УДК 616.65-006:616-006.6 DOI: 10.18699/SSMJ20250502
Обзор литературы / Review article

Targeting the feminized nature of prostate cancer exploring estrogen-driven metabolic reprogramming and its therapeutic intervention: a narrative review

M.M. Akl[1], A. Ahmed[2]

[1] Mansoura University
Egypt, 35516, Mansoura, Elgomhouria st., 25
[2] The Public Health Department, Riyadh First Health Cluster
Saudi Arabia, 13524, Riyadh, King Fahd Rd., 4499

Abstract

Prostate cancer (PCa) has long been classified as an androgen-driven malignancy; however, mounting evidence underscores the pivotal role of estrogen in its initiation, progression, and therapeutic resistance. This review establishes that PCa exhibits intrinsic estrogen dependence through intratumoral aromatization, positioning it within the spectrum of estrogen-driven malignancies. Through integrative molecular analyses, we elucidate how estrogen orchestrates metabolic reprogramming, shifting prostate tumors toward enhanced lipid oxidation and glucose uptake a hallmark of glucolipotoxicity. Mechanistically, estrogen signaling, primarily via the PI3K/AKT pathway, drives the upregulation of carnitine palmitoyltransferase 1 and glucose transporter 1, fueling a metabolic storm characterized by oxidative stress, mitochondrial dysfunction, and chronic inflammatory signaling. This metabolic adaptation enables androgen-independent survival, presenting a critical vulnerability overlooked by conventional androgen-targeted therapies. Our findings necessitate a paradigm shift in the classification and treatment of PCa, advocating for a novel therapeutic framework targeting the estrogen–metabolic axis. We propose a precision strategy integrating aromatase inhibition, estrogen receptor blockade, and metabolic stress modulation to counteract castration-resistant disease. Recognizing PCa as an estrogen-driven, metabolically adaptive malignancy transforms its clinical understanding and therapeutic approach, demanding urgent reconsideration of current oncologic paradigms.

Key words: prostate cancer, estrogen signaling, metabolic reprogramming, glucolipotoxicity, therapeutic resistance.

Conflict of interest. The authors declare no conflict of interest.
Financing. The authors received no financial support for the research and publication of this article.
Correspondence author. Akl M.M., e-mail: maherakl555@gmail.com
Citation. Akl M.M., Ahmed A. Targeting the feminized nature of prostate cancer exploring estrogen-driven metabolic reprogramming and its therapeutic intervention: a narrative review. *Sibirskij nauchnyj medicinskij zhurnal = Siberian Scientific Medical Journal.* 2025;45(5):14–26. [In Russian]. doi: 10.18699/SSMJ20250502

Целевая терапия феминизированной природы рака предстательной железы: изучение эстроген-зависимой метаболической перепрограммировки и ее терапевтического вмешательства: нарративный обзор

М.М. Акль, А. Ахмед

[1] Университет Эль-Мансура
Египет, 35516, г. Эль-Мансура, ул. Эль-Гумхурия, 25
[2] Департамент общественного здравоохранения Первого медицинского объединения Эр-Рияда
Саудовская Аравия, 13524, г. Эр-Рияд, ш. короля Фахда, 4499

Резюме

Рак предстательной железы (РПЖ) традиционно рассматривается как андроген-зависимое злокачественное новообразование. Однако накапливающиеся данные подчеркивают ключевую роль эстрогенов в его инициации, прогрессии и резистентности к терапии. Данный обзор устанавливает, что РПЖ обладает внутренней эстрогеновой зависимостью за счет интраопухолевой ароматизации, что позволяет рассматривать его в спектре эстроген-зависимых новообразований. Путем интегративного молекулярного анализа мы демонстрируем, как эстрогены регулируют метаболическую перепрограммировку, смещая опухоли предстательной железы к усиленному окислению липидов и захвату глюкозы признакам глюколипотоксичности. Механистически эстрогеновая сигнализация, преимущественно через путь PI3K/AKT, способствует повышенной экспрессии карнитинпальмитоилтрансферазы-1 и транспортера глюкозы-1, что запускает метаболическую бурю, характеризующуюся окислительным стрессом, митохондриальной дисфункцией и хроническим воспалительным сигналингом. Эта метаболическая адаптация позволяет опухолевым клеткам выживать независимо от андрогенов, создавая критическую уязвимость, которую игнорируют традиционные методы андроген-таргетной терапии. Наши выводы требуют пересмотра классификации и лечения РПЖ, предлагая новый терапевтический подход, нацеленный на ось «эстроген–метаболизм». Мы предлагаем точечную стратегию, включающую ингибирование ароматазы, блокаду эстрогеновых рецепторов и модуляцию метаболического стресса для борьбы с кастрационно-резистентной формой заболевания. Признание РПЖ как эстроген-зависимой метаболически адаптивной злокачественности изменяет его клиническое понимание и терапевтический подход, требуя срочного пересмотра существующих онкологических парадигм.

Ключевые слова: рак предстательной железы, эстрогеновая сигнализация, метаболическое перепрограммирование, глюколипотоксичность, терапевтическая резистентность.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Автор для переписки. Акль М.М., e-mail: maherakl555@gmail.com

Для цитирования. Акль М.М., Ахмед А. Целевая терапия феминизированной природы рака предстательной железы: изучение эстроген-зависимой метаболической перепрограммировки и ее терапевтического вмешательства: нарративный обзор. *Сиб. науч. мед. ж.* 2025;45(5):14–26. doi: 10.18699/SSMJ20250502

Introduction

Prostate cancer is one of the most prevalent malignancies in men, ranking as the second most diagnosed cancer and a leading cause of cancer-related mortality, with a median age of diagnosis around 66 years [1]. Its pathophysiology is driven by a complex interplay of genetic, hormonal, and immune-mediated mechanisms, primarily through androgen receptor (AR) signaling, which, when dysregulated via genetic mutations, epigenetic modifications, or amplification, leads to uncontrolled proliferation and disease progression [2].

Additionally, key molecular pathways such as PI3K/Akt and TGF-β, alongside immune-suppressive interactions within the tumor microenvironment involving tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells, contribute to tumor immune evasion [3]. The current cornerstone of treatment remains androgen deprivation therapy, achieved through surgical or pharmacological castration to suppress AR activity; however, the inevitable emergence of castration-resistant prostate cancer (CRPC) underscores the need for alternative therapeutic strategies [4]. Growing evidence suggests that estrogenic signaling may play a more significant role in prostate carcinogenesis than previously recognized, particularly through the age-related upregulation of aromatase, an enzyme responsible for converting testosterone into estrogen within the prostate, thereby shifting the androgen-to-estrogen balance in favor of tumor-promoting estrogen receptor (ER)-mediated pathways [5]. While ERα activation has been associated with proliferative and inflammatory responses, ERβ appears to exert tumor-suppressive effects, highlighting the complexity of estrogen's role in prostate cancer progression [6]. This review proposes a paradigm shift in the understanding of prostate cancer by redefining it as an estrogen-driven malignancy, akin to hormone receptor-positive female cancers such as breast and endometrial cancer, which could open new therapeutic avenues such as selective estrogen receptor modulators and aromatase inhibitors. By challenging the traditional androgen-centric model, this perspective aims to enhance our understanding of prostate cancer pathogenesis and introduce novel treatment strategies that could improve patient outcomes.

Material and methods

A comprehensive narrative review was conducted to explore the estrogen-driven metabolic reprogramming of prostate cancer and its therapeutic

implications. A systematic literature search was performed using PubMed, Scopus, and Web of Science databases, incorporating Medical Subject Headings (MeSH) terms and free-text keywords such as "Estrogen Signaling in Prostate Cancer," "Aromatase and Prostate Tumorigenesis," "Metabolic Reprogramming in Hormone-Driven Malignancies," "Glucolipotoxicity in Cancer Progression," and "Targeting the Estrogen Metabolic Axis in Castration-Resistant Prostate Cancer." Boolean operators (AND/OR) were applied to optimize sensitivity and specificity. The review included peer-reviewed studies published in English from 1995 to 2024, spanning clinical, preclinical, and mechanistic research on estrogen signaling, metabolic dysregulation, and therapeutic strategies targeting the estrogen–metabolic axis in prostate cancer. Reference lists of key articles were manually screened to identify additional relevant publications. Studies were selected based on their investigation of intratumoral aromatization, ER signaling, metabolic alterations, and therapeutic resistance mechanisms in prostate cancer.

Exclusion criteria included non-English studies, case reports with limited statistical power, articles without full-text availability, and studies lacking direct relevance to estrogen-mediated metabolic reprogramming. The selection process followed a two-stage screening approach, initially retrieving 823 studies, with 215 duplicates removed. Title and abstract screening excluded 392 studies based on irrelevance, leaving 216 for full-text review. Among these, 90 studies were included for qualitative synthesis, focusing on estrogen-driven lipid and glucose metabolism, oxidative stress, and the oncogenic implications of metabolic adaptation in prostate cancer.

Quality assessment was conducted using the SANRA (Scale for the Assessment of Narrative Review Articles) checklist, evaluating six domains: justification of the review, clarity of objectives, literature search methodology, inclusion of primary references, evidence-based reasoning, and data synthesis. Studies scoring ≥9/12 were considered methodologically rigorous. Although this review does not present direct experimental data, it synthesizes preclinical and clinical evidence to assess the role of estrogen-induced metabolic reprogramming in prostate cancer progression and resistance. The analysis integrates findings on PI3K/AKT-mediated lipid oxidation, GLUT1-driven glucose uptake, reactive oxygen species (ROS)-mediated oxidative stress, and therapeutic interventions such as aromatase inhibitors, estrogen receptor modulators, and metabolic stress regulators. This framework establishes a foundation for future translational research and targeted therapeutic strategies against estrogen-driven prostate cancer.

The role of aromatase in prostate cancer

Mechanism of aromatase enzyme and the conversion of testosterone to estrogen

Aromatase, encoded by the CYP19A1 gene, is a cytochrome P450 enzyme complex responsible for the biosynthesis of estrogens through the aromatization of androgens. This enzymatic reaction occurs in the smooth endoplasmic reticulum of cells and involves the conversion of testosterone into estradiol and androstenedione into estrone via a three-step oxidative process. Aromatase catalyzes the removal of the C19 methyl group from androgens, introducing an aromatic ring into the steroid structure. This reaction is facilitated by molecular oxygen and NADPH-cytochrome P450 reductase, which provides the necessary electrons for the oxidative conversion. The enzymatic activity of aromatase is tightly regulated by several factors, including tissue-specific promoters, transcriptional regulators, and inflammatory cytokines such as IL-6 and TNF-α, which can enhance aromatase expression through activation of the PI3K/Akt and NF-κB pathways. In prostate tissue, increased aromatase expression leads to a local rise in estrogen levels, influencing cellular proliferation, differentiation, and tumor progression via ER-mediated signaling cascades [7].

Age-related changes in aromatase activity in men

Aging is associated with a shift in steroid hormone metabolism, with a progressive increase in aromatase activity observed in peripheral tissues, including adipose tissue and the prostate. This upregulation is partly driven by epigenetic modifications in the CYP19A1 gene and enhanced inflammatory signaling, particularly through IL-1β and COX-2-mediated pathways [7, 8]. The increased expression of aromatase in the prostate microenvironment contributes to a higher local estrogen-to-androgen ratio, altering the hormonal milieu that regulates prostate homeostasis [9]. Additionally, senescence-associated secretory phenotype factors, such as TGF-β and IL-8, promote aromatase activity, further amplifying estrogen biosynthesis [10]. The interplay between these inflammatory and hormonal changes establishes a permissive environment for estrogen-driven oncogenic signaling, facilitating prostate epithelial cell proliferation, genomic instability, and increased susceptibility to malignant transformation.

Hormonal changes in aging men

With advancing age, men experience a gradual decline in circulating testosterone levels, a phenomenon referred to as andropause. This decline is attributed to reduced Leydig cell

function, decreased hypothalamic gonadotropin-releasing hormone secretion, and increased activity of sex hormone-binding globulin, which lowers bioavailable testosterone [10, 11]. Concurrently, estradiol levels remain stable or even increase due to heightened aromatization of residual androgens. The altered androgen-to-estrogen ratio affects prostate physiology by modulating ER signaling pathways. ERα activation has been implicated in pro-proliferative and pro-inflammatory responses, while ERβ exerts tumor-suppressive effects [12]. However, in aging prostate tissue, the ERα:ERβ ratio becomes skewed in favor of ERα, leading to increased proliferation, inflammation, and a greater predisposition to neoplastic transformation [13]. This hormonal imbalance also influences stromal-epithelial interactions, promoting fibroblast-to-myofibroblast differentiation via TGF-β1 signaling, contributing to a desmoplastic tumor microenvironment [14].

Declining testosterone and rising estrogen: impact on prostate health and aberrant cell growth

Testosterone exerts a regulatory effect on prostate epithelial cell differentiation and apoptosis through AR-dependent transcriptional programs, including modulation of genes such as *NKX3-1* and *PTEN* [15]. With age-related testosterone decline and compensatory estrogen elevation, these protective androgen-mediated effects are diminished. Elevated estrogen levels, particularly through ERα activation, stimulate mitogenic pathways such as MAPK/ERK and JAK/STAT, leading to increased cell proliferation and survival [16]. Additionally, estrogen promotes oxidative stress by inducing NADPH oxidase (NOX) activity, generating ROS that cause DNA damage and chromosomal instability [17]. Estrogenic signaling also modulates epithelial-mesenchymal transition through upregulation of Snail and Twist transcription factors, facilitating tumor invasiveness and progression to CRPC [18]. The chronic exposure of prostate cells to elevated estrogen levels further disrupts epigenetic regulation, including hypermethylation of tumor suppressor genes and histone modifications that promote oncogenic gene expression [19].

Clinical and epidemiological evidence supporting the role of aromatase in prostate cancer

Epidemiological studies have demonstrated a strong correlation between obesity a condition associated with increased aromatase activity and elevated prostate cancer risk. Adipose tissue, particularly visceral fat, serves as a major site of extragonadal estrogen synthesis, where pro-inflammatory adipokines such as leptin and IL-6 enhance aromatase transcription via the STAT3 and NF-κB pathways [20]. This metabolic-inflammatory axis leads to increased estrogen bioavailability and sustained ERα-driven oncogenic signaling within the prostate [21]. Clinical studies have shown that men with higher estradiol-to-testosterone ratios exhibit increased prostate cancer incidence and more aggressive tumor phenotypes, reinforcing the concept of estrogen-mediated Tumorigenesis [22, 23]. Moreover, pharmacological inhibition of aromatase with agents such as anastrozole has been associated with reduced prostate cancer cell proliferation and delayed disease progression in preclinical models [24, 25].

Expression of ERα and ERβ in prostate cancer subtypes

The presence of ERα and ERβ in prostate cancer cells provides further molecular evidence of estrogen's role in disease progression. ERα is predominantly expressed in basal and luminal epithelial cells, where its activation promotes cyclin D1-mediated cell cycle progression and suppresses apoptotic pathways via Bcl-2 upregulation [26]. In contrast, ERβ, which is generally associated with tumor suppression, undergoes downregulation in high-grade prostate cancer due to promoter hypermethylation and chromatin remodeling. This shift towards ERα-dominant signaling enhances tumor growth, angiogenesis, and resistance to apoptosis. Functional studies have demonstrated that ERα antagonism or selective ERβ activation can inhibit prostate cancer cell proliferation and restore apoptotic sensitivity, suggesting a potential therapeutic approach targeting estrogen signaling [27].

Chronic estrogen exposure and cellular transformations in the prostate

Prolonged estrogen exposure exerts profound effects on prostate epithelial homeostasis, leading to phenotypic alterations that predispose cells to malignant transformation. Chronic estrogenic stimulation disrupts normal differentiation programs by modulating Wnt/β-catenin and Hedgehog signaling pathways, resulting in the expansion of progenitor-like cell populations with enhanced self-renewal capacity [28]. Additionally, estrogen-induced DNA damage through activation of AID/APOBEC cytidine deaminases generates mutational burdens characteristic of aggressive prostate cancers [29]. The estrogen-driven inflammatory microenvironment further promotes tumorigenesis by recruiting immunosuppressive myeloid cells and inhibiting cytotoxic T-cell responses, creating an immune-privileged niche that facilitates tumor progression

[30]. Clinical evidence from hormone replacement therapy studies in aging men has shown that prolonged exposure to exogenous estrogens increases prostate cancer risk, underscoring the oncogenic potential of estrogenic signaling in this disease [31].

Molecular mechanisms of estrogen-induced prostate carcinogenesis

Estrogen-induced cell proliferation via ER

Estrogen stimulates prostate cancer cell proliferation primarily through its interaction with ER, particularly ERα and ERβ. ERα, encoded by ESR1, is highly expressed in stromal and luminal prostate epithelial cells and promotes oncogenic signaling when activated by estradiol [32]. Upon ligand binding, ERα undergoes conformational changes that enable dimerization and nuclear translocation, where it binds to estrogen response elements in the promoter regions of target genes [33]. This leads to the transcriptional activation of mitogenic genes such as *CCND1* (cyclin D1), *MYC*, and *BCL2*, facilitating cell cycle progression and inhibiting apoptosis [34]. Additionally, estrogen-activated ERα triggers extranuclear signaling cascades, including the PI3K/Akt and MAPK/ERK pathways, which further enhance cell survival and proliferation. ERβ, encoded by ESR2, exerts opposing effects by activating tumor suppressor pathways, such as p21 and PTEN, leading to growth inhibition and increased apoptosis [35]. However, in prostate cancer, ERβ expression is often downregulated due to promoter hypermethylation, shifting the ERα:ERβ balance toward a pro-tumorigenic phenotype [36].

Comparison with breast cancer: er signaling pathways in hormone-driven malignancies

While both prostate and breast cancers share hormone-dependent growth mechanisms, their estrogen signaling pathways exhibit distinct tissue-specific variations. In breast cancer, ERα signaling is the predominant driver of tumorigenesis, with estrogen serving as the primary mitogenic hormone [37]. Similar to prostate cancer, ERα activation in breast epithelial cells leads to increased cyclin D1 expression and enhanced cell proliferation via MAPK and PI3K/Akt signaling [38]. However, breast cancer cells exhibit a higher dependency on estrogen-driven transcriptional programs, including FOXA1-mediated chromatin remodeling, which facilitates ERα binding to oncogenic enhancers [39]. Conversely, prostate cancer cells rely on a complex interplay between estrogen and AR signaling [40]. Estrogen can crosstalk with AR pathways through ERα-mediated activation of Src kinase and subsequent phosphorylation of AR, enhancing its transcriptional activity even in low androgen conditions [41]. This crosstalk contributes to CRPC, where estrogen-driven pathways compensate for androgen deprivation, sustaining tumor growth [42].

ERα and ERβ: differential effects on prostate cancer progression

ERα and ERβ exert distinct effects on prostate cancer progression, largely due to their differential gene regulatory functions. ERα promotes tumorigenesis by enhancing cell proliferation, survival, and angiogenesis [43]. It activates STAT3 and NF-κB signaling, which upregulate pro-inflammatory cytokines such as IL-6 and TNF-α, creating a tumor-promoting microenvironment [44]. In contrast, ERβ activation has been shown to inhibit epithelial-mesenchymal transition and suppress tumor invasion by downregulating Snail and Twist, key transcription factors involved in metastatic progression [45]. Furthermore, ERβ can antagonize ERα-driven oncogenic signaling by recruiting corepressors such as NCOR1, limiting ERα-mediated gene transcription [46]. Loss of ERβ expression in advanced prostate cancer stages removes this protective effect, allowing unopposed ERα activity to drive aggressive tumor behavior [47].

Oxidative stress and ROS in estrogen-induced carcinogenesis

Estrogen contributes to oxidative stress in prostate cancer through multiple mechanisms, including mitochondrial dysfunction and NOX activation [48]. Estrogen metabolism generates catechol estrogen intermediates, such as 4-hydroxyestradiol (4-OHE2), which undergo redox cycling and produce ROS [49]. These ROS include superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), which cause oxidative DNA damage and disrupt cellular homeostasis [50]. In addition, ERα activation enhances NOX1 and NOX4 expression, leading to sustained ROS production in prostate epithelial cells [51]. Excessive ROS accumulation results in lipid peroxidation, protein oxidation, and activation of redox-sensitive transcription factors such as HIF-1α and NF-κB, which promote angiogenesis and inflammatory signaling [52]. The oxidative stress induced by estrogen not only contributes to genomic instability but also enhances the survival of cancer cells by upregulating antioxidant defense mechanisms such as manganese superoxide dismutase and glutathione peroxidase 1, which mitigate ROS-induced apoptosis [53].

Mechanisms of estrogen-driven free radical generation

Estrogen enhances free radical production primarily through its metabolic conversion into

genotoxic quinones. The cytochrome P450 enzymes CYP1A1 and CYP1B1 catalyze the oxidation of estradiol into 4-hydroxyestradiol, which undergoes auto-oxidation to form semiquinones and quinones [54]. These estrogen-derived quinones can react with DNA, forming stable adducts that lead to base modifications and strand breaks [55]. Additionally, quinones undergo redox cycling with glutathione, leading to depletion of cellular antioxidant reserves and amplifying oxidative stress [56]. In prostate cancer cells, this estrogen-induced ROS production triggers a DNA damage response mediated by ATM and ATR kinases, activating downstream effectors such as p53 and CHK1 [57]. However, chronic estrogen exposure can lead to p53 inactivation via MDM2-mediated degradation, allowing cells to bypass cell cycle arrest and accumulate mutations that drive tumor progression [58].

DNA damage and mutational landscape in estrogen-driven prostate cancer

Estrogen-induced oxidative stress contributes to genomic instability by generating DNA lesions, including 8-oxo-dG adducts, double-strand breaks, and crosslinks. ROS-mediated damage activates base excision repair and homologous recombination pathways; however, prolonged estrogen exposure can overwhelm these repair mechanisms, leading to error-prone repair via non-homologous end joining [59]. This results in the accumulation of chromosomal aberrations, such as deletions in tumor suppressor genes like *PTEN* and *RB1*, and amplifications of oncogenes such as *MYC* [60]. Whole-genome sequencing studies of prostate tumors have revealed an enrichment of C>T transitions at CpG dinucleotides, a mutational signature associated with estrogen metabolism and oxidative stress. These mutations contribute to clonal expansion and increased tumor heterogeneity, driving disease progression [61].

Immunomodulatory effects of estrogen in the prostate

Estrogen modulates the immune landscape of the prostate by influencing both innate and adaptive immune responses. ERα activation in tumor-associated macrophages promotes an M2-like phenotype characterized by upregulation of IL-10, TGF-β, and arginase-1, which suppress cytotoxic T-cell responses and enhance immune evasion [62]. Additionally, estrogen signaling in dendritic cells reduces antigen presentation by downregulating MHC class II molecules, impairing T-cell activation. In prostate cancer, estrogen-driven immunosuppression is further reinforced by increased regulatory T-cell infiltration, mediated by CCL22 and CXCL12 chemokine signaling. This immunosuppressive microenvironment allows prostate tumors to evade immune surveillance and promotes sustained tumor growth [62-63].

Estrogen's role in chronic inflammation and tumor microenvironment remodeling

Chronic estrogen exposure induces a persistent inflammatory state in the prostate, contributing to tumor initiation and progression. Estrogen promotes NF-κB activation, leading to increased secretion of pro-inflammatory cytokines such as IL-6, IL-8, and COX-2-derived prostaglandins [64]. These factors stimulate fibroblast proliferation and extracellular matrix remodeling, creating a fibrotic tumor microenvironment that supports angiogenesis and immune evasion [65]. Additionally, estrogen enhances the recruitment of cancer-associated fibroblasts through TGF-β1 signaling, which increases collagen deposition and tissue stiffness. The altered biomechanical properties of the prostate stroma facilitate tumor invasion and metastasis by activating integrin-mediated mechanotransduction pathways [66].

Impact of estrogen on the tumor microenvironment

Estrogen-driven changes in the tumor microenvironment support prostate cancer progression through multiple mechanisms, including angiogenesis, immune modulation, and metabolic reprogramming. ERα activation upregulates VEGF expression, promoting neovascularization and increased tumor perfusion [67]. Additionally, estrogen enhances glucose metabolism in prostate cancer cells by upregulating GLUT1 and HK2, leading to a glycolytic phenotype similar to the Warburg effect observed in breast cancer [68]. This metabolic shift supports rapid cell proliferation and resistance to apoptosis. Furthermore, estrogen alters the lipid composition of the tumor microenvironment by stimulating SREBP1-mediated lipid biosynthesis, creating a pro-survival lipid-rich environment that facilitates cancer cell adaptation to hypoxic and nutrient-deprived conditions [69].

Clinical and experimental evidence

Clinical and experimental research has increasingly implicated estrogenic signaling in prostate carcinogenesis, challenging the conventional androgen-driven paradigm. Clinical studies have investigated the correlation between circulating estrogen levels and prostate cancer incidence, revealing that men with elevated estrogen-to-androgen ratios, particularly in aging populations,

exhibit a higher predisposition to aggressive prostate malignancies [70]. Large-scale epidemiological analyses have demonstrated that increased estradiol levels are associated with high-grade prostate tumors, with a significant correlation between elevated intraprostatic estrogen concentrations and disease progression [71]. Furthermore, studies on patients undergoing androgen deprivation therapy indicate that the subsequent rise in systemic estrogens may paradoxically promote tumor adaptation and resistance mechanisms [72].

The therapeutic implications of aromatase inhibitors, which block the enzymatic conversion of testosterone to estrogen, provide further clinical insights into the role of estrogen in prostate cancer [73]. Some retrospective analyses suggest that aromatase inhibitor administration may reduce prostate cancer incidence and slow disease progression, particularly in cases exhibiting high intratumoral aromatase expression [74]. However, clinical trials investigating the efficacy of aromatase inhibitors as a primary or adjunctive treatment remain inconclusive, warranting further controlled studies to delineate patient subgroups that may benefit from estrogen-targeted interventions [75].

Experimental animal models have provided compelling evidence for the oncogenic role of estrogen in prostate carcinogenesis [76]. Rodent models exposed to chronic estrogen stimulation, particularly in combination with androgen deprivation, exhibit hyperplastic and neoplastic transformations in the prostate epithelium [76, 77]. Mechanistic studies reveal that estrogen exposure induces genomic instability through oxidative DNA damage, promotes inflammatory microenvironments via cytokine dysregulation, and alters epithelial-mesenchymal transition pathways, leading to enhanced tumor invasiveness [78]. Additionally, the differential activation of ERα and ERβ in animal models further supports the hypothesis that ERα promotes pro-tumorigenic signaling, whereas ERβ exerts protective effects [79, 80].

Therapeutic applications based on estrogen-driven prostate carcinogenesis

Emerging evidence highlights the significant role of estrogenic signaling in prostate cancer progression, necessitating therapeutic strategies that directly target estrogen synthesis, receptor activation, and associated metabolic stress. Based on the molecular mechanisms underpinning estrogen-induced prostate carcinogenesis, a combination of anastrozole (aromatase inhibitor), raloxifene (selective estrogen receptor modulator), and metformin (metabolic stress modulator) presents a promising therapeutic paradigm aimed at mitigating the oncogenic effects of estrogen within the prostate microenvironment.

Aromatase inhibition via anastrozole

Anastrozole, a potent non-steroidal aromatase inhibitor, blocks the enzymatic conversion of testosterone to estradiol, thereby reducing intraprostatic estrogen levels [81]. Studies have demonstrated that prostate tumors exhibit aberrant aromatase expression, particularly in obese patients with elevated adipose-derived estrogen production [82, 83]. Inhibition of aromatase activity effectively suppresses estrogen-mediated activation of ERα and ERβ, preventing downstream oncogenic pathways such as PI3K/AKT and MAPK signaling, both of which are implicated in enhanced cell proliferation and survival [84]. Experimental models show that anastrozole treatment reduces tumor burden, induces apoptosis, and attenuates epithelial-mesenchymal transition, a critical step in metastatic progression [85].

Estrogen receptor modulation via raloxifene

Beyond estrogen synthesis inhibition, direct modulation of ER activity is crucial for effectively neutralizing estrogen-driven oncogenesis. Raloxifene, a selective estrogen receptor modulator, exerts antagonistic effects on ERα, the receptor subtype predominantly implicated in prostate cancer proliferation [86]. Unlike classical anti-androgen therapies, which indirectly influence estrogenic activity, raloxifene directly blocks estrogen-induced transcriptional activation of oncogenic targets such as cyclin D1 and Bcl-2, reducing cellular proliferation and enhancing apoptotic responses. Moreover, preclinical studies indicate that raloxifene promotes tumor regression in ER-positive prostate cancer models, highlighting its potential as a precision therapy in molecularly stratified patient cohorts [87].

Metformin as a metabolic and redox regulator

Estrogen-driven carcinogenesis is closely linked to oxidative stress and metabolic dysregulation, as evidenced by the increased generation of ROS in estrogen-exposed prostate cells. Metformin, an AMP-activated protein kinase activator, mitigates ROS-induced DNA damage, thereby reducing mutational burden and preventing malignant transformation. Additionally, metformin downregulates mTOR signaling, a pathway frequently activated by estrogenic stimulation, leading to a marked reduction in glycolytic flux and ATP production, effectively starving tumor cells of essential metabolic substrates [88]. Clinical and epidemiological data further support the anticancer effects of metformin, showing

that diabetic patients on metformin therapy exhibit a significantly lower incidence of aggressive prostate cancer, reinforcing its role as a metabolic adjuvant in estrogen-targeted therapy [89]. The tripartite combination of anastrozole, raloxifene, and metformin offers a multifaceted approach to disrupting estrogen-driven prostate tumorigenesis. Anastrozole curtails estrogen biosynthesis at its source, raloxifene blocks estrogenic activation at the receptor level, and metformin counteracts estrogen-induced metabolic and oxidative stress, collectively exerting synergistic anti-tumor effects. This strategy is particularly advantageous in patient subgroups with high intraprostatic estrogen levels, including elderly men and those with metabolic syndrome, where traditional androgen-centric therapies may be suboptimal.

Discussion

Prostate cancer has traditionally been classified as an androgen-driven malignancy; however, emerging evidence challenges this paradigm by demonstrating a significant role for estrogenic signaling in its pathogenesis, progression, and therapeutic resistance. This manuscript establishes that prostate cancer exhibits a fundamental dependency on estrogen through intratumoral aromatization, a process by which androgens are converted into estrogens via the enzyme aromatase. This finding positions prostate cancer within the broader spectrum of hormonally regulated malignancies, drawing parallels with estrogen-driven cancers such as breast and endometrial carcinomas. The ability of prostate tumors to synthesize and respond to estrogen suggests a need for reclassification, acknowledging its dependency on a hormone traditionally associated with female malignancies. This shift in perspective not only refines our understanding of prostate cancer biology but also exposes novel therapeutic vulnerabilities that have remained largely unexplored due to the prevailing androgen-centric view.

Estrogen exerts its oncogenic influence in prostate cancer through both genomic and non-genomic mechanisms, activating key signaling pathways that drive tumor survival, proliferation, and metabolic adaptation. At the genomic level, ERα activation promotes transcriptional programs favoring cell cycle progression, anti-apoptotic signaling, and metabolic reprogramming. Conversely, ERβ exhibits context-dependent effects, with some studies suggesting tumor-suppressive functions, while others indicate oncogenic roles under specific microenvironmental conditions. The non-genomic actions of estrogen, mediated through PI3K/AKT and MAPK signaling, further reinforce its role in sustaining prostate tumor viability, particularly in CRPC, where androgen signaling is no longer the dominant driver.

A critical but often overlooked consequence of estrogenic activation in prostate cancer is its profound effect on cellular metabolism. This manuscript integrates these molecular insights with the glucolipotoxicity hypothesis, establishing a mechanistic link between estrogen signaling and the metabolic shifts that underpin tumor progression and therapeutic resistance. The metabolic landscape of prostate cancer is characterized by an enhanced reliance on both lipid oxidation and glucose metabolism, a hallmark of tumors that have evolved mechanisms to sustain energy production under conditions of androgen deprivation.

This metabolic plasticity allows prostate cancer cells to circumvent the energetic constraints imposed by androgen-targeted therapies, ensuring continued proliferation and survival [90]. Recent genomic and metabolic profiling studies support this notion by demonstrating that advanced prostate cancer exhibits a preferential reliance on lipid metabolism over androgen-driven pathways. Notably, androgen-resistant prostate tumors have been shown to upregulate key enzymes involved in fatty acid oxidation, including CPT1, the rate-limiting enzyme responsible for shuttling long-chain fatty acids into mitochondria for beta-oxidation. The overexpression of CPT1 in castration-resistant tumors highlights the metabolic shift that enables these cells to utilize lipids as a primary energy source, compensating for the loss of androgenic stimulation. Estrogen signaling further amplifies this metabolic adaptation by enhancing CPT1 expression via PI3K/AKT activation, reinforcing fatty acid oxidation as a central metabolic pathway in aggressive prostate cancer phenotypes.

In parallel, estrogen upregulates GLUT1, facilitating increased glucose uptake and utilization. This metabolic rewiring aligns with the glucolipotoxicity hypothesis, wherein chronic exposure to excessive lipids and glucose leads to cellular stress, mitochondrial dysfunction, and an inflammatory microenvironment that drives tumor aggressiveness. The simultaneous elevation of lipid oxidation and glycolysis generates a metabolic storm, characterized by heightened ROS production, lipid peroxidation, and endoplasmic reticulum stress. These stressors not only fuel tumor progression but also contribute to the development of resistance to standard therapies, including AR-targeted agents.

Moreover, the failure of androgen deprivation therapy in a subset of prostate cancers further supports the notion that estrogenic and metabolic pathways serve as adaptive escape mechanisms, allowing tumor cells to bypass androgen dependency. The upregulation of

intratumoral aromatase in androgen-deprived tumors facilitates local estrogen biosynthesis, perpetuating ERα-driven oncogenesis even in the absence of androgens. This adaptive resistance mirrors the metabolic dysfunction observed in type 2 diabetes, where chronic glucolipotoxicity disrupts cellular homeostasis, precipitating oxidative stress and impairing metabolic regulation. In prostate cancer, estrogen exacerbates this metabolic dysfunction by intensifying lipid peroxidation and ROS production, thereby fostering an environment conducive to tumor progression. Given the intricate interplay between estrogen signaling, metabolic dysregulation, and therapeutic resistance, a reclassification of prostate cancer based on estrogenic and metabolic signatures is warranted. Current evidence suggests that targeting estrogen-driven metabolic reprogramming could provide a novel therapeutic avenue, particularly in CRPC and treatment-resistant cases.

A multi-pronged approach combining aromatase inhibition, estrogen receptor modulation, and metabolic intervention represents a rational therapeutic strategy: aromatase inhibitors (e.g., anastrozole) – by suppressing intratumoral estrogen synthesis, these agents prevent ERα-mediated oncogenesis, disrupting a key driver of tumor progression; selective estrogen receptor modulators (e.g., raloxifene) – by antagonizing ERα signaling, these compounds block downstream proliferative and survival pathways, effectively inhibiting estrogen-driven oncogenic programs; metabolic stress regulators (e.g., metformin) – by mitigating glucolipotoxic stress, metformin modulates AMP-activated protein kinase activity, suppresses mTOR signaling, and reduces ROS production, thereby restoring metabolic homeostasis and enhancing therapeutic efficacy. By simultaneously targeting estrogen synthesis, receptor activation, and metabolic adaptation, this approach addresses the root cause of therapy resistance, offering a paradigm shift in prostate cancer management. The recognition of prostate cancer as a metabolically adaptive, estrogen-influenced malignancy necessitates a revision of current therapeutic frameworks, emphasizing estrogen blockade and metabolic intervention as critical components of precision oncology.

Conclusion

Prostate cancer should no longer be viewed solely through an androgen-centric lens but rather as an estrogen-driven malignancy with a metabolic survival advantage. The convergence of estrogen signaling and metabolic dysregulation, as demonstrated in this study, necessitates a fundamental reclassification of prostate cancer based on estrogenic dependency and metabolic phenotype. By targeting this oncogenic axis, a paradigm shift in prostate cancer therapy can be realized one that moves beyond androgen deprivation toward a more precise and effective treatment strategy that directly disrupts the tumor's survival mechanisms.

Acknowledgments

I extend my deepest gratitude to all warriors of disease across the globe, whose resilience inspires every scientific effort to enhance their quality of life. I dedicate this work to my mother, whose boundless support has been my strength, and to my life partner, whose encouragement, pride, and unwavering belief in my potential have fueled my journey, even when the true value of my contributions was yet unseen. Together, you have given me the courage to pursue knowledge relentlessly, with the hope of crafting solutions that may one day bring comfort and healing to those who need it most.

References

1. Rawla P. Epidemiology of prostate cancer. *World J. Oncol*. 2019;10(2):63–89. doi: 10.14740/wjon1191

2. Koochekpour S. Androgen receptor signaling and mutations in prostate cancer. *Asian J. Androl*. 2010;12(5):639–657. doi: 10.1038/aja.2010.89

3. Chen L., Xu Y.X., Wang Y.S., Ren Y.Y., Dong X.M., Wu P., Xie T., Zhang Q., Zhou J.L. Prostate cancer microenvironment: multidimensional regulation of immune cells, vascular system, stromal cells, and microbiota. *Mol. cancer.* 2024;23(1):229. doi: 10.1186/s12943-024-02137-1

4. Polotti C.F., Kim C.J., Chuchvara N., Polotti A.B., Singer E.A., Elsamra S. Androgen deprivation therapy for the treatment of prostate cancer: a focus on pharmacokinetics. *Expert, Opin, Drug Metab, Toxicol*. 2017;13(12):1265–1273. doi: 10.1080/17425255.2017.1405934

5. Nicholson T.M., Ricke W.A. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. *Differentiation*. 2011;82(4-5):184–199. doi: 10.1016/j.diff.2011.04.006

6. Belluti S., Imbriano C., Casarini L. Nuclear estrogen receptors in prostate cancer: From genes to function. *Cancers (Basel)*. 2023;15(18):4653. doi: 10.3390/cancers15184653

7. di Nardo G., Zhang C., Marcelli A.G., Gilardi G. Molecular and structural evolution of cytochrome P450 aromatase. *Int. J. Mol. Sci*. 2021;22(2):631. doi: 10.3390/ijms22020631

8. Maharjan C.K., Mo J., Wang L., Kim M.C., Wang S., Borcherding N., Vikas P., Zhang W. Natural and synthetic estrogens in chronic inflammation and

breast cancer. *Cancers (Basel)*. 2021;14(1):206. doi: 10.3390/cancers14010206

9. Ellem S.J., Risbridger G.P. Aromatase and regulating the estrogen:androgen ratio in the prostate gland. *J. Steroid Biochem. Mol. Biol*. 2010;118(4-5):246–251. doi: 10.1016/j.jsbmb.2009.10.015

10. Coppé J.P., Desprez P.Y., Krtolic A., Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu. Rev. Pathol*. 2010;5:99–118. doi: 10.1146/annurev-pathol-121808-102144

11. Golan R., Scovell J.M., Ramasamy R. Age-related testosterone decline is due to waning of both testicular and hypothalamic-pituitary function. *Aging Male*. 2015;18(3):201–204. doi: 10.3109/13685538.2015.1052392

12. Belluti S., Imbriano C., Casarini L. Nuclear estrogen receptors in prostate cancer: from genes to function. *Cancers (Basel)*. 2023;15(18):4653. doi: 10.3390/cancers15184653

13. Pepe G., Locati M., Della Torre S., Mornata F., Cignarella A., Maggi A., Vegeto E. The estrogen–macrophage interplay in the homeostasis of the female reproductive tract. *Hum. Reprod. Update*. 2018;24(6):652–672. doi: 10.1093/humupd/dmy026

14. Kim K.K., Sheppard D., Chapman H.A. TGF-β1 signaling and tissue fibrosis. *Cold Spring Harb. Perspect. Biol*. 2018;10(4):a022293. doi: 10.1101/cshperspect.a022293

15. Tan P.Y., Chang C.W., Chng K.R., Wansa K.D., Sung W.K., Cheung E. Integration of regulatory networks by NKX3-1 promotes androgen-dependent prostate cancer survival. *Mol. Cell. Biol*. 2012;32(2):399–414. doi: 10.1128/MCB.05958-11

16. Chimento A., de Luca A., Avena P., de Amicis F., Casaburi I., Sirianni R., Pezzi V. Estrogen receptors-mediated apoptosis in hormone-dependent cancers. *Int. J. Mol. Sci.* 2022;23(3):1242. doi: 10.3390/ijms23031242

17. Vermot A., Petit-Härtlein I., Smith S.M.E., Fieschi F. NADPH oxidases (NOX): an overview from discovery, molecular mechanisms to physiology and pathology. *Antioxidants*. 2021;10(6):890. doi: 10.3390/antiox10060890

18. di Zazzo E., Galasso G., Giovannelli P., di Donato M., Bilancio A., Perillo B., Sinisi A.A., Migliaccio A., Castoria G. Estrogen receptors in epithelial-mesenchymal transition of prostate cancer. *Cancers (Basel)*. 2019;11(10):1418. doi: 10.3390/cancers11101418

19. Chin S.P., Dickinson J.L., Holloway A.F. Epigenetic regulation of prostate cancer. *Clin. Epigenetics*. 2011;2(2):151–169. doi: 10.1007/s13148-011-0041-7

20. Mair K.M., Gaw R., MacLean M.R. Obesity, estrogens and adipose tissue dysfunction – implications for pulmonary arterial hypertension. *Pulm. Circ*. 2020;10(3):2045894020952019. doi: 10.1177/2045894020952023

21. Prins G.S., Korach K.S. The role of estrogens and estrogen receptors in normal prostate growth and disease. *Steroids*. 2008;73(3):233–244. doi: 10.1016/j.steroids.2007.10.013.

22. Nelles J.L., Hu W.Y., Prins G.S. Estrogen action and prostate cancer. *Expert. Rev. Endocrinol. Metab*. 2011;6(3):437–451. doi: 10.1586/eem.11.20

23. di Zazzo E., Galasso G., Giovannelli P., di Donato M., di Santi A., Cernera G., Rossi V., Abbondanza C., Moncharmont B., Sinisi A.A., Castoria. G., Migliaccio A. Prostate cancer stem cells: the role of androgen and estrogen receptors. *Oncotarget*. 2016;7(1):193–208. doi: 10.18632/oncotarget.6220

24. Santen R.J., Petroni G.R., Fisch M.J., Myers C.E., Theodorescu D., Cohen R.B. Use of the aromatase inhibitor anastrozole in the treatment of patients with advanced prostate carcinoma. *Cancer*. 2001;92(8):2095–2101. doi: 002/1097-0142(20011015)92:8<2095::aid-cncr1550>3.0.co;2-y

25. Bayala B., Zoure A.A., Baron S., de Joussineau C., Simpore J., Lobaccaro J.M.A. Pharmacological modulation of steroid activity in hormone-dependent breast and prostate cancers: effect of some plant extract derivatives. *Int. J. Mol. Sci*. 2020;21(10):3690. doi: 10.3390/ijms21103690

26. Zhou Z., Qiao J.X., Shetty A., Wu G., Huang Y., Davidson N.E., Wan Y. Regulation of estrogen receptor signaling in breast carcinogenesis and breast cancer therapy. *Cell. Mol. Life Sci*. 2014;71(8):1549. doi: 10.1007/s00018-013-1376-3

27. Brait M., Banerjee M., Maldonado L., Ooki A., Loyo M., Guida E., Izumchenko E., Mangold L., Humphreys E., Rosenbaum E., … Hoque M.O. Promoter methylation of MCAM, ERα and ERβ in serum of early stage prostate cancer patients. *Oncotarget*. 2017;8(9):15431–15440. doi: 10.18632/oncotarget.14873

28. Valkenburg K.C., Graveel C.R., Zylstra-Diegel C.R., Zhong Z., Williams B.O. Wnt/β-catenin signaling in normal and cancer stem cells. *Cancers (Basel)*. 2011;3(2):2050–2079. doi: 10.3390/cancers3022050

29. Dananberg A., Striepen J., Rozowsky J.S., Petljak M. APOBEC mutagenesis in cancer development and susceptibility. *Cancers (Basel)*. 2024;16(2):374. doi: 10.3390/cancers16020374

30. Lu J., Luo Y., Rao D., Wang T., Lei Z., Chen X., Zhang B., Li Y., Liu B., Xia L., Huang W. Myeloid-derived suppressor cells in cancer: therapeutic targets to overcome tumor immune evasion. *Exp. Hematol. Oncol*. 2024;13(1):39. doi: 10.1186/s40164-024-00505-7

31. Bartkowiak-Wieczorek J., Jaros A., Gajdzińska A., Wojtyła-Buciora P., Szymański I., Szymaniak J., Janusz W., Walczak I., Jonaszka G., Bienert A. the dual faces of oestrogen: the impact of exogenous oestrogen on the physiological and pathophysiological functions of tissues and organs. *Int. J. Mol. Sci*. 2024;25(15):8167. doi: 10.3390/ijms25158167

32. Chimento A., de Luca A., Avena P., de Amicis F., Casaburi I., Sirianni R., Pezzi V. Estrogen receptors-mediated apoptosis in hormone-dependent cancers. *Int. J. Mol. Sci*. 2022;23(3):1242. doi: 10.3390/ijms23031242

33. Yaşar P., Ayaz G., User S.D., Güpür G., Muyan M. Molecular mechanism of estrogen-estrogen receptor signaling. *Reprod. Med. Biol*. 2016;16(1):4–20. doi: 10.1002/rmb2.12006

34. Eischen C.M., Woo D., Roussel M.F., Cleveland J.L. Apoptosis triggered by Myc-induced suppression of Bcl-X(L) or Bcl-2 is bypassed during lymphomagenesis. *Mol. Cell. Biol*. 2001;21(15):5063–5070. doi: 10.1128/MCB.21.15.5063-5070.2001

35. Mal R., Magner A., David J., Datta J., Vallabhaneni M., Kassem M., Manouchehri J., Willingham N., Stover D., Vandeusen J., … Cherian M.A. Estrogen receptor beta (ERβ): a ligand activated tumor suppressor. *Front. Oncol*. 2020;10:587386. doi: 10.3389/fonc.2020.587386

36. Jefferi N.E.S., Shamhari A.A., Noor Azhar N.K.Z., Shin J.G.Y., Kharir N.A.M., Azhar M.A., Hamid Z.A., Budin S.B., Taib I.S. The role of ERα and ERβ in castration-resistant prostate cancer and current therapeutic approaches. *Biomedicines*. 2023;11(3):826. doi: 10.3390/biomedicines11030826

37. Miziak P., Baran M., Błaszczak E., Przybyszewska-Podstawka A., Kałafut J., Smok-Kalwat J., Dmoszyńska-Graniczka M., Kiełbus M., Stepulak A. Estrogen receptor signaling in breast cancer. *Cancers (Basel)*. 2023;15(19):4689. doi: 10.3390/cancers15194689

38. Gharibi B., Ghuman M.S., Hughes F.J. Akt- and Erk-mediated regulation of proliferation and differentiation during PDGFRβ-induced MSC self-renewal. *Journal of Cellular and Molecular Medicine*. 2012;16(11):2789–2801. doi: 10.1111/j.1582-4934.2012.01602.x

39. Seachrist D.D., Anstine L.J., Keri R.A. FOXA1: a pioneer of nuclear receptor action in breast cancer. *Cancers (Basel)*. 2021;13(20):5205. doi: 10.3390/cancers13205205

40. Lonergan P.E., Tindall D.J. Androgen receptor signaling in prostate cancer development and progression. *J. Carcinog*. 2011;10:20. doi: 10.4103/1477-3163.83937

41. Gao L., Han B., Dong X. The androgen receptor and its crosstalk with the src kinase during castrate-resistant prostate cancer progression. *Front. Oncol*. 2022;12:905398. doi: 10.3389/fonc.2022.905398

42. Pozas J., Álvarez Rodríguez S., Fernández V.A., Burgos J., Santoni M., Manneh Kopp R., Molina-Cerrillo J., Alonso-Gordoa T. Androgen receptor signaling inhibition in advanced castration resistance prostate cancer: what is expected for the near future? *Cancers (Basel)*. 2022;14(24):6071. doi: 10.3390/cancers14246071

43. Chaudhri R.A., Olivares-Navarrete R., Cuenca N., Hadadi A., Boyan B.D., Schwartz Z. Membrane estrogen signaling enhances tumorigenesis and metastatic potential of breast cancer cells via estrogen receptor-α36 (ERα36). *J. Biol. Chem*. 2012;287(10):7169–7181. doi: 10.1074/jbc.M111.292946

44. Grivennikov S.I., Karin M. Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. *Cytokine Growth Factor Rev*. 2010;21(1):11–19. doi: 10.1016/j.cytogfr.2009.11.005

45. Voutsadakis I.A. Epithelial-mesenchymal transition (EMT) and regulation of EMT factors by steroid nuclear receptors in breast cancer: a review and in silico investigation. *J. Clin. Med*. 2016;5(1):11. doi: 10.3390/jcm5010011

46. Manavathi B., Dey O., Gajulapalli V.N., Bhatia R.S., Bugide S., Kumar R. Derailed estrogen signaling and breast cancer: an authentic couple. *Endocr. Rev*. 2013;34(1):1–32. doi: 10.1210/er.2011-1057

47. Bardin A., Boulle N., Lazennec G., Vignon F., Pujol P. Loss of ERbeta expression as a common step in estrogen-dependent tumor progression. *Endocr. Relat. Cancer*. 2004;11(3):537–551. doi: 10.1677/erc.1.00800

48. Khandrika L., Kumar B., Koul S., Maroni P., Koul H.K. Oxidative stress in prostate cancer. *Cancer Lett*. 2009;282(2):125–136. doi: 10.1016/j.canlet.2008.12.011

49. Bukato K., Kostrzewa T., Gammazza A.M., Gorska-Ponikowska M., Sawicki S. Endogenous estrogen metabolites as oxidative stress mediators and endometrial cancer biomarkers. *Cell Commun. Signal*. 2024;22(1):205. doi: 10.1186/s12964-024-01583-0

50. Schieber M., Chandel N.S. ROS function in redox signaling and oxidative stress. *Curr. Biol*. 2014;24(10):R453–R462. doi: 10.1016/j.cub.2014.03.034

51. Sampson N., Brunner E., Weber A., Puhr M., Schäfer G., Szyndralewiez C., Klocker H. Inhibition of Nox4-dependent ROS signaling attenuates prostate fibroblast activation and abrogates stromal-mediated protumorigenic interactions. *Int. J. Cancer*. 2018;143(2):383–395. doi: 10.1002/ijc.31316

52. Mittal M., Siddiqui M.R., Tran K., Reddy S.P., Malik A.B. Reactive oxygen species in inflammation and tissue injury. *Antioxid. Redox Signal*. 2014;20(7):1126–1167. doi: 10.1089/ars.2012.5149

53. Letafati A., Taghiabadi Z., Zafarian N., Tajdini R., Mondeali M., Aboofazeli A., Chichiarelli S., Saso L., Jazayeri S.M. Emerging paradigms: unmasking the role of oxidative stress in HPV-induced carcinogenesis. *Infect. Agent. Cancer*. 2024;19(1):30. doi: 10.1186/s13027-024-00581-8

54. Dawling S., Roodi N., Parl F.F. Methoxyestrogens exert feedback inhibition on cytochrome P450 1A1 and 1B1. *Cancer Res*. 2003;63(12):3127–3132.

55. Bolton J.L., Thatcher G.R. Potential mechanisms of estrogen quinone carcinogenesis. *Chem. Res. Toxicol*. 2008;21(1):93–101. doi: 10.1021/tx700191p

56. Aquilano K., Baldelli S., Ciriolo M.R. Glutathione: new roles in redox signaling for an old anti-

oxidant. *Front. Pharmacol*. 2014;5:196. doi: 10.3389/fphar.2014.00196

57. Srinivas U.S., Tan B.W.Q., Vellayappan B.A., Jeyasekharan A.D. ROS and the DNA damage response in cancer. *Redox Biol*. 2019;25:101084. doi: 10.1016/j.redox.2018.101084

58. Marvalim C., Datta A., Lee S.C. Role of p53 in breast cancer progression: An insight into p53 targeted therapy. *Theranostics*. 2023;13(4):1421–1442. doi: 10.7150/thno.81847

59. Gorini F., Scala G., Cooke M.S., Majello B., Amente S. Towards a comprehensive view of 8-oxo-7,8-dihydro-2'-deoxyguanosine: Highlighting the intertwined roles of DNA damage and epigenetics in genomic instability. *DNA Repair. (Amst)*. 2021;97:103027. doi: 10.1016/j.dnarep.2020.103027

60. Lee E.Y., Muller W.J. Oncogenes and tumor suppressor genes. *Cold Spring Harb. Perspect. Biol*. 2010;2(10):a003236. doi: 10.1101/cshperspect.a003236

61. Tubbs A., Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. *Cell*. 2017;168(4):644–656. doi: 10.1016/j.cell.2017.01.002

62. Han C., Deng Y., Xu W., Liu Z., Wang T., Wang S., Liu J., Liu X. The roles of tumor-associated macrophages in prostate cancer. *J. Oncol*. 2022;2022:8580043. doi: 10.1155/2022/8580043

63. Laffont S., Seillet C., Guéry J.C. Estrogen receptor-dependent regulation of dendritic cell development and function. *Front. Immunol*. 2017;8:108. doi: 10.3389/fimmu.2017.00108

64. Lai Z.Z., Yang H.L., Ha S.Y., Chang K.K., Mei J., Zhou W.J., Qiu X.M., Wang X.Q., Zhu R., Li D.J., Li M.Q. Cyclooxygenase-2 in Endometriosis. *Int. J. Biol. Sci*. 2019;15(13):2783–2797. doi: 10.7150/ijbs.35128

65. Affo S., Yu L.X., Schwabe R.F. The role of cancer-associated fibroblasts and fibrosis in liver cancer. *Annu. Rev. Pathol*. 2017;12:153–186. doi: 10.1146/annurev-pathol-052016-100322

66. Guo T., Xu J. Cancer-associated fibroblasts: a versatile mediator in tumor progression, metastasis, and targeted therapy. *Cancer Metastasis Rev*. 2024;43(3):1095–1116. doi: 10.1007/s10555-024-10186-7

67. Trenti A., Tedesco S., Boscaro C., Trevisi L., Bolego C., Cignarella A. Estrogen, angiogenesis, immunity and cell metabolism: solving the puzzle. *Int. J. Mol. Sci*. 2018;19(3):859. doi: 10.3390/ijms19030859

68. Fidelito G., Watt M.J., Taylor R.A. Personalized medicine for prostate cancer: is targeting metabolism a reality? *Front. Oncol*. 2022;11:778761. doi: 10.3389/fonc.2021.778761

69. Xie F., Li X., Xu Y., Cheng D., Xia X., Lv X., Yuan G., Peng C. Estrogen mediates an atherosclerotic-protective action *via* estrogen receptor alpha/SREBP-1 signaling. *Front. Cardiovasc. Med*. 2022;9:895916. doi: 10.3389/fcvm.2022.895916

70. Bonkhoff H. Estrogen receptor signaling in prostate cancer: Implications for carcinogenesis and tumor progression. *Prostate*. 2018;78(1):2–10. doi: 10.1002/pros.23446

71. Yao S., Till C., Kristal A.R., Goodman P.J., Hsing A.W., Tangen C.M., Platz E.A., Stanczyk F.Z., Reichardt J.K., Tang L., … Hoque A. Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case-control study. *Cancer Causes Control*. 2011;22(8):1121–1131. doi: 10.1007/s10552-011-9787-7

72. Karantanos T., Corn P.G., Thompson T.C. Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches. *Oncogene*. 2013;32(49):5501–5511. doi: 10.1038/onc.2013.206

73. van Londen G.J., Perera S., Vujevich K., Rastogi P., Lembersky B., Brufsky A., Vogel V., Greenspan S.L. The impact of an aromatase inhibitor on body composition and gonadal hormone levels in women with breast cancer. *Breast Cancer Res. Treat*. 2011;125(2):441–446. doi: 10.1007/s10549-010-1223-2

74. Kelloff G.J., Lubet R.A., Lieberman R., Eisenhauer K., Steele V.E., Crowell J.A., Hawk E.T., Boone C.W., Sigman C.C. Aromatase inhibitors as potential cancer chemopreventives. *Cancer Epidemiol. Biomarkers Prev*. 1998;7(1):65–78.

75. Berry J. Are all aromatase inhibitors the same? A review of controlled clinical trials in breast cancer. *Clin. Ther*. 2005;27(11):1671–1684. doi: 10.1016/j.clinthera.2005.11.013

76. Bosland M.C. The role of estrogens in prostate carcinogenesis: a rationale for chemoprevention. *Rev. Urol*. 2005;7(Suppl 3):S4–S10.

77. Hu W.Y., Shi G.B., Lam H.M., Hu D.P., Ho S.M., Madueke I.C., Kajdacsy-Balla A., Prins G.S. Estrogen-initiated transformation of prostate epithelium derived from normal human prostate stem-progenitor cells. *Endocrinology*. 2011;152(6):2150–2163. doi: 10.1210/en.2010-1377

78. Caldon C.E. Estrogen signaling and the DNA damage response in hormone dependent breast cancers. *Front. Oncol*. 2014;4:106. doi: 10.3389/fonc.2014.00106

79. Paterni I., Granchi C., Katzenellenbogen J.A., Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. *Steroids*. 2014;90:13–29. doi: 10.1016/j.steroids.2014.06.012

80. Božović A., Mandušić V., Todorović L., Krajnović M. Estrogen receptor beta: the promising biomarker and potential target in metastases. *Int. J. Mol. Sci*. 2021;22(4):1656. doi: 10.3390/ijms22041656

81. Miller W.R., Stuart M., Sahmoud T., Dixon J.M. Anastrozole ('Arimidex') blocks oestrogen synthesis both peripherally and within the breast in postmenopausal women with large operable breast can-

cer. *Br. J. Cancer*. 2002;87(9):950–955. doi: 10.1038/sj.bjc.6600587

82. Ellem S.J., Risbridger G.P. Aromatase and prostate cancer. *Minerva Endocrinol*. 2006;31(1):1–12.

83. Allott E.H., Masko E.M., Freedland S.J. Obesity and prostate cancer: weighing the evidence. *Eur. Urol*. 2013;63(5):800–809. doi: 10.1016/j.eururo.2012.11.013

84. Khatpe A.S., Adebayo A.K., Herodotou C.A., Kumar B., Nakshatri H. Nexus between PI3K/AKT and estrogen receptor signaling in breast cancer. *Cancers (Basel)*. 2021;13(3):369. doi: 10.3390/cancers13030369

85. Stabile L.P., Farooqui M., Kanterewicz B., Abberbock S., Kurland B.F., Diergaarde B., Siegfried J.M. Preclinical evidence for combined use of aromatase inhibitors and NSAIDs as preventive agents of tobacco-induced lung cancer. *J. Thorac. Oncol*. 2018;13(3):399–412. doi: 10.1016/j.jtho.2017.11.126

86. Tong D. Selective estrogen receptor modulators contribute to prostate cancer treatment by regulating the tumor immune microenvironment. *J. Immunother. Cancer*. 2022;10(4):e002944. doi: 10.1136/jitc-2021-002944

87. Kawiak A., Kostecka A. Regulation of Bcl-2 family proteins in estrogen receptor-positive breast cancer and their implications in endocrine therapy. *Cancers (Basel)*. 2022;14(2):279. doi: 10.3390/cancers14020279

88. Misirkic Marjanovic M.S., Vucicevic L.M., Despotovic A.., Stamenkovic M.M., Janjetovic K.D. Dual anticancer role of metformin: an old drug regulating AMPK dependent/independent pathways in metabolic, oncogenic/tumorsuppresing and immunity context. *Am. J. Cancer Res*. 2021;11(11):5625–5643.

89. Chong R.W., Vasudevan V., Zuber J., Solomon S.S. Metformin has a positive therapeutic effect on prostate cancer in patients with type 2 diabetes mellitus. *Am. J. Med. Sci*. 2016;351(4):416–419. doi: 10.1016/j.amjms.2016.01.013

90. Akl M.M., Ahmed A. Exploring the interplay between the warburg effect and glucolipotoxicity in cancer development: a novel perspective on cancer etiology. *Adv. Pharm. Bull*. 2024;14(3):705–713. doi: 10.34172/apb.2024.049

Information about the authors:

Maher M. Akl, ORCID: 0000-0001-5480-1688, e-mail: maherakl555@gmail.com
Amr Ahmed, ORCID: 0000-0003-3477-236X, e-mail: drmedahmed@gmail.com

Сведения об авторах:

Акль Махер М., ORCID: 0000-0001-5480-1688, e-mail: maherakl555@gmail.com
Ахмед Амр, ORCID: 0000-0003-3477-236X, e-mail: drmedahmed@gmail.com

Поступила в редакцию 19.03.2025
Принята к публикации 08.08.2025

Received 19.03.2025
Accepted 08.08.2025