Estrogens and Prostate Cancer: Etiology, Mediators, Prevention, and Management

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Abstract

The relationship between hormones and the pathogenesis of prostate cancer (PCa) has been studied extensively. All the mainstay targets for hormonal PCa therapies are based on negating androgen action. Recent epidemiologic and experimental data have clearly pinpointed the key roles of estrogens in PCa development and progression. Racial and geographical differences, as well as age-associated changes, in estrogen synthesis and metabolism contribute significantly to the etiology by increasing the ratio of circulating estrogen to androgen, sex hormone binding globulin synthesis, and aromatase activity and reducing androgen glucuronidation and tissue bioactivation. Promotion of aberrant cell growth, evasion of apoptosis, increased oxidative stress and inflammation, and gains in adiposity and bioactivation to genotoxic carcinogens during adulthood are probable mechanisms of estrogen carcinogenicity, while "estrogen imprinting" via epigenetics in early-life also determines PCa risk. Although the effects of estrogens are known to be mediated by genomic actions of the two estrogen receptor (ER) subtypes (ERα and ERβ), other non-canonical mediators, including the different ERβ isoforms, membrane and mitochondrial ERs, and G protein-coupled receptor 30, may have major actions diverging from classical ER actions. These new discoveries have led to renewed interest among the public and the medicinal field in estrogens and antiestrogens as singular and adjuvant PCa treatment and prevention regimens. This review summarizes current knowledge on how different estrogens/antiestrogens/estrogen mimics contribute to prostate carcinogenesis, the roles of the different mediators of estrogen in the process, and the potentials of new estrogenic/antiestrogenic compounds as targeted therapies for prevention and treatment of PCa.

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Keywords

Racial disparity; aging; sex steroid–binding globulin; estrogen receptor; ER spliced variants; GPR30; aromatase; antiestrogens; selective estrogen receptor modulator (SERM); nuclear receptor co-regulators; DNA methylation; developmental reprogramming; apigenin; phytoestrogen; apoptosis; oxidative stress; genomic damages; prostate cancer risk; hormonal therapy; epigenetics; genistein; resveratrol; raloxifene; toremifene; fulvestrant; estramustine; catecholestrogen

Androgens are traditionally recognized as the major hormone promoting normal and aberrant growth of the prostate. Recent literature, however, suggests that estrogen could also be an important mediator of these processes. Estrogen alone or in synergy with androgen is responsible for the pathogenesis of prostate cancer (PCa). More important, recent experimental data suggest that estrogen or its mimics could determine the risk of PCa development as early as the prenatal stage via a process known as "estrogen imprinting." Here we a) review research findings that support a role for estrogens, estrogen mimics and estrogen metabolites in prostate carcinogenesis; b) discuss how different estrogen receptors (ER) mediate the action of estrogen in promoting the development and progression of PCa; and c) evaluate the potentials of estrogens, xenoestrogens, phytoestrogens, antiestrogens, and SERMs as therapeutics for prevention and treatment of PCa.

Epidemiologic and Animal-model Studies of the Relationship between Estrogens and Pathogenesis of PCa

Results from epidemiologic studies have suggested a role for estrogen in the pathogenesis of PCa. Racial/ethnic and geographical differences in the levels of estrogens provide a probable explanation for the disparity in the prevalence of PCa among various populations throughout the world.[1-3] Apropos to this view is the finding that levels of circulating estrogens in African-American men, whose incidence of PCa is the highest in United States, are higher than those in Caucasian Americans throughout their adult life.[4-8] In contrast, Japanese men, whose incidence of PCa is low, have lower circulating levels of estrogen than do Dutch-European men.[9] A global study on 5,003 men aged 65 years or older showed that blacks (in the US and in West Africa) had higher estrogen levels than Caucasians or Asians (in the US and in their homelands), with levels of total and free estradiol-17β (E2) 10–16% higher and levels of estrone (E1) 27–39% higher than in the latter group.[10] Moreover, the ratios of total E2 to total testosterone (T) and E1 to androstenedione were higher in blacks than in the other groups.[10] A comprehensive analysis of the levels of androgens, estrogens, and their metabolites in circulation led to the conclusion that two fundamental metabolic processes, increased aromatase activity and reduced androgen glucuronidation, are major factors governing the ratio of estrogen to androgen in elderly men.[10]

Age is also a key risk factor for PCa.[1] The prevalence of PCa increases dramatically as men age; this is paralleled by a significant increase in the ratio of circulating estrogen to androgen levels, which may increase by up to 40%.[11-17] This age-related hormonal change, often referred to as "andropause," is caused by several endocrine events, including a decline in testicular function, and increases in adiposity, extragonadal aromatization, and the production of sex hormone–binding globulin (SHBG) as men age.[12;18-21] The level of 5α-dihydrotestosterone (DHT) was found to decrease whereas those of estrogen (both E2 and E1) in the epithelial cells, to increase in the aging prostate (Figure 1).[22] Since estrogens can be synthesized *de novo* via aromatase activity in the prostate,[23] tissue estrogen levels may be more important than circulating estrogen levels in promoting prostate carcinogenesis and progression. In this regard, recent studies utilizing laser capture microdissection samples demonstrated that stromal rather than epithelial aromatase activity may be important in

upregulating the E2:T ratio in the tumor site via an alternative promoter activation mechanism during prostate carcinogenesis.[24;25] Furthermore, aromatase-knockout mice, which cannot produce E2 locally in the prostate, have elevated levels of circulating T and DHT and, with age, are prone to the development of benign prostatic hyperplasia (BPH) but not PCa.[26] Collectively, increased estrogenic influences on the prostate due to racial differences or andropause[27] may elevate the risk of neoplastic transformation of the prostatic epithelium in men.[3;28;29]

Experimental models also support the suggestion that estrogens, alone or synergistically with androgens, are potent inducers of aberrant growth and neoplastic transformation in the prostate.[1;2;30-33] Prenatal exposure to maternal estrogens or adult exposure to pharmacologic doses of estrogens induces a benign lesion termed *squamous metaplasia*, which is derived from the basal-cell proliferation of the prostates of various species, including humans.[34] In a susceptible rat strain (Noble rats), chronic exposure to T plus E2 in adulthood promoted the evolution of a precancerous lesion similar to human prostatic intraepithelial neoplasia (PIN) and a high incidence of full-blown PCa[31;35-37] via the alteration of levels of estrogen to androgen in a manner mimicking that in aging men.[35-38] Paradoxically, dietary soy that is rich in phytoestrogens can mitigate the tumor-promoting effect of T plus E2 in this rat model.[39] Moreover, treatment of the nude mice with T plus E2 could promote the progression of PCa and metastasis at distant organs in the tissue recombinants composed of mouse mensenchyme and a human prostatic epithelial cell line.[40] Cellular and molecular changes implicated as the mechanisms leading to prostate carcinogenesis include a) a dramatic increase in the proliferation of epithelial cells;[37] b) upregulation of growth factor–signaling pathways (e.g. TGFα/EGF receptor signaling;[41] TGFβ signaling,[42] IGF-1 and VEGF signaling,[43] and ER signaling);[44] c) prolactinemia or increased prolactin-receptor signaling;[45] d) mitogen-activated protein kinase (MAPK) activation, possibly through Id-1;[46;47] e) increased cell-survival potential through the overexpression of anti-apoptotic mediators (e.g., metallothionein[48] and TRPM-2/clusterin);[49;50] f) elevation in oxidative stress-induced DNA damage;[51-53] g) changes in gene-expression profiles related to cell proliferation, DNA damage, activation of proto-oncogenes and transforming factors, IL-1B signaling, and TNF-α activation;[54;55] and h) breakdown of epithelial basement membrane and stromal extracellular matrix due to the increase in gelatinolytic proteinase activity and altered expression of glycoconjugates in smooth muscles and their associated extracellular matrix.[56-58] Another potential culprit associated with estrogen-induced/promoted PCa is hormone-induced chronic inflammation,[38;59-61]although this view is not uniformly supported by all studies.[62]

Influence of Estrogen Bioactivation and Detoxification on PCa Risk

The carcinogenic action of estrogen could be caused, in part, by metabolic activation of the natural estrogens E1 and E2 to genotoxic metabolites, such as 2- and 4-hydroxyl catechol estrogens, and their quinone/semiquinone intermediates that act as chemical carcinogens.[63] The bioactivation process is mediated principally by two cytochrome P450 enzymes, CYP1A1 and CYP1B1, whereas the enzyme catechol-O-methyltransferase (COMT) is responsible for the inactivation and removal of these genotoxic estrogen-derived intermediates.[63-66] Once formed, these genotoxic metabolites can cause genomic damages through processes such as the formation of DNA adducts.[67] Supporting the suggestion that the genotoxicity of estrogen metabolites is involved in prostate carcinogenesis is the observation of increased DNA strand breakage[52] and nuclear staining of 8-hydroxy-2′-deoxy-guanosine[60] in the prostates of rats treated with T plus E2. Conversely, increased expression or activity of COMT was shown to protect against estrogen-induced cancer by mediating the conversion of catechol estrogens into methoxyestrogens that have potent apoptotic activity against rapidly growing PCa cells,[68] prompting the testing of combinatory

therapies involving methoxyestrogens and other standard therapies, such as hormone deprivation,[69] docetaxel,[70] and eugenol[71] against PCa growth in model systems.

Furthermore, the aforementioned estrogen metabolites and their intermediates induce oxidative stress and likely promote the generation of high levels of reactive oxygen species (ROS), with damaging effects on proteins, lipids, and DNA in target tissues.[29;66] Therefore, several isoforms of glutathione S-transferases (GSTs) have been reported to have protective effects against estrogen genotoxicity through the detoxification of ROS. Genetic polymorphisms that alter enzyme activity and epigenetics- or mutation-mediated silencing of the cognate genes are expected to affect the PCa risk by modulating the extent of lifelong exposure to genotoxic estrogen metabolites.[29;72] Thus, polymorphisms of the *CYP1A1m1* allele, the *CYP1B1*-Leu432Val, *COMT* at codon 62 and 158, and the *GSTM1*-null genotype have been shown to modify PCa risk in certain populations.[73-80] In addition, a *CYP1A1* variant (*CYP1A1v*) that resides preferentially in the nucleus and mitochondria was found to confer higher carcinogenic potential than its wild-type cytosolic counterpart.[81] This finding is in agreement with the hypothesis that genotoxic estrogen metabolites produced in nuclei are potent tumor initiators.

Another metabolic pathway of relevance to estrogen carcinogenicity in the prostate is the *in situ* production of estrogen from androgen via aromatase encoded by *CYP19*.[25] The enzyme and its activity have been demonstrated in the specimens of PCa and BPH.[25;82] Clinical trials designed to test the efficacy of aromatase inhibitors in treating BPH[83-85] and PCa[86-89] have been reported. Polymorphisms in *CYP19* including intron 4[TTTA]n repeat[90] and C/T versus T/T genotype[91] are associated with familial PCa. Continued investigation of the use of aromatase inhibitors as monotherapies or adjuvants for the treatment of PCa is warranted.[26;92]

Determination of PCa Risk during Early Life

The risk of developing PCa as an adult could be determined by early-life exposure to natural or environmental estrogens through a mechanism known as "estrogen imprinting."[93] Perinatal and neonatal exposure of rats[94-97] or mice[98-100] to estrogens or estrogen mimics induces inflammation, permanent changes in the levels of androgen and estrogen receptors, stromal hypertrophy, and elevated proliferative potentials in the prostatic epithelium of the adult aged gland.[96;101-103] If the "estrogenized" adult glands are exposed to an elevated estrogen challenge during adult life (the "second hit"), full-blown PIN develops in the affected glands.[104] An environmental estrogen, bisphenol A (BPA), is equally effective in sensitizing the adult prostate to increased estrogenic influence during adulthood with regard to the induction of PIN. An unbiased screening has identified permanent alterations in the methylation status of a CpG island in the promoter of phosphodiesterase 4D4 *(Pde4e4)*, an enzyme responsible for regulating cellular cAMP.[104] This finding suggests estrogen imprinting may involve epigenetic reprogramming of prostatic transcription programs in early life. Whether analogous phenomena exist in humans is unclear. However, circulating E2 levels have been found to be higher in pregnant African-American women than in pregnant Caucasian-American women.[105;106] These data are consistent with the hypothesis that exposure to higher levels of E2 *in utero* may explain some of the differences in PCa risk among ethnic groups. Moreover, some indicators of high levels of estrogen during pregnancy, such as high birth weight and jaundice in the newborn, are associated with increased risk of PCa, whereas indicators of low estrogen levels, such as pre-eclampsia, are related to decreased risk.[107;108] The male offspring of women who took diethylstilbestrol (DES) during pregnancy may have a higher risk of PCa.[109] These data, taken together, indicate that PCa may be considered a fetus-based disease. In addition, the window of susceptibility for early-life reprogramming may extend to perinatal and peripubertal periods

and exposures to environmental estrogens may have the same impact as natural estrogens. Of relevance to these hypotheses are studies reporting significant exposure of human fetuses to BPA, likely caused by maternal use of BPA-containing products.[110-116] Perinatal exposure to BPA has also been documented.[117-119] Paradoxically, concerns about developmental reprogramming of PCa risk by soy infant formulas containing high concentrations of phytoestrogens have seldom been raised.[120-122] Yet, the results of numerous human studies examining the risks and benefits of adult consumption of soy and phytoestrogens for prevention of PCa have been inconclusive.[123-127] In summary, if PCa risk can be reprogrammed in early life, cancer prevention strategies should be directed at the aforementioned early developmental stages.

Estrogen Receptors (ERα and ERβ) as Functionally Divergent Mediators of Estrogen Action in the Prostate

The actions of estrogens are now believed to be mediated primarily by two ER subtypes, ERα and ERβ and their variant forms.[28;32;128;129] Both of the ERs have six common domains (A-F). They share a highly homologous DNA-binding domain (97% amino acid homology) but have very dissimilar N- and C-termini.[130] In addition, their ligand-binding domains are 56% homologous. These structural differences are the basis of the reported significant functional differences between the two receptor subtypes. Furthermore, it has been reported that the binding of the two receptors to the same ligand can initiate recruitments of different co-regulators and trigger the utilization of different *cis*-regulatory elements, thus further increasing the functional diversity of these two receptors.[130-135] Finally, the recent discovery of variant forms of ERα and ERβ (isoforms) caused by alternative splicing or mutations has added complexity to estrogen action because these variants clearly show distinct functional disparity and patterns of tissue-/cell type-specific distribution.[129;132;136;137]

Many reports have shown differential expression patterns of the two receptors in the epithelial and stromal compartments of the normal and malignant human prostate (Figure 1).[33;137-144] In the normal human prostate, the wild-type ERβ (also known as ERβ1) is localized mainly in the basal epithelial compartment, where ERα is almost never found, while ERα, along with ERβ, is expressed in the stroma.[141] Both ER subtypes are absent in the luminal epithelial compartment.[141] A gradual loss of ERβ1 expression is apparent during the progression to high-grade PCa in the primary site [115;139;140;145;146] The progressive silencing of ERβ is accompanied by hypermethylation of a CpG island in the proximal promoter of the gene.[147] Paradoxically, ERβ, but not ERα, is expressed at high levels in PCa metastasized to the bone and regional lymph nodes,[141] with a concomitant loss of methylation in the CpG island of ERβ.[147] Fine mapping of the CpG island revealed that this reversible silencing and reactivation of ERβ expression is attributable to cytosine methylation of an AP2 site within the CpG island of the ERβ promoter.[148] Moreover, antiestrogen-based therapies involving DES or PC-SPES lowered the level of ERβ1 expression in bone metastases of the treated patients.[149]

It is now established that ERβ1 exerts an antiproliferative effect on the prostate epithelia[131;133] and inhibits epithelial-mesenchymal transition.[150] However, less is known about the biological roles of its spliced variants. We recently demonstrated that ERβ2 and ERβ5 promote metastasis and that their expression is associated with shorter metastasis-free survival in patients with PCa.[137] In support of a divergent functional role of various ERβ isoforms, when a pan-ERβ antibody was used, the retention of ERβ expression in primary PCa was associated with increased mortality.[139] The co-expression of ERβ with endothelial nitric oxide synthase (eNOS) and hypoxia-inducible factor 2α (HIF-2α) suggests that an estrogen-mediated NO-enriched environment may influence the aggressive phenotype of

PCa significantly.[151] Thus, ERβ appears to play differential roles in human prostate carcinogenesis through differential expression of the various spliced variants and possibly alternative promoter utilization.[152] Differential binding of the receptor to different ligands and crosstalk with other transcriptional factor-signaling cascades may also introduce additional divergence in ERβ action.[131;153;154]

Studies in animal models have provided strong evidence of the antiproliferative role of ERβ in the prostate gland. ERβ knockout mice have been found to develop prostatic hyperplasia in old age, a phenomenon not seen in ERα knockout mice.[155] Jiang et al.[156] observed an age-dependent decline in ERβ expression in the canine prostate. Chang and Prins[157] reported that neonatal exposure of rats to estrogen causes the downregulation of ERβ; the upregulation of ERα; and the development of hyperplastic, dysplastic, and neoplastic lesions in the adult ventral prostates. Consistent with the hypothesis of the antiproliferative role ERβ, Risbriger et al. demonstrated that the administration of ERβ agonists, but not of an ERα agonist, to aromatase knockout mice suppressed the prostate epithelial cell growth and promoted apoptosis[158] and that the action of the receptor is mediated via TNF-α signaling.[133]

Apart from ERβ expression, ERα, which is expressed primarily in the stromal compartment of the prostate, may contribute to the pathogenesis of PCa. Higher levels of ERα were observed in the prostatic stroma of Hispanic and Asian men than in that of Caucasian and African-American men, who are at a higher risk for PCa.[159] In a genotyping and allelic frequency analysis of six different polymorphic loci of ERα in a Japanese population, polymorphism in codon 10 was found to be associated with a higher PCa risk.[160] These findings are in stark contrast to results from studies of genetic polymorphisms of ERβ[161-164] that reported no strong association of various polymorphic loci with PCa risk, with the exception of one promoter single-nucleotide polymorphism (SNP).[165;166]

Finally, during fetal development of the human prostate, ERβ is the first to appear in the prostate (by the seventh week of gestation) and is the only ER subtype expressed in the epithelial and stromal cells during the early ductal morphogenesis.[34;167] ERβ expression begins by week 15 of gestation and is strongly associated with the squamous metaplasia in the distal periurethral ducts and utricle.[167] These findings suggested that ERβ, perhaps in concert with the AR, mediates the very early stage of fetal prostate development, followed by the action of ERα. Thus, selective ERβ-activating compounds may play an important role in prenatal estrogen imprinting of PCa risk.

Non-canonical Actions of Estrogen and a New Therapeutic Target (G Protein-Coupled Receptor 30)

Apart from acting as transcription factors, ERα and ERβ can trigger rapid non-genomic signal transduction at the cell membrane level through the activation of specific kinase activity or induction of a calcium influx.[168-170] These membrane ER-mediated events can activate gene-transcription activities with or without synergy with the classical genomic actions of nuclear ERs.[171] In this regard, membrane ERα has been shown to tether onto the epidermal growth factor receptor (EGFR) signaling pathway for the activation of the MAPK[172] and phosphoinositide 3-kinase (PI3K) signaling.[173] In addition, ERβ found localized in the mitochondria has been demonstrated to act as a mitochondrial transcription factor that regulates mitochondrial gene expression.[174] ERβ has been reported to move from the mitochondria to the nucleus during neoplastic transformation.[175] However, the functions of cell membrane or mitochondrial ERα and ERβ in the prostate and PCa remain unknown and need further elucidation.

Estrogen has recently been found to be able to exert its action via the G protein-coupled receptor 30 (GPR30).[176] GPR30 has been localized in the cell membrane and endoplasmic recticulum of various estrogen-sensitive tissues and cell lines[176-178] and to mediate the non-genomic action of E2 in breast, endometrial, and ovarian cancer cells through the activation of Erk1/2 and cAMP pathways.[179;180] GPR30 is expressed in the immortalized normal prostate stroma cell line WPWY-1 but does not appear to mediate the growth response induced by high-dose E2.[181] A recent study demonstrated positive staining of GPR30 in both plasma membrane and cytoplasm in the normal and cancerous prostate, and its predominant expression in the luminal epithelium.[182] Activation of GPR30 by a non-estrogenic, synthetic, GPR30-specific ligand G-1 inhibited PCa cell growth *in vitro* by activating Erk1/2 and upregulating p21-mediated G2-M arrest and attenuated the growth of human PCa xenografts in nude mice.[183] These new findings suggest that GPR30 is a novel estrogen mediator in the prostate and that a specific GPR30 ligand such as G-1 may have therapeutic potential for PCa.

Estrogen-related receptors (ERRs) are orphan nuclear receptors that are highly homologous to ERs, especially in the DNA- and ligand-binding domains.[184] However, they do not bind natural estrogens and may have yet-to-be discovered endogenous ligands. There are at least three EERs, namely ERR-α, -β,[185] and -γ.[186;187] They regulate gene expression through transactivation via *cis*-elements such as the ERE, steroidogenic factor-1 response element (SFRE), and estrogen-related receptor response element (ERRE).[188-192] Similar to ERs, different ERRs have distinct differential expression patterns in normal and cancerous prostate tissues/cells.[193] Finally, although they do not bind natural estrogens, ERRβ and ERRγ do bind DES, tamoxifen, 4-hydroxytamoxifen, flavones, and isoflavone phytoestrogens[194-196] and therefore should be considered in devising estrogen- or antiestrogen-based therapies for PCa.

Prevention of and Therapy for PCa with Selective ER Modulators (SERMs), Aromatase Inhibitors, Phytoestrogens, and Other Estrogen-/Antiestrogen-based Treatments

The first effective drug therapy for PCa was found about 70 years ago. DES, a xenoestrogen, was applied for the treatment of metastatic PCa[197] but fell out of favor because of its cardiovascular toxicity and other serious adverse effects.[33;198;199] Other ER-based treatments for PCa include antiestrogens, selective ER modulators (SERMs), and aromatase inhibitors. SERMs are estrogenic compounds that act as either ER agonists or antagonists according to the presence of different co-regulators in a cell-/tissue-specific manner. Consequently, the ERs can be either stimulated or inhibited in the cell/tissue.[200] However, clinical trials have shown that different generations of SERMs, such as tamoxifen, toremifene, raloxifene, and fulvestrant, have limited efficacy as alternatives to DES.[33;201-207] Their lack of efficacy could be due to their original design for targeting the transactivation of ERα on an ERE and/or blocking the traditional genomic action of estrogen. With our growing knowledge of the wide range of genomic and non-genomic actions of estrogen and the variable expression of ERβ and its isoforms in the prostate and PCa, as well as of the significance of the non-canonical ER, GPR30, the future design of estrogen/antiestrogen therapies and chemopreventive agents will have to take into account the complex nature of estrogen action in the development and progression of PCa.

In this regard, it is important to recognize that many specificities or off-target effects of estrogenic/antiestrogenic drugs are due to their broad spectrum of activities not restricted to their estrogenicity. Traditionally, estrogen-induced PCa regression is believed to be mediated by its action on the hypothalamic-pituitary axis, thereby inhibiting testosterone

synthesis.[208] However, it is now known that many estrogens/antiestrogens/phytoestrogens/ SERMs including DES, 2-methoxy-E2, genistein, resveratrol, licochalcone, raloxifene, toremifene, fulvestrant, and estramustine, have antitumor effects independent of this pathway.[209-225] The ability of these compounds to suppress PCa cell growth has been attributed to a broad range of actions, including direct cytotoxicity,[223] interruption of cell-cycle progression,[210;221;226] induction of apoptosis,[211;221;224;225] depolymerization of microtubules,[209] inhibition of DNA synthesis,[213] inhibition of topoisomerase II,[217] blockade of tyrosine kinase,[217;218] disruption of apoptotic regulators,[222] and activation of death-domain receptors.[214;219] Some of these estrogenic/antiestrogenic compounds are also potent inhibitors of angiogenesis and metastasis, through their actions in upregulating expression of genes related to anti-angiogenesis or anti-metastasis,[215] activating the cell adhesion–signaling molecule focal adhesion kinase,[216] and reduction in metastatic spreading via the lymphatic system.[220]

As a recent development in the treatment of PCa, the application of estrogen patches has grown in popularity.[227-229] The advantages include reduction in cardiovascular toxicity and the maintenance of adequate hormonal levels for a convenient time period.[230] as well as the additional advantage of allevating hot flashes and improving bone density after endocrine treatment of PCa. [231;232] Estrogen patches have recently been tested in a phase II clinical trial as a first-line hormonal therapy in patients with locally advanced or metastatic PCa. Preliminary results produced the levels of testosterone and a PSA response similar to those of castration.[228]

Aside from treating PCa, the potential of SERMs for preventing PCa has turned out to be a promising proposition. The rationale stems from several lines of investigation. SERMS were shown to decrease testosterone levels by suppressing the hypothalamic-pituitary axis.[233] Furthermore, age-related increases in PCa prevalence parallel increases in serum estrogen levels, and the incidence of PCa is low in countries with diets rich in phytoestrogens.[234] A multicentered, double-blind randomized study involving 514 men with high-grade PIN and no cancer reported a significant reduction in PCa incidence in patients treated daily with 20 mg of toremifene for 6-12 months as compared with placebo.[235] These promising results have prompted the initiation of a large phase III study to examine the potential for toremifene as a chemopreventive agent.

Phytoestrogens are another important class of estrogen-based chemopreventive agents. The most common phytoestrogens, soy isoflavones such as genistein, equol, and daidzein, which are abundant in soy beans and its products, have been found to have estrogenic or antiestrogenic activity.[236-239] They have been some of the most popular agents in studies of the potential of PCa chemoprevention and therapy because of the low incidence of PCa, along with the high levels of phytochemicals, in the diets of Asian populations.[240] Although there is an abundance of *in vitro* and *in vivo* experimental data about the anti-tumor properties of phytoestrogens, the value of their protective or therapeutic effects in cohort studies still remains controversial.[241-248] Nevertheless, a number of phase I clinical trials evaluating the use of phytoestrogen supplementation in patients with PCa have generally seen beneficial effects without any toxicity.[212;249-252]

Summary

Traditionally, androgens have been considered to be the major sex hormones regulating the normal and malignant growth of the prostate. However, recent epidemiologic findings and experimental data suggest that estrogens and their mimics can be responsible for the pathogenesis of PCa. The carcinogenicity of estrogens in the prostate during adulthood is believed to be mediated by the combined effects of the hormone-induced unscheduled cell

proliferation and epigenetic silencing of anti-tumor genes, along with the bioactivation of estrogens to genotoxic carcinogens. Thus, individuals or ethnic groups with polymorphisms in genes encoding ERs and/or estrogen-metabolizing enzymes can modify the risk for PCa caused by altered responsiveness to the hormone and exposure to its carcinogenic metabolites over a lifetime. The age-dependent hormonal shift from androgen to estrogen could also be an important contributing factor to increased estrogen bioavailability. Although PCa has a long latency and starts to develop in men around middle age, recent data strongly suggest that PCa risk could be determined even as early as during pre- and perinatal life stages by a process known as the "estrogen imprinting." Thus, primary PCa prevention should probably begin in early life. Among the various cellular mediators, ERβ appears to be a key determinant in the pathogenesis, progression, and metastasis of PCa. Therapeutic approaches targeting its activation/inactivation may have important ramifications in the prevention and treatment of PCa. Epigenetic mechanisms such as DNA methylation play important roles in regulating the expression of the two ER subtypes. A change in the methylation status of proximal promoters of these genes constitutes an "on/off" switch for reversible gene regulation. Moreover, the differential expression of different ER-spliced variants (isoforms) could explain some conflicting observations related to estrogen action in the initiation and progression of PCa. Apart from the canonical genomic action of ERα and ERβ, the therapeutic potential of ER and its variants that function in multiple non-genomic pathways, such as membrane ERα, mitochondrial ER, ERRs, and GPR30, may further contribute to the pathogenesis of PCa. Finally, various estrogenic/antiestrogenic/SERM-like compounds have demonstrable efficacies in causing PCa regression through the utilization of pathways independent of the hypothalamic-pituitary axis. As the treatment of advanced PCa with transdermal estrogen has gained in popularity, several SERMS, including toremifene, have shown promise as chemopreventive or therapeutic agents in clinical trials. Although data from clinical trials are not conclusive, phytoestrogen supplements, including dietary soy, continue to be used by patients as complementary alternative medicine for PCa. With a greater understanding of the molecular mechanism underlying estrogen carcinogenicity in the prostate, the applicability of estrogen/antiestrogen-based prevention and treatment therapies, as first-line or adjuvant therapies, will gain ground in the clinic. Thus, it is timely in devising a new generation of estrogenic/antiestrogenic therapies with higher specificity against PCa and fewer off-target effects.

Acknowledgments

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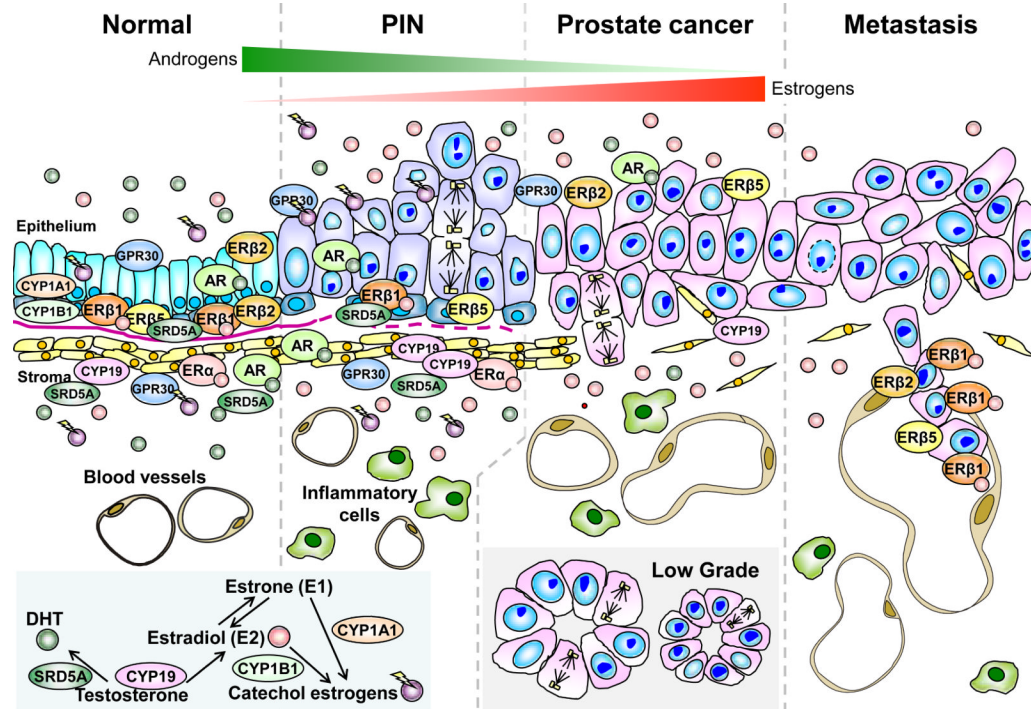
Figure. 1.
Expression of various hormone receptors and levels of hormones during the development and progression of prostate cancer (PCa). In the normal human prostate (far left panel), androgen receptor (AR), estrogen receptor alpha (ERα), different estrogen receptor beta (ERβ) isoforms, and G protein–coupled receptor 30 (GPR30) are expressed differentially in the stroma, and luminal and basal epithelium of the prostate. The epithelial cell compartment expresses only ERβ and AR, whereas the stromal compartment expresses both ERα and AR. GPR30 is expressed in both compartments. During tumor progression from high grade PIN (second to the far left panel) to prostate cancer (second to the far right panel), expression of AR and ERα remains unchanged, while expression of the antiproliferative ERβ1 is lost in the basal epithelial cells along with the disruption of the basement membrane (pink line). Two ERβ isoforms, ERβ2 and ERβ5, which have been shown to have pro-metastatic potential, are expressed in the normal epithelium, but their co-expression in PCa specimens is associated with a poor prognosis and shorter metastasis-free survival. In prostate metastases (far right panel), ERβ1 is re-expressed at high levels. Other non-canonical ERs such as GPR30 and ERRs are differentially expressed in normal and malignant prostate tissues but their roles in prostate carcinogenesis remains to be elucidated. Throughout the development and progression of PCa, tissue estrogen levels [estradiol-17β (E2) and estrone (E1)] increase with concomitant decreases in levels of 5α-dihydrotestosterone (DHT). These changes are due in part to an increase in CYP19 (aromatase) activity and a loss of SRD5A (5α-reductase) expression in the primary site (insert). SRD5A expression is completely lost in metastases. Additionally, an age-related reduction in testicular testosterone (T) synthesis, an increase in levels of sex hormone–binding globulin, and increases in adiposity and peripheral aromatase activity, collectively contribute to an increase in the estrogen to androgen ratio in circulation that further raise prostatic estrogen levels. In summary, a life-time over-exposure to estrogens and/or catecholestrogens could be an etiological factor in prostate carcinogenesis. The localizations of these enzymes as well as mediators of estrogen/androgen actions are indicated.