtype of prostate cancer and are closely linked to disease initiation, progression, and biological heterogeneity. Understanding these genetic alterations has enhanced molecular classification of prostate cancer and continues to inform biomarker development and therapeutic research.

Properties of Phytochemicals: Phytochemicals have attracted increasing interest in prostate cancer research due to their ability to influence multiple cellular processes simultaneously. Curcumin, the principal active constituent of turmeric, demonstrates broad biological activity by targeting inflammatory, epigenetic, and oncogenic signalling networks. Experimental studies show that curcumin attenuates pro-inflammatory transcriptional activity and suppresses enzymes involved in chronic inflammatory signalling, processes commonly dysregulated in prostate tumours. In parallel, curcumin interferes with epigenetic regulators responsible for aberrant gene silencing, thereby restoring expression of growth-regulatory genes. Its ability to downregulate SPINK1 (Serine Peptidase Inhibitor, Kazal Type 1), a marker linked with aggressive prostate cancer phenotypes, further highlights its relevance. Although native curcumin exhibits limited systemic availability, advanced delivery systems such as nano-formulations have substantially improved intracellular accumulation and therapeutic persistence, supporting ongoing clinical evaluation in advanced disease settings.

Quercetin, a flavonoid abundant in onions, exhibits antiproliferative and pro-apoptotic activity through modulation of cell-cycle checkpoints and apoptosis-related pathways. By activating tumour-suppressive signalling and reducing anti-apoptotic protein expression, quercetin limits cancer cell survival. Additionally, sulphur-containing compounds associated with Allium species enhance cellular detoxification capacity through activation of antioxidant response elements and disrupt androgen receptor signalling by impairing receptor trafficking. These combined effects suggest potential utility as chemosensitizing agents, although robust clinical confirmation remains limited.

Fucoidan, a sulphated polysaccharide isolated from red sea moss, displays distinct immunological and anti-metastatic properties. Preclinical evidence indicates that fucoidan enhances immune recognition of tumour cells while simultaneously limiting immune suppression within the tumour microenvironment. Its capacity to interfere with chemokine-mediated metastatic signalling further supports investigation as an adjunct strategy, particularly in advanced and treatment-resistant prostate cancer. Collectively, these phytochemicals exemplify multi-target biological modulation, warranting continued evaluation within controlled therapeutic frameworks.

Preclinical and Clinical Evidence: Preclinical studies have consistently demonstrated that selected natural compounds exert measurable biological effects in prostate cancer models through defined molecular mechanisms. Curcumin has been shown in vitro and in animal studies to inhibit NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and COX-2 signalling, reduce histone deacetylase and DNA methyltransferase activity, and suppress expression of oncogenic drivers such as SPINK1. These effects are associated with reduced tumour cell proliferation

and increased apoptotic activity. Nano-formulated curcumin has demonstrated improved bioavailability and tissue distribution in animal models. Early-phase clinical studies have reported acceptable safety profiles and suggest potential benefit when curcumin is used alongside androgen-receptor–targeted therapies in castration-resistant prostate cancer, although definitive efficacy data are pending. Quercetin has been shown experimentally to induce cell-cycle arrest and apoptosis through modulation of p53-dependent pathways and downregulation of anti-apoptotic proteins. Onion-derived organosulfur compounds activate Nrf2-regulated detoxification enzymes and inhibit androgen receptor nuclear translocation *in-vitro*. Limited clinical studies indicate that quercetin may enhance chemotherapy tolerance, but robust outcome data are lacking.

Fucoidan, a sulfated polysaccharide, has demonstrated immunomodulatory effects and inhibition of CXCL12/CXCR4-mediated metastatic signalling in preclinical prostate cancer models. Early clinical evaluations are currently assessing its safety in advanced disease. Overall, existing evidence supports further controlled clinical investigation rather than routine therapeutic use.

Specifications of Botanicals:

Turmeric (*Curcuma longa*): *Curcuma longa*, a rhizomatous species of the Zingiberaceae family, is rich in bioactive molecules dominated by curcuminoids, along with terpenoid and phenolic fractions. Curcumin constitutes the principal curcuminoid, supported by volatile oil constituents and polysaccharides such as ukonans.

These compounds collectively account for the biological and pharmacological effects documented in prostate cancer research. At the mechanistic level, curcumin consistently suppresses tumour-associated inflammatory signalling by limiting activation of transcriptional regulators and downstream mediators involved in chronic inflammation (*in-vitro*, *in-vivo*). It reduces oxidative stress by scavenging reactive oxygen species and limiting oxidative DNA injury (*in-vitro*, *in-vivo*). Curcumin further inhibits cancer cell proliferation through disruption of kinase-driven growth pathways and modulation of cell-cycle regulatory proteins, leading to growth arrest (*in-vitro*, *in-vivo*). Induction of programmed cell death occurs *via* regulation of apoptosis-associated proteins and proteolytic cascades *(in-vitro, in-vivo*). Additional experimental findings include reduced angiogenic signalling (*in-vivo*), interference with androgen-dependent transcriptional activity (*in-vitro*), epigenetic regulation of gene expression (*in-vitro*), and attenuation of invasive behaviour through inhibition of extracellular matrix–degrading enzymes (*in-vitro, in-vivo*).

From a therapeutic perspective, curcumin has demonstrated potential as a chemopreventive agent, a sensitiser to androgen-targeted and cytotoxic therapies, and a modulator of treatment-related inflammation in experimental systems. Early clinical investigations indicate acceptable safety and suggest possible adjunctive benefit; however, therapeutic efficacy remains unconfirmed. Owing to variability in formulation quality, limited bioavailability, and potential drug interactions, curcumin should be regarded strictly as an adjunct or investigational therapeutic, not a replacement for established prostate cancer treatments.

Onion (Quercetin): *Allium cepa*, a member of the Amaryllidaceae family, is a widely consumed dietary plant enriched with bioactive compounds relevant to cancer biology. Its phytochemical profile is dominated by flavanols, particularly quercetin, along with related flavonoids such as kaempferol and myricetin. Onion also contains organosulfur compounds (including allicin, diallyl disulfide, and S-allyl cysteine), phenolic acids (caffeic and ferulic acids), fermentable carbohydrates (fructans and oligosaccharides), essential minerals (selenium, manganese, potassium), and water-soluble vitamins. At the mechanistic level, quercetin exhibits strong antioxidant activity by reducing intracellular reactive oxygen species and limiting oxidative DNA damage in prostate cancer cell models (evidence: *in-vitro, in-vivo*). It demonstrates anti-inflammatory effects through suppression of NF-κB activation and downregulation of COX-2 expression, thereby attenuating pro-tumorigenic inflammatory signalling (evidence: *in-vitro, in-vivo*). Quercetin has been shown to induce apoptosis by modulating mitochondrial pathways and apoptosis-regulating proteins (evidence: in vitro). Additionally, it exerts antiproliferative effects by disrupting PI3K/Akt and MAPK

signalling cascades, resulting in reduced tumour cell growth (evidence: *in-vitro, in-vivo*). Anti-angiogenic activity, associated with inhibition of endothelial cell proliferation and angiogenic signalling, has also been reported (evidence: *in-vitro*). From a therapeutic standpoint, quercetin is being investigated primarily as a chemopreventive and adjunctive agent. Experimental and early clinical observations suggest it may enhance responsiveness to conventional therapies while reducing treatment-associated oxidative and inflammatory stress. However, clinical evidence remains limited, and variability in bioavailability and dosing necessitates further controlled trials. Consequently, quercetin should be considered an investigational supportive compound rather than a primary therapeutic intervention in prostate cancer.

Red Sea Moss: Red sea moss, derived from red algae of the Rhodophyceae class, including *Chondrus crispus* and Gracilaria species, is a marine source of structurally complex bioactive compounds. Its chemical profile is dominated by sulfated polysaccharides (carrageenans, agar, galactans), along with phenolic compounds, flavonoids, carotenoids, phytosterols, omega-3 fatty acids, essential amino acids such as taurine, and a broad spectrum of minerals and vitamins. At the mechanistic level, sulfated polysaccharides isolated from red sea moss have demonstrated anti-inflammatory activity by reducing expression of pro-inflammatory cytokines, including IL-6 (Interleukin-6)and TNF-α (Tumour Necrosis Factor-α), in cellular and animal inflammation models (evidence: *in-vitro, in-vivo*). The antioxidant fraction, composed of phenolics, flavonoids, and carotenoids, has been shown to attenuate oxidative stress and limit oxidative DNA injury in experimental systems (evidence: *in-vitro, in-vivo*). Several studies report cytotoxic and pro-apoptotic effects of algal polysaccharides against prostate cancer cell lines, associated with activation of intrinsic apoptotic pathways (evidence: *in-vitro*). Red sea moss–derived phytosterols have been proposed to influence steroid-related signalling, including androgen-associated pathways, although this effect remains largely experimental (evidence: *in-vitro*). Additionally, polysaccharide fractions enhance immune cell activation, supporting immunomodulatory activity (evidence: *in-vitro, in-vivo*). Anti-metastatic effects, including suppression of matrix metalloproteinase activity and reduced invasive behaviour, have been observed in preclinical models (evidence: *in-vitro*). From a therapeutic standpoint, red sea moss constituents are being explored as immunomodulatory and anti-metastatic adjuncts, particularly in advanced prostate cancer. However, clinical evidence is currently insufficient, and variability in extraction methods, composition, and dosing limits translational applicability. Consequently, red sea moss should be regarded as an investigational supportive agent, requiring further standardisation and controlled clinical evaluation before therapeutic recommendation.

Future Prospective: Although phytochemicals have demonstrated reproducible biological effects in controlled experimental systems, their transition into clinical prostate cancer management remains constrained by several unresolved issues. Variability in source material, formulation inconsistency, and limited systemic exposure continue to undermine reproducibility and comparability across studies. Moreover, the absence of adequately powered, methodologically rigorous clinical trials restricts definitive conclusions regarding clinical benefit. Future research should therefore prioritise methodological refinement rather than expansion of compound catalogues. This includes the development of reproducible formulations with defined pharmacokinetic profiles, alongside systematic validation of molecular targets and exposure–response relationships. Patient stratification based on molecular and metabolic characteristics may further reduce heterogeneity and improve the interpretability of outcomes. In parallel, growing evidence suggests that host biological factors, including microbial metabolism, may substantially influence compound activity and warrant structured investigation. From a clinical and regulatory perspective, phytochemicals should be evaluated strictly within controlled experimental or adjunctive frameworks. Their incorporation into prostate cancer management must be supported by mechanistic clarity, standardised manufacturing, and confirmatory clinical data. Until these criteria are met, such compounds should remain investigational, serving as tools for hypothesis-driven research rather than established therapeutic interventions.

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REFERENCES:

1. Grayhack JT and Kozlowski JM: Development of the human prostate. J Urol 1996; 155(2): 610–616.
2. Lowsley OS: The development of the human prostate gland. Am J Anat 1912; 13: 299–349.
3. McNeal JE: The zonal anatomy of the prostate. Prostate 1981; 2(1): 35–49.
4. Thomson AA and Cunha GR: Prostate organogenesis. Dev Dyn 2015; 244(1): 20–32.
5. Abate-Shen C and Shen MM: Molecular genetics of prostate development and cancer. Cold Spring Harb Perspect Med 2011; 2(9): 006049.
6. Goldstein AS: Identification of basal stem cells in the prostate. Proc Natl Acad Sci USA 2010; 107(6): 2479–2484.
7. Wang X: Luminal epithelial stem cells as cells of origin for prostate cancer. Nature 2009; 461(7263): 495–500.
8. Shen MM and Abate-Shen C: Molecular genetics of prostate cancer. Genes Dev 2010; 24(18): 1967–2000.
9. Huggins C and Hodges CV: Effect of castration and estrogen on prostate cancer. Cancer Res 1941; 1: 293–297.
10. Feldman BJ and Feldman D: Androgen-independent prostate cancer. Nat Rev Cancer 2001; 1(1): 34–45.
11. Heinlein CA and Chang C: Androgen receptor in prostate cancer. Endocr Rev 2004; 25(2): 276–308.
12. Labbé DP and Brown M: AR-mediated transcriptional networks. Nat Rev Cancer 2018; 18(5): 291–297.
13. Chung LW: Stromal–epithelial interaction in prostate growth. Cancer Surv 1995; 23: 33–42.
14. Chung LW: Tumour microenvironment in prostate cancer. J Urol 2005; 173(1): 10–20.
15. Sun Z: Stromal androgen signalling as a tumour niche. Nat Commun 2022; 13: 3458.
16. De Marzo AM: Proliferative inflammatory atrophy. Am J Pathol 1999; 155(6): 1985–1992.
17. Bostwick DG: High-grade prostatic intraepithelial neoplasia. Cancer 1996; 78(2): 347–354.
18. Rubin MA: Clonal relationship between HGPIN and carcinoma. J Natl Cancer Inst 2000; 92(23): 1912–1915.
19. Nelson WG: Inflammation and oxidative stress in prostate carcinogenesis. Cancer Res 2003; 63(18): 6283–6291.
20. Gurel B: Chronic inflammation in prostate cancer. Proc Natl Acad Sci USA 2014; 111(15): 5522–5527.
21. Balk SP and Knudsen KE: AR and cell-cycle regulation. Nat Rev Cancer 2008; 8(5): 343–358.
22. Mani RS: Epigenetic regulation of AR binding. Nat Med 2012; 18(1): 58–70.
23. Tomlins SA: TMPRSS2-ERG gene fusion. Science 2005; 310(5748): 644–648.
24. Zhou Q: TMPRSS2-ERG oncogenic transcription. Cancer Cell 2007; 12(6): 519–531.
25. Taylor BS: Integrated genomic profiling. Cancer Cell 2010; 18(1): 11–22.
26. Barbieri CE: SPOP and FOXA1 mutations. Nat Genet 2012; 44(6): 685–689.
27. Fraser M: Genomic hallmarks of aggressive prostate cancer. Nature 2017; 541(7638): 359–364.
28. Watson PA: AR resistance mechanisms. Nat Rev Cancer 2015; 15(12): 701–711.
29. Antonarakis ES: AR-V7 and therapy resistance. N Engl J Med 2014; 371(11) 1028–1038.
30. Beltrán H: Neuroendocrine prostate cancer. Clin Cancer Res 2011; 17(12): 3870–3880.
31. Mateo J: DNA repair defects and PARP inhibition. N Engl J Med 2015; 373(18): 1697–1708.
32. de Bono J: Olaparib in metastatic CRPC. N Engl J Med 2020; 382(22): 2091–2102.
33. Tannock IF: Docetaxel in mCRPC. N Engl J Med 2004; 351(15): 1502–1512.
34. Scher HI: Enzalutamide post-chemotherapy. N Engl J Med 2012; 367(13): 1187–1197.
35. Beer TM: Enzalutamide chemotherapy-naïve. N Engl J Med 2014; 371(5): 424–433.
36. Fizazi K: Abiraterone in CRPC. N Engl J Med 2011; 364(21): 1995–2005.
37. Parker C: Radium-223 dichloride. N Engl J Med 2013; 369(3): 213–223.
38. Morris MJ: Lu-PSMA-617 therapy. N Engl J Med 2021; 385(12): 1091–1103.
39. James ND: STAMPEDE platform trial. Lancet 2017; 389(10087): 1176–1185.
40. Lilja H: Prostate-specific antigen biology. Nat Rev Cancer 2008; 8(4): 268–278.
41. Balk SP: Biology of PSA. J Clin Oncol 2003; 21(2): 383–391.
42. Costello LC and Franklin RB: Zinc in prostate cancer. Prostate 1998; 35(4): 285–296.
43. Franklin RB and Costello LC: Metabolic reprogramming in prostate cancer. Mol Cancer 2014; 13: 24.
44. Silver DA: PSMA expression in prostate cancer. Clin Cancer Res 1997; 3(1): 81–85.
45. Hofman MS: ^{68}Ga-PSMA PET imaging. Lancet Oncol. 2018; 19(6): 825–833.
46. Pernar CH: Global epidemiology of prostate cancer. Cold Spring Harb Perspect Med 2018; 8(12): a030361.
47. Siegel RL: Cancer statistics 2025. CA Cancer J Clin 2025; 75(1): 7–33.
48. Kenfield SA: Smoking and prostate cancer mortality. JAMA 2011; 305(24): 2548–2555.
49. Islami F: Smoking and prostate cancer meta-analysis. Cancer Epidemiol 2020; 66: 101736.
50. Lei Y: Curcumin in prostate cancer: systematic review. Front Pharmacol 2024; 15: 1379389.
51. Wang L: Curcumin molecular targets. Transl Androl Urol 2024; 13(6): 131–140.
52. Zhang X: Phytochemicals in prostate cancer. Phytother Res 2022; 36(4): 1123–1132.
53. Mohler JL: NCCN Prostate Cancer Guidelines. J Natl Compr Canc Netw 2023; 21(4): 355–392.

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