

# A Comprehensive Review and Androgen Deprivation Therapy and Its Impact on Alzheimer's Disease Risk in Older Men with Prostate Cancer

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**Abstract:** Prostate cancer (PCa) is one of the most prevalent malignancies affecting males worldwide. Despite reductions in mortality rates due to advances in early identification and treatment methods, PCa remains a major health concern. Recent research has shed light on a possible link between PCa and Alzheimer's disease (AD), which is a significant neurological ailment that affects older males all over the world. Androgen deprivation therapy (ADT), a cornerstone therapeutic method used in conjunction with radiation and palliative care in advanced metastatic PCa cases, is critical for disease management. Evidence reveals a relationship between ADT and cognitive impairment. Hormonal manipulation may cause long-term cognitive problems through processes such as amyloid beta (A $\beta$ ) aggregation and neurofibrillary tangles (NFTs). Fluctuations in basal androgen levels can upset the delicate balance of genes that are sensitive to androgen levels, contributing to cognitive impairment. This detailed review dives into the various aspects of PCa aetiology and its relationship with cognitive decline. It investigates the discovery of particular biomarkers, as well as microRNAs (miRNAs), which play important roles in pathogenic progression. The review attempts to identify potential biomarkers associated with ADT-induced cerebral changes, including A $\beta$  oligomer buildup, NFT formation, and tauopathy, which can contribute to early-onset dementia and cognitive impairment. Besides it further aims to provide insights into innovative diagnostic and therapeutic avenues for alleviating PCa and ADT-related cognitive sequelae by unravelling these complicated pathways and molecular mechanisms.

**Keywords:** metastatic cancer, dementia, cognitive defects, androgen, testosterone

## Introduction

Prostate cancer (PCa) is a major community health concern, placed as the second most common cancer in males worldwide. Its occurrence varies significantly by geography, with industrialized countries, notably in North America and Europe, reporting higher rates than developing countries.<sup>1</sup> Additionally, Australia/New Zealand, Northern Europe, and North America have the greatest incidence rates.<sup>2</sup> Despite advances in diagnosis and medication, PCa continues the most common cause of cancer-related mortality in men. However, mortality rates have significantly decreased in many countries, owing to improved therapeutic techniques and integrated medical systems.<sup>3</sup>

PCa is a type of cancer affecting the prostate gland, a small, walnut-sized organ positioned behind the bladder and in front of the rectum.<sup>4</sup> The prostate gland is important in the male reproductive system because it produces and secretes seminal fluid to sustain sperm. PCa impacts mainly elderly males, having the probability of increasing significantly

beyond the age of 50.<sup>5</sup> PCa demonstrates higher occurrence rates among various ethnicities, with African American men exhibiting the highest rates globally, trailed by Caribbean men of African descent and the lowest incidence rates among Asian men. The correlation between diet and PCa susceptibility is intricate and not fully elucidated but some research does suggest that diets abundant in red meat and high-fat dairy products while lacking in fruits and vegetables may elevate PCa risk. On the other hand, diets rich in fruits, vegetables, and specific nutrients like lycopene, may confer protective benefits.<sup>6</sup> Additionally, lifestyle factors such as obesity and sedentary habits have been linked to heightened PCa risk and engaging in regular physical activity and maintaining a healthy body weight reduces it.

While the initial stage of PCa might start with modest or no signs and symptoms, later stages can cause a variety of urinary and sexual dysfunctions (blood in the urine or sperm, erectile dysfunction, and pain in the pelvis, hips, and lower back), greatly affecting the quality of life.<sup>7</sup> The prostate gland's propensity to neoplastic transformation is caused by a complex interplay of hereditary, environmental, and hormonal variables.<sup>8</sup> Androgens, particularly testosterone, serve a critical part in modulating prostate growth and functioning, rendering androgen deprivation therapy (ADT) a key component in the treatment of advanced conditions of PCa.<sup>9</sup> Men with elevated amounts of testosterone or its metabolite, dihydrotestosterone (DHT), are potentially at a higher risk. This explains precisely why ADT, which lowers testosterone levels, is a preferred therapeutic option for advanced PCa. Recent research suggests that long-term ADT treatment in PCa patients may be linked to an elevated risk of AD. This link is postulated because testosterone is essential for brain function, cognition, and neuroprotection. ADT may influence the brain by lowering testosterone levels, potentially leading to an increased risk of AD.<sup>10</sup> Also, genetics have a substantial impact on PCa risk as men with a family history of PCa, are more likely to develop the disease. Furthermore, genetic mutations, like BRCA1 and BRCA2, are linked to an increased probability of PCa.<sup>11</sup>

Meanwhile, Alzheimer's Disease (AD) places a significant strain on worldwide healthcare systems, particularly in ageing populations. AD is characterized by increasing cognitive decline and memory impairment and affects both patients and their carers economically. The aetiology of AD is complex, with extensive molecular events resulting in the formation of abnormal protein complexes in the brain, disrupting neuronal function and transmission.<sup>12</sup> Based on contemporary scientific understanding, AD is a neurodegenerative ailment that impairs memory, thinking, and cognition. It is the leading cause of dementia in the elderly, accounting for 60–80% of all cases, usually characterized by the aggregation of abnormal protein ( $A\beta$ ) deposits in the brain, resulting in plaques and tangles that impede normal brain function. AD's symptoms often begin with moderate memory loss and disorientation increases with the progression of the disease.<sup>13</sup> Individuals may struggle to speak, have difficulty recognizing known individuals, and conduct daily duties independently as the disease develops. PCa has been observed to be closely regulated by the levels of androgen in the body, which is also a critical factor in governing the expression of amyloid precursor protein (APP) APP is a precursor to the  $A\beta$  whose unchecked expression triggers the initiation of the first stage cognitive impairment with dementia, which in severe case can lead to the development of Alzheimer's Disease (AD).<sup>14</sup>

It is crucial to emphasize that research in this field is still underway, and causality has yet to be proven. The probable association between PCa and AD, on the other hand, underscores the importance of closely monitoring cognitive function in older men undergoing ADT.<sup>10</sup> This paper highlights all the possible connections between PCa and AD in the male population and the mechanism that may cause the prevalence of AD after androgen deprivation therapy. The research study by Driver et al, published in 2012, was one of the earliest studies to indicate a link between Pca and the risk of AD. For many years, the researchers monitored over 5000 people aged 65 and older and discovered that a history of cancer was linked to a lower incidence of AD, implying a possible inverse association between the two disorders.<sup>15</sup> Then, in 2015, Jayadevappa et al investigated the link between ADT and the risk of dementia, including AD. The researchers examined data from bigger cohorts, including over 150,000 men with PCa, and observed that those who took ADT had a higher chance of getting dementia, particularly when ADT was used for a lengthy period.<sup>16</sup> Another study, conducted by Nead KT, Gaskin G, Chester et al 2016; looked at the relationship between ADT for PCa and the risk of AD. The researchers examined approximately 16,000 males with PCa's medical records and discovered that those who took ADT had a considerably higher probability of acquiring AD than those who did not receive ADT. The risk appeared to rise as the length of ADT treatment increased. He later extended prior studies by looking at the link between ADT for PCa and the risk of dementia, including AD. The study, which included data from over 9000 men with PCa, discovered that ADT

related to a greater risk of dementia, particularly in men aged 70 and older, and was published in 2017.<sup>9</sup> It has been concluded from the published studies that males diagnosed with PCa are more likely to get AD if they undergo ADT for the disease.<sup>15</sup> Recent studies have revealed a probable link between PCa, AD, and ADT, enticing further research into the underlying mechanisms and clinical implications.<sup>17</sup>

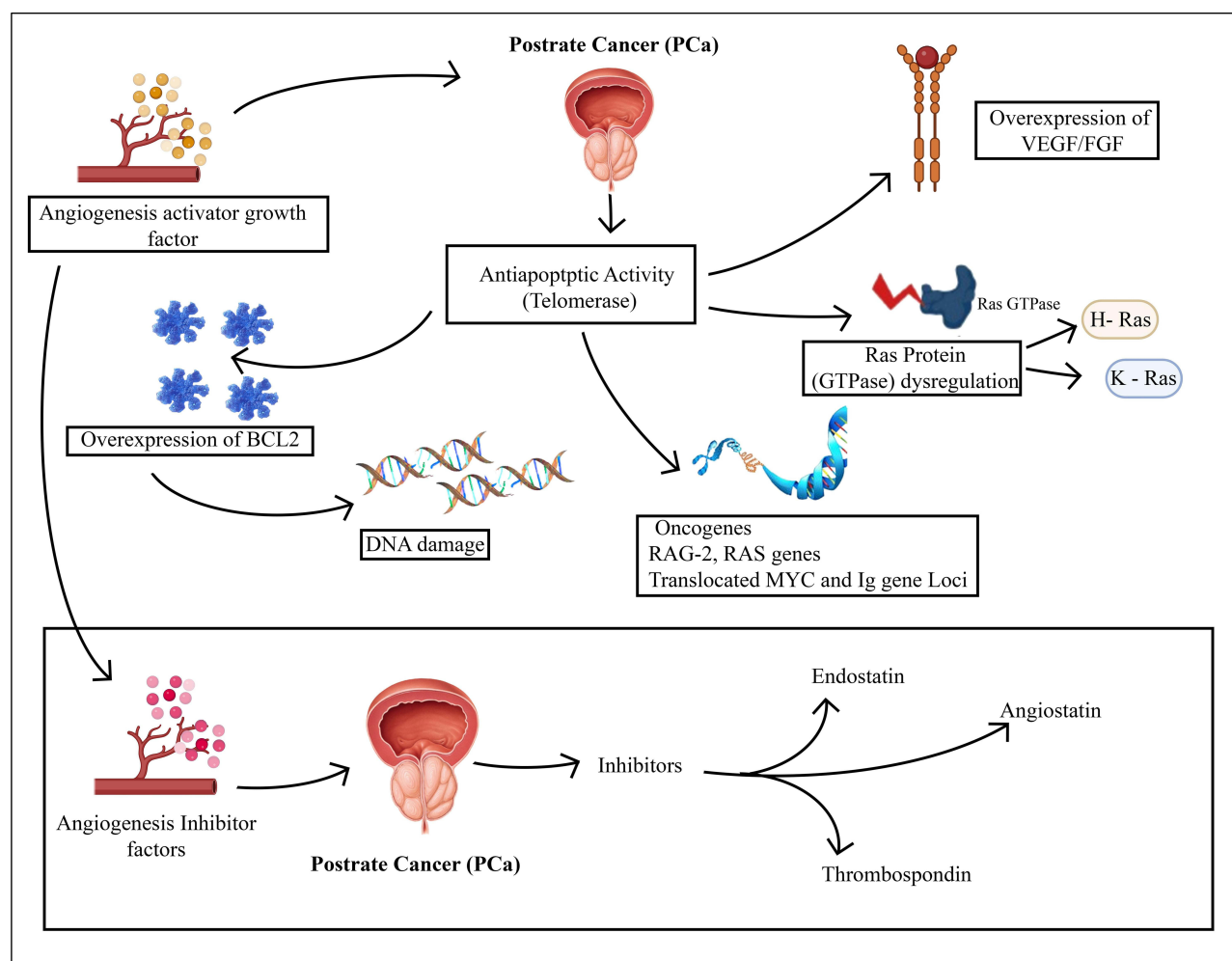
ADT, a conventional treatment strategy in advanced PCa, seeks to decrease androgen signalling, hence preventing tumour development and progression. However, research studies suggest that extended ADT might have unforeseen consequences for cognitive function, possibly exposing people to neurodegenerative illnesses like AD. This review aims to thoroughly investigate the complex link between PCa, AD, and ADT by distilling findings and elucidating underlying mechanisms. With detailing the complex relationship involving hormonal regulation, neurodegeneration, and therapeutic interventions, we hope to provide clinicians and researchers with a more comprehensive knowledge of the effects of ADT on AD risk in older men with PCa.

## Progression of Pathophysiology in Prostate Cancer

Identifying genes involved in the beginning and progression of PCa requires identifying the primary controllers and their connected genomic networks from a wide range of pathways. Furthermore, while cancer has a constant course as a disease, each type of cancer is dependent on various genes that play critical roles in its manifestation. Likewise, PCa has been linked to a variety of DNA mutations, including single nucleotide polymorphisms (SNPs), also known as point mutations, translocations, gene amplification, DNA rearrangements, and insertional mutagenesis.<sup>18</sup> PCa is an adenocarcinoma, recognized when the epithelial cells of the prostate tissue lining begin to multiply unrestrictedly (Figure 1). Neuroendocrine tumour and transitional cell carcinoma are two of the most uncommon malignancies classified as PCa. These tumours have an accelerated growth rate and spread to the linked surrounding lymph nodes, which are not typical PCa characteristics. However, if the tumour grows and gains access to blood arteries, it causes cell deposition on bones throughout the body, and PCa is said to have metastasized to the bones at this stage.<sup>19</sup> Epidemiologists have Targeting Prostate Cancer, the “Tousled Way” period. It is noteworthy that, despite its classification as cancer, prostate cancer (PCa) often exhibits a benign tumour-like behaviour for an extended period during its progression. Even in cases where PCa has metastasised, symptoms and advanced conditions can be effectively managed, enabling individuals affected to maintain a satisfactory quality of life for many years. This stands in stark contrast to most other types of cancer. Interestingly, microarrays, a crucial technology for observing genomic regulatory networks and protein-protein interactions, have recently been utilised to elucidate the key genes and pathways associated with PCa.<sup>20</sup> There is a growing body of evidence emphasizing the significance of genetics in the genesis of certain cancer types, overshadowing any epigenetic influence. Consequently, numerous studies in recent years have sought to establish connections between specific malignancies and other life-threatening conditions. Among these studies, one of the most striking revelations has been the correlation between PCa and AD.<sup>21</sup>

## Key Genetic Regulators in Prostate Cancer

Researchers have worked tirelessly to identify the core modulators and regulators that play an essential part in displaying disease-like features in PCa. Patients with PCa show expression and suppression of different genes, which eventually leads to the progression of the disease.<sup>22,23</sup> Such protein interactions have also been linked to cancer-related properties including anchorage-independent growth, anti-apoptotic characteristics, defective signalling pathways, and angiogenesis activator overexpression. One of the most striking traits seen in PCa patients is their cells’ anti-apoptotic tendency, which can be ascribed to the existence of an enzyme known as telomerase. Telomerase synthesizes telomeric ends (non-coding ends) for chromosomes during cell division, making normal cells eternal. Conversely, the increase of anti-apoptotic protein Bcl2 in PCa patients helps afflicted cells avoid cell death. Bcl2 may also help cells cope with DNA damage and survive circumstances that would normally cause apoptosis.<sup>24</sup> In contrast to normal cells, cancerous cells do not use extracellular matrix (ECM) anchoring proteins such as integrin, which are required to maintain proper shape and structural functions.<sup>25</sup> Additionally, the MAP/ERK pathway, which regulates cell proliferation, is dysregulated in PCa. In malignant situations, the Ras protein, which is a GTPase, is faulty. Ras protein is typically attached to GDP; however, in malignant circumstances, Ras protein becomes permanently bound to GTP rather than GDP, resulting in a constitutive



**Figure 1** The diagrammatic representation of factors responsible for the pathophysiological progression of prostate cancer.

**Abbreviations:** VEGF, Vascular endothelial growth factor; FGF, Fibroblast growth factors; H – Ras, proto-oncogene (GTPase); K – Ras, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; RAG2, Recombination Activating 2 genes; RAS, Rat sarcoma genes; BCL2, B-cell lymphoma 2.

response and uncontrolled cell proliferation.<sup>26</sup> Angiogenesis, a critical step for tumour progression, is distinguished by the overexpression of angiogenesis growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), especially in PCa. However, angiogenesis inhibitors such as angiostatin, endostatin, and thrombospondin are used to counteract angiogenesis activator growth factors and maintain equilibrium, hence avoiding tumorigenicity.<sup>27</sup> In addition to specific protein interactions, certain genes are linked to an increased risk of developing PCa. The RAG-2 Gene, which regulates lymphocyte lineage cell development, has been identified as a key regulatory control point. Patients with a mutant version of RAG-2 are unable to synthesize functional proteins required for lymphocyte maturation, increasing the risk of cancer.<sup>23</sup> RAS oncogenes are monomeric GTP-binding proteins that control cellular division. Mutation in the 12th position causes a substitution of amino acids from valine to glycine, resulting in the production of a mutant RAS protein with constitutive expression in GTP binding and a higher risk of producing PCa [24]. Furthermore, translocation in the MYC gene and IG gene locus causes the MYC gene and IG gene to switch locations on chromosomes 8 and 14, respectively. This translocation mutation causes overexpression of the MYC gene, which increases the production of proteins that regulate transcription factors for cell division, resulting in an increase in cell division levels in PCa-affected individuals.<sup>28</sup> While various existing protein-protein interaction and gene regulation networks for the diseased condition have been documented, it is worth noting that specific protein interactions and genes are highly conserved for a particular form of cancer.<sup>29</sup> Furthermore, understanding the dominant key regulators

and associated genomic networks, among multiple other pathways, is critical for identifying the specific genes involved in PCa formation and progression.<sup>30</sup>

All mentioned proteins in Table 1 are either categorized under the class of ribosomal proteins (RP) or non-ribosomal proteins (NRP). Numerous studies have shown that RNA-binding proteins (RP) or non-coding RNA-binding proteins (NRP) are either responsible for their production in PCa or they interact with one another to activate PCa-specific responses.<sup>30</sup> Moreover, several microRNAs (miRNAs) have received attention for their regulatory involvement in PCa. miRNAs, in addition to their role in normal protein translational pathways, are occasionally involved in silencing mutant mRNA caused by epigenetic factors.<sup>31</sup> miRNA expression profiling is often used in PCa cases because they are consistently expressed in malignant tissues compared to normal tissues. These profiling studies often measure the expression of primitive miRNA (pri-miRNA) transcripts as well as active mRNA at the same time.<sup>32</sup>

In addition, some studies have shown that the expression of pri-miRNA and miRNA does not necessarily synergistically influence protein expression. This behaviour is regulated by tissue-specific miRNAs, which can increase or decrease gene expression in PCa. As a result, different miRNA expression profiles serve as biomarkers for PCa, such as let-7, which targets RAS oncogenes.<sup>45,46</sup> Another example is miR16, which suppresses the BCL2 anti-apoptotic factor.<sup>47</sup> Furthermore, miRNAs such as miR125a and miR125b cooperate to inhibit the oncogenes ERBB2 and ERBB3.<sup>32,48</sup>

## Sequential Progression of PCa and Its Therapeutic Intersection with ADT

PCa has been exposed to a variety of early precursor compounds, like - testosterone, which is ADT's primary modulatory molecule.<sup>49</sup> Testosterone transmits the first stimulus, which leads to various secondary activations of heat shock protein

**Table 1** Proteins and Genes Involved in the Regulation of Prostate Cancer

S. No	Genes	Encoded Protein	Relevance with Prostate Cancer	References
1.	RPL19	60s ribosomal protein L19	Protein overexpression was employed prognostic marker in PCa. Prostate, gastric, lung cancer	[33,34]
2.	RPL11	60s ribosomal protein L11	Binding of co-activator TRRAP to MYC promoter is prevented or silencing via miRNA -RISC complex. Promotes MYC degradation or disable c-MYC transcription	[35]
3.	RPL23A	60s ribosomal protein L23A	Inhibiting RAS-mediated tumorigenesis and stabilizes p53 gene. Protein leads to inhibit cell growth arrest and promote apoptosis	[36]
4.	RPL5 RPL6	60s ribosomal protein L5 & L6	Stabilizes TAp73 / p53 and evades their ubiquitination. Induces apoptosis and arrest cell growth	[37]
5.	AHSA1	Activator heat shock 90 ATPase-1enzyme	It helps in the proper regulation of Wnt pathway aka $\beta$ -catenin signalling pathway. Protein induces cell growth, apoptosis, migration, and invasion	[38]
6.	CUL7	E3 ubiquitin-protein ligase complex	Induces cyclin-A overexpression, leading to accumulation of $\alpha$ -tubulin microtubule via influencing ERK-SNAI-2 signalling. Induces metastasis in epithelial-mesenchyme and inhibit cell proliferation, apoptosis	[39,40]
7.	EIF3A	Eukaryotic translation initiation factor subunit A protein	Influences mTOR pathway's translational initiation and regulation. Control gene's translation involved in cell division, differentiation, and apoptosis	[41]
8.	NOP2	Putative ribosomal RNA methyltransferase enzyme	Protein influences cell cycle progression from G1 to S phase. Employed as cell transformation's biomarker.	[42]
9.	HSPA5	Heat shock 70 protein 5	Mediate protein folding as a response to extra-ribosomal stress. Ensures cell escape death in cancerous condition.	[43,44]

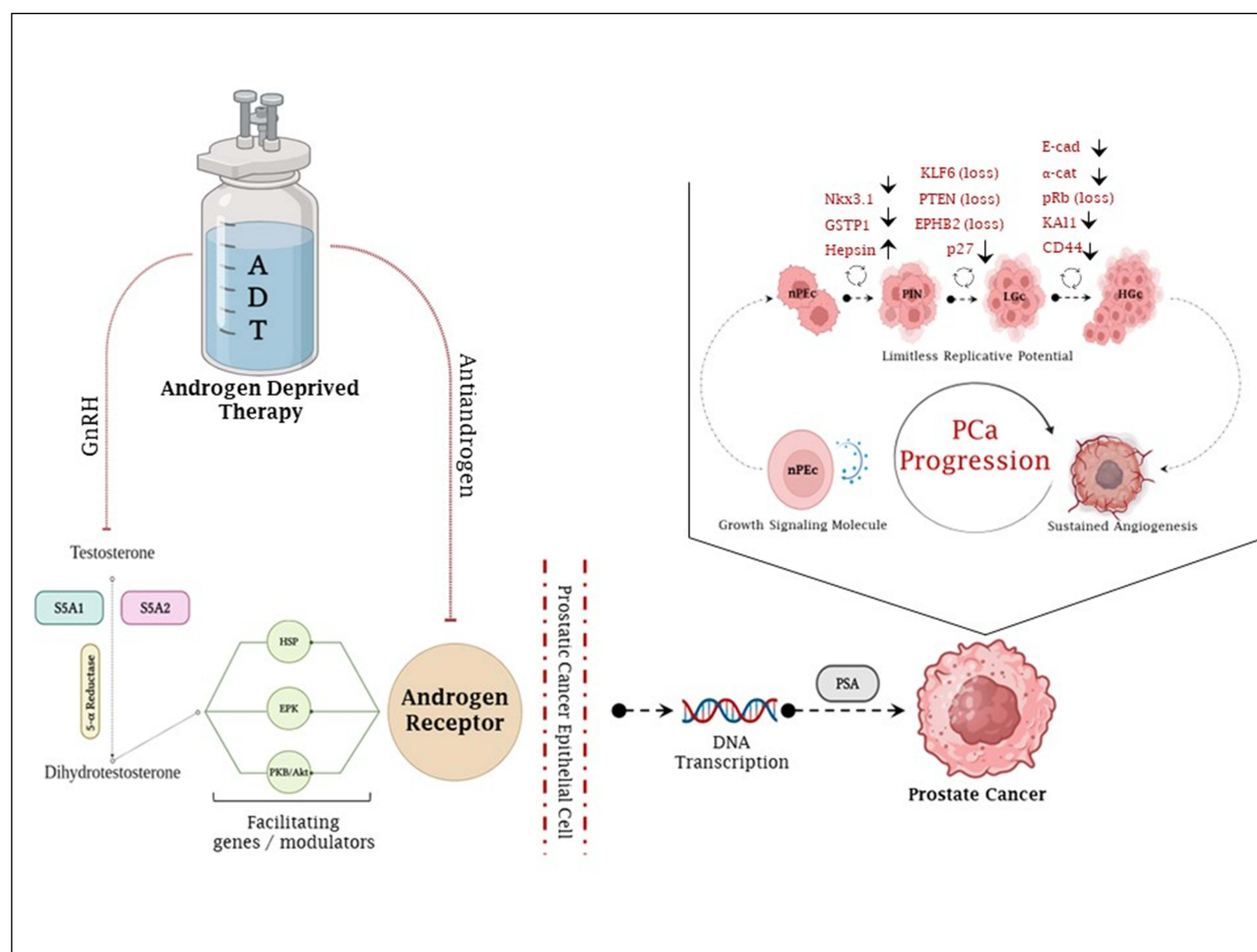


(HSP), EPK, and the PKB/Akt signalling cascade, culminating in the activated androgen receptor (AR), one of the most potent oncogenes in PCa.<sup>50</sup> Also, activated AR is transcriptionally active and enters prostatic epithelial cells, changing DNA replication and directing the transcription machinery to accumulate tumorigenic traits as evidenced by the rise in prostate-specific antigen (PSA), resulting in PCa (Figure 1). The sequential advancement of PCa is followed by various pathogenesis stages, which begin with normal prostatic epithelial cells (nPEc) and proceed to prostatic intraepithelial neoplasia (PIN), low-grade carcinoma (LGc), and high-grade carcinoma. Throughout the cancer progression, there are some increases and losses in the amounts of specific genes and proteins that contribute to its growth.

The first line of treatment used in PCa patients is ADT, which directly suppresses or inhibits testosterone and AR levels by administering gonadotropin-releasing hormone agonists (GnRH) and anti-androgens to their respective targets. GnRH directly lowers the levels of testosterone produced by the testis. This accounts for 25% of total testosterone levels in humans, whereas anti-androgen specifically binds to the androgen receptor, making it unavailable for dihydrotestosterone (DHT) binding. Thus, resulting in the inhibition of cellular proliferation and terminating PCa progression. (Figure 2).<sup>51,52</sup>

## Relationship Between Alzheimer's and Prostate Cancer

PCa ranks as one of the most common tumours in males, but its potential link to AD remains a relatively unexplored field of research. However, over the last decade, research has appeared that highlights the interplay and connection between



**Figure 2** Sequential progression of prostate cancer pathogenesis and the intersection of ADT in the pathology.

**Abbreviations:** S5A1, steroid 5 alpha-reductase 1; S5A2, steroid 5 alpha-reductase 2; HSP, heat shock protein; PSA, prostate-specific antigen; nPEc, normal prostate epithelial cell; PIN, prostatic intraepithelial neoplasia; LGc, low grade carcinoma; HGc, high grade carcinoma; ADT, androgen deprived therapy; GnRH, gonadotropin-releasing hormone agonist; Nkx3.1, NK3 homeobox 1; GSTP, glutathione S-transferase Pi; KLF6, kruppel-like factor 6; PTEN, phosphatase and TENsin homolog; EPHB2, EPH receptor B; E-cad, e-cadherin; α-cat, alpha-cadherin; pRb, retinoblastoma protein; Kall1, Kallmann syndrome I sequence 1; CD44, cell surface adhesion receptor 44.

the two subsets and has also indicated that PCa therapies may contribute to the onset of AD.<sup>53</sup> ADT, which is regarded as the primary treatment for advanced PCa, not only acts as the conventional technique for monitoring metastatic progression, but it also helps to avoid past therapies such as prostatectomy and radiotherapy. ADT is a potential therapy option for prostate cancer because it efficiently suppresses testicular androgen output or deactivates circulating androgen receptors.<sup>54</sup> Despite its therapeutic potential, the risk-benefit ratio of ADT is not well recognized. ADT-related complications include chronic systemic side effects, metabolic abnormalities, sexual dysfunction, insulin resistance, and an increased risk of bone fractures. The probable association between ADT and dementia is particularly concerning, given all of these issues are associated with low testosterone levels in the blood.<sup>55</sup>

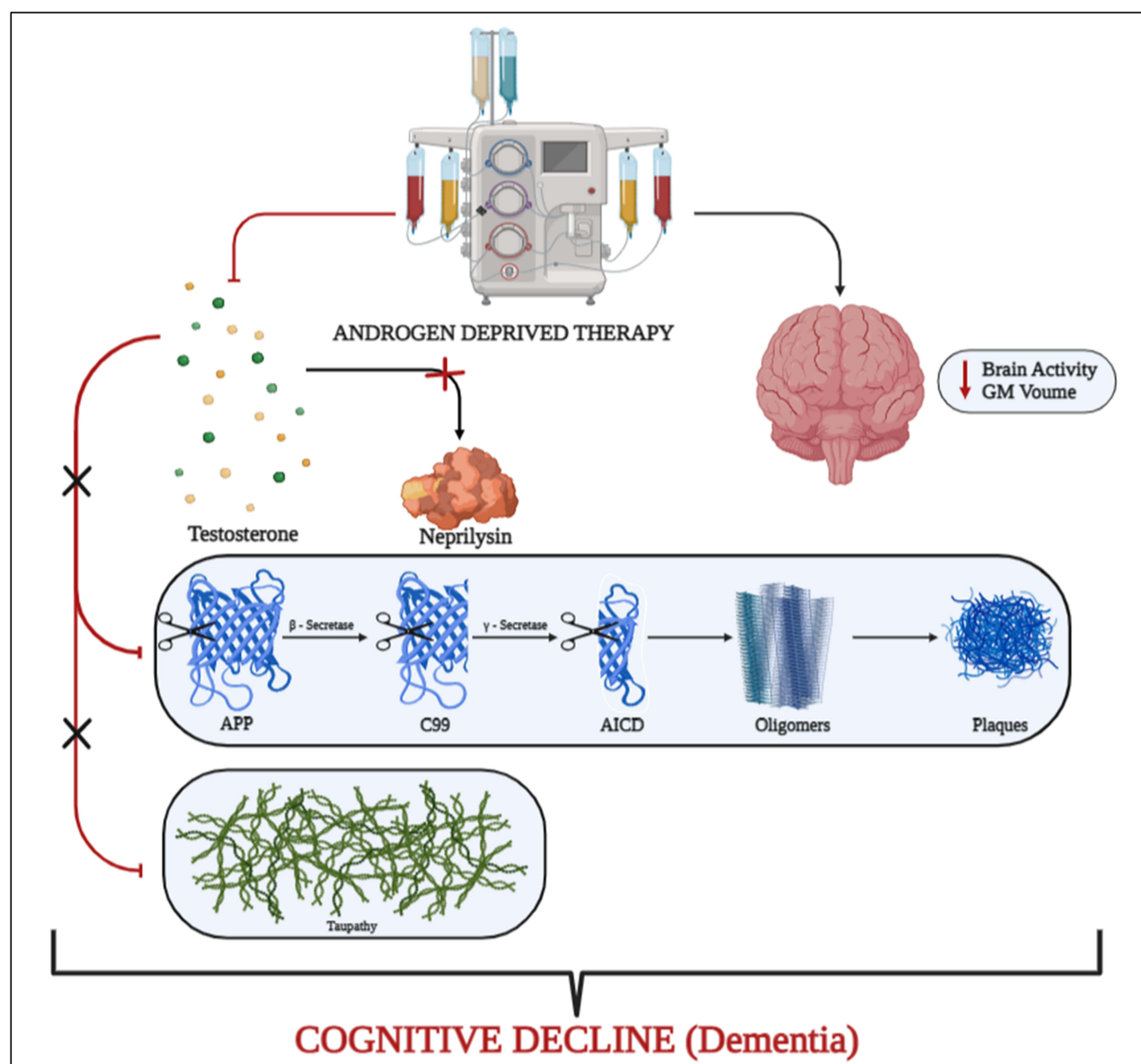
## The Link Between Androgen Deprivation Therapy (ADT) and Cognitive Dysfunction in PCa

Dementia has recently emerged as one of the most often reported mental disorders worldwide, marked by a loss in cognitive functions that impair the daily functioning of the patients. Individuals over the age of 60 are thought to be the most affected demographic. Subsequently, ADT as a side effect, drastically lowers testosterone levels in patients, affecting their systems. Testosterone activates the neprilysin (NEP) protein, which regulates the aggregation and deposition of A $\beta$  oligomers into amyloid plaques.<sup>56</sup> The pathophysiology of dementia begins with a mutation in the amyloid precursor protein (APP), which is mostly located in cortical regions of the brain. Hydrolysis of the APP's C99 domain causes the buildup of A $\beta$  peptides through an amyloidogenic pathway, which is directly linked to the onset of AD.<sup>18,57</sup> Overexpression of A $\beta$  oligomers is encouraged by the APP's intracellular domain (ACID), a product of APP's transcriptional modifying action, leading to AD-related dysfunction. Also, uncontrolled aggregation of A $\beta$  oligomers worsens the condition and causes tauopathy, characterized by NFTs. As a result, several diseases associated with cognitive decline emerge, including dementia, though many medicinal plant based drug targets are being explored by the researchers to control the progression of AD (Figure 3).<sup>58–60</sup> Androgen acts as a precursor to testosterone production, and high androgen levels suggest approximately equal testosterone synthesis in the human body. ADT causes a drop in androgen levels, which lowers testosterone levels and triggers the emergence of dementia-related disease. While males have higher testosterone levels, this reduction is less harmful, but it poses considerable hazards to females, who have naturally lower testosterone levels. Despite the lack of prostates, females have Skene's glands, which are similar to prostate glands, and cancer affecting these glands is known as female PCa.<sup>61</sup>

R. Jayadevappa et al conducted a large cohort study in 2019 with 154,089 primarily older male participants newly diagnosed with PCa, which shed insight into the impact of ADT. Among the individuals, 62,330 received two years of ADT treatment, while 91,759 did not. The study found that older PCa patients who had been exposed to ADT for two years were later diagnosed with early-stage dementia or AD over a ten-year follow-up period.<sup>62</sup>

As dementia progresses, it exhibits characteristics such as aberrant amyloid protein deposition, amyloid plaque formation and contributes to the formation of tauopathy paving the path for early stages of AD.<sup>61</sup> Patients receiving ADT experience different effects based on their gender. For example, postmenopausal women suffer diminishing oestrogen levels, whilst males receiving ADT experience lower androgen levels, both of which are linked to the aetiology of AD. Recent research suggests that oestrogen may play a protective role in cognitive decline, which supports the observation that dementia caused by ADT occurs more frequently in females than males. This disparity may be because females require testosterone for oestrogen production. However, the precise mechanism of AD caused by ADT in males is unknown, while testosterone levels may play a role.<sup>63,64</sup>

Similarly, androgens are thought to regulate the prevalence of antibodies in the cortical region, which is important in regulating the production of amyloid plaques involved in the pathogenesis of AD.<sup>65</sup> According to studies, testosterone, like oestrogen, may act as an endogenous neuroprotective agent, slowing the progression of AD. This putative neuroprotective action of testosterone could include increasing nerve growth, reducing neuron loss, suppressing antibody buildup in the brain, and regulating tau protein hyperphosphorylation.<sup>66</sup> According to studies, individuals, particularly males aged 60–79 years, have lower levels of testosterone in their brains than those who do not have AD. This shows that



**Figure 3** Schematic representation showcasing the consequences of taking Androgen-deprived therapy that led to the onset of cognitive decline (dementia).

**Abbreviations:** GM, Gray Volume; APP, Amyloid Precursor Protein; C99, C99 Domain of APP; AICD, Amyloid Precursor Protein Intracellular Domain.

testosterone levels in the bloodstream may provide neuroprotective effects, as indicated by a direct relationship between testosterone levels and cognitive function.<sup>12,65,67,68</sup>

Various other probable molecular pathways can help us better comprehend the link between PCa and AD. To begin, aberrant APP cleavages are a major factor in the development of AD and APP is a type 1 transmembrane protein found in the central nervous system (CNS). Previous research suggests that APP is an androgen-responsive gene that stimulates cell proliferation in PCa-affected cells.<sup>69</sup> Any abnormalities in either of these pathways could cause dysregulation of the normal system, spurring further inquiry into the link between AD and PCa. ADT on the other hand, in PCa patients may also cause an oxidative stress environment, which could explain this relationship. Oxidative stress is a key component that causes APP overexpression, leading to the initiation of AD.<sup>70</sup> ADT also decreases the function of acetylcholinesterase in PCa patients, which adds to the advancement of AD. However, lowering acetylcholinesterase activity enhances cancer cell proliferation in PCa patients.<sup>71</sup>



## Current Theragnostic Tools in PCa Treatment

Over the last decade, there have been significant advances in the technology and procedures used to treat prostate cancer (PCa). There is a growing urge to investigate novel techniques for managing this condition, which has led to the incorporation of nanotechnology into PCa prognosis as discussed in Table 2.<sup>72</sup> Given the strong link between PCa and age, there is an urgent need for superior and distinguishable alternatives in PCa detection, diagnosis, and prospective drug delivery systems.<sup>73</sup> Furthermore, these systems must be trustworthy, efficient, and, most crucially, cost-effective, especially given our society's ageing demography. When we talk about novel prognostic strategies, we include approaches for diagnostic tools as well as potential drug compositions related to carrier systems.<sup>74</sup>

There has been much discussion about the careful detection and personalized treatment of high-grade prostate cancer (PCa), and advances in non-invasive methods have led to growing usage. As a result, the convergence of nanotechnology and next-generation biomarkers is driving a new era of more precise and accurate PCa control.<sup>81</sup> The ongoing advancement of nanotechnologies, particularly in the development of innovative nanoparticles and nanomaterials, is poised to increase interest in the clinical application of biomarkers by improving their efficacy and providing deeper insights into their advantages over conventional biomarkers such as prostate-specific antigen (PSA).<sup>82</sup> Researchers and analysts have worked extensively to identify biomarkers with high specificity and sensitivity. Biomarkers such as the TMPRSS-ETS fusion gene, SCHLAP1, and PCA3 were found through extensive PCa profiling (see Table 3). These next-generation markers enable more accurate risk assessment and molecular subtyping, providing valuable molecular insights.<sup>83,84</sup>

The innovative technique stands out for its increased sensitivity and specificity, as well as its outstanding cost-effectiveness, clinical feasibility, and analytical detection capabilities. Notably, the tactics used by this technique do not require any specialized sample preparation, allowing for highly reproducible results.<sup>94</sup> The use of Next-Gen biomarkers in nano diagnostics gives us the ability and effectiveness to identify PCa at an early stage. Early detection and subsequent treatment measures are extremely desirable, especially since both PCa and AD are associated with testosterone levels in the body, which are projected to decrease with age. As a result, Next-Gen biomarkers have tremendous promise for future diagnostic interventions in these illnesses.<sup>95</sup>

**Table 2** Nanotechnology Employed for Biomarkers Detection of Prostate Cancer

Applied Nanotech	Material Type	Biomarker	Limit of Detection	References
Silicon nanowire	Nanomaterial	Prostate serum antigen (PSA) protein	0.9 pg/mL	[75]
Quantum dots	Nanoparticle	PSA protein	0.33 pg/mL	[76]
Carbon nanotubes	Nanomaterial	PSA protein	4 pg/mL	[77]
Iron oxide paramagnetic nanoparticle	Nanoparticle	Entire tumorigenic PCa cell, TMPRSS2-ERG, PCA3 and SCHLAP1 mRNA	ng/mL (protein) 1000 copies (RNA)	[78,79]
Graphene	Nanomaterial	PSA protein	8 pg/mL	[80]

**Table 3** Next-Gen Biomarkers Associated with Prostate Cancer

Biomarkers	Description	Sampling Source	References
TMPRSS2-ETS Fusion	Chromosomal rearrangement of ETS transcription factor and TMPRSS2 gene	Tissue, blood, and urine	[85,86]
AR-V7	Androgen receptor's splice variant lacking binding domain	Blood (CTC)	[87,88]
SCHLAP-I	Long antisense RNA, exceedingly overexpressed in subjects with aggressive PCa	Tissue and urine	[83,89]
PTEN	Regular deletion and mutation of tumour suppressor gene in PCa	Tissue and blood	[90,91]
PCA3	Long antisense RNA, distinctly overexpressed in prostate tissue and PCa	Tissue, blood, and urine	[92,93]

## Discussion

The link between PCa and AD highlights the complexities of their interactions, which are controlled by deep genetic and metabolic mechanisms.<sup>96,97</sup> Attempting to reduce this association to a single biomarker may decrease diagnostic sensitivity and specificity. As a result, a comprehensive set of important biomarkers is required to attain the necessary precision in assessing PCa risk.<sup>98</sup> Emerging insights from next-generation biomarkers imply that early diagnosis has the potential for more successful therapeutic approaches by providing enough time to reduce the probability of developing cognitive dysfunction during the treatment.<sup>99,100</sup> For instance, falling testosterone levels have been demonstrated to reduce one of the key regulators in the pathogenesis of AD, neprilysin (NEP). This suppression lays the groundwork for neurocognitive impairments, impaired brain function, and, ultimately, dementia.<sup>57</sup> Several studies recommend using ADT minimally, aiming to optimize the risk-to-benefit ratio associated with ADT regimes.<sup>101</sup> Additionally, convincing evidence supports the importance of specific lifestyle factors in reducing the negative effects of ADT in PCa patients.<sup>102</sup> Multiple studies have shown that physical activity can help reduce cognitive impairments induced by ADT. These findings highlight the need to take a comprehensive approach to reducing the risk of AD in older men with PCa undergoing ADT. Comprehensive screening, early detection, and lifestyle changes may provide opportunities for minimizing the cognitive risks associated with PCa treatment, ultimately improving the quality of life for those affected.

## Conclusion

In conclusion, the changing landscape of modern medicine has expanded our understanding of the link between dementia and PCa. While ADT remains a key therapeutic method against PCa, its use has a variety of long-term effects, including probable cognition impairment in PCa patients. Androgen suppression in PCa patients has been shown to have a major impact on quality of life.

Several PCa biomarkers have demonstrated sensitivity to changes in testosterone levels, implying their potential relevance in the setting of AD aetiology. Imbalances in androgen levels have a significant impact on the course of AD pathology. As a result, rigorous clinical research is needed to unravel the complex association between dementia and PCa, to gain a thorough understanding of the potential implications of ADT in PCa patients. Existing clinical trials investigating similar indications have highlighted the need for gene-centric research to better understand this nexus. A clearer picture emerges when we focus on the direct link between PCa and AD via ADT. Looking ahead, techniques like personalised medicine show potential for closing the existing gaps in the present ADT therapy regimen. Through continuing research and clinical inquiry, we may try to optimise therapeutic effects while minimising the possible hazards associated with ADT, ultimately improving PCa care and prognosis in older men.

## Abbreviations

Pca, Prostate Cancer; ADT, Androgen Deprived Therapy; AD, Alzheimer's disease; NFT, Neurofibrillary Tangles; A $\beta$ , Amyloid Beta; SNP, Single Nucleotide Polymorphism; ECM, Extra Cellular Matrix; GTPase, Guanosine Diphosphatase; VEGF, Vascular Endothelial, Growth Factor; FGF, Fibroblast Growth Factor; RP, Ribosomal Proteins; NRP, Non-Ribosomal Proteins; miRNA, Micro-RNA; Pri-miRNA, Primary miRNA; HSP, Heat Shock Protein; AR, Androgen Receptor; NEP, Neprilysin; APP, Amyloid Precursor Protein; ACID, Amyloid Precursor Protein Intracellular Domain.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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