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Review Article

Hormones and prostate carcinogenesis: Androgens and estrogens

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Abstract

Prostate cancer is the leading non-skin malignancy detected in US males and the second cause of death due to male cancer in the US. Androgenic hormones are generally believed to be causatively associated with prostate carcinogenesis, but human evidence, mostly epidemiological, for this is minimal. Circulating hormone levels are not associated with the risk of prostate cancer and neither are polymorphisms in various genes encoding the androgen metabolizing enzymes or androgen receptors. Evidence in support of the involvement of androgens in prostate cancer development is derived from clinical trials with 5α-reductase inhibitors, which reduced the risk by approximately 25%. Animal studies using rat models, however, provide clear evidence that testosterone can induce prostate cancer and can act as a strong tumor promoter in concert with genotoxic carcinogens. One such genotoxic factor may be 17β-estradiol, which is generated from testosterone by the aromatase enzyme. Estradiol can be converted to catecholestrogens, which through redox cycling, generate reactive metabolites that can adduct the DNA and potentially lead to mutations. Animal studies and limited human evidence suggest that estrogens can be involved in prostate carcinogenesis by such a genotoxic mechanism. However, how androgens exert their tumor-promoting effect is not clear. It is likely that hormonal and non-hormonal factors as well as genetic and non-genetic (environmental) factors interact in a highly complex and poorly understood manner to determine the risk of prostate cancer.

Keywords: Adrogens, estrogens, hormonal carcinogenesis, prostate cancer, steroid hormones

INTRODUCTION

Prostate cancer is the leading non-skin malignancy detected in US males and the second cause of death due to male cancer in the US.[1] The causes of this malignancy are not entirely certain, but it is generally assumed that androgenic hormones play a major role in prostate carcinogenesis.[2] The author has previously reviewed the evidence for causative involvement of steroid hormones in prostate cancer, particularly androgens.[2] The purpose of the current article is to summarize more recent information regarding the role of steroid hormones in prostate carcinogenesis and critically put these data into context. Data on the emerging role of estrogens in prostate carcinogenesis, in particular, will be discussed, as well as recent data indicating novel mechanisms by which androgens can interact with estrogens and cause molecular changes leading to prostate cancer.

The basis for the assumption that androgenic hormones play a causative role in prostate carcinogenesis is that the prostate gland is an androgen-dependent tissue and prostate cancer is an androgen-dependent malignancy.[2] The underlying

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mechanism has been postulated to be the androgenic stimulation of cell proliferation, resulting in an increased risk of oncogenic genetic alterations.[3] However, the evidence for all this is indirect and very limited at best.

There is no evidence that androgens cause sustained cell proliferation in the prostate. A classical experiment is to surgically castrate rats which causes involution of the prostate gland by apoptosis and cessation of secretory activity, and give androgen back at physiological levels after a couple of weeks; this will cause a few waves of cell proliferation in the prostate, but after a few days, cell proliferation returns to levels found in intact control rats.[4] Further growth of the prostate upon continued androgen treatment is caused by increased secretion, not cell proliferation.[4,5] There are no human data of the effects of androgen treatment and prostatic cell proliferation, as these are extremely difficult to obtain, and data only exists on the effects of androgen treatment on serum levels of prostate specific antigen (PSA), which do not necessarily reflect cell proliferation and may indicate effects on the level of PSA production by the prostate and prostate cancer cells.[6] A study of intermittent androgen suppression with serial tumor biopsies of advanced prostate cancer patients was not informative, because it indicated a highly variable cell proliferation (Ki-67 staining) response to the cessation of androgen ablation, although serum PSA responded with the expected rebound after cessation of hormone ablation.[7]

In the following sections, the current knowledge about the role of steroid hormones in prostate carcinogenesis will be summarized, first focusing on studies of androgens in human populations and clinical trials, followed by laboratory animal model research. Subsequently, the focus will shift to the role of estrogens followed by a final summary of current hypotheses.

CIRCULATING ANDROGEN LEVELS AND RISK OF PROSTATE CANCER

There have been many attempts to determine the association between the levels of androgens and other sex steroid hormones and the risk of prostate cancer later in life. A meta-analysis, in 1999, of eight such studies, did not find any evidence for such an association of risk with total and free testosterone, 5α-dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA) sulfate, estrone, estradiol, sex hormone binding globulin (SHBG), luteinizing hormone (LH) or prolactin; but for androstanediol glucuronide there was a very weak positive association with a risk (risk ratio 1.05; 95% confidence interval (CI) 1.00 – 1.11).[8] In a more recent pooled analysis of these and other prospective studies (n = 18), including as many as 3886 prostate cancer cases and 6438 controls, there was also no evidence of any association of sex steroid hormones levels with subsequent prostate cancer risk, with the exception of SHBG, for which there was a modest negative association (relative risk 0.86; 95% CI 0.75 – 0.98), but this was not reflected in a positive association for either free testosterone or free estradiol.[9] Thus, overall, there is no evidence that circulating levels of sex steroid hormones were associated with risk of prostate cancer. A major problem with these studies is that they involved only a single hormone measurement, which does not reflect variations over time. Most importantly, serum hormone levels provide little information about hormone concentrations in prostate tissue, which are controlled by intraprostatic metabolism of androgens, and are not reflective of the epithelial or stromal cell type in which the androgens are metabolized or act on the androgen receptor.[10,11] In older studies of populations that differed in the risk of prostate cancer, higher levels of 3α,17β-androstanediol glucuronide were found in the higher risk populations (such as US males) than in men at lower risk (such as Japanese males) leading to the hypothesis that the risk of prostate cancer is associated with the activity of 5α-reductase, converting testosterone into DHT, which is catabolized to 3α,17β-androstanediol by 3α-hydroxysteroid dehydrogenase type 3 (or AKR1C2).[2,12] However, the above-mentioned pooled analysis of 18 prospective studies did not yield any support for this idea.[9] Androstanediol glucuronide reflects the overall catabolism of DHT, but this happens in both the prostate and liver. The other main DHT metabolite, 3β,17β-androstanediol formed by the AKR1C1 enzyme, has a weak estrogenic activity, which could be inhibitory on tumor growth via acting on the estrogen receptor-β.[13]

POLYMORPHISMS IN GENES RELATED TO ANDROGEN ACTION OR METABOLISM AND PROSTATE CANCER RISK

To obtain information about steroid hormone metabolism and prostate cancer risk, hypotheses were developed from a multigenic model on the role of these hormones in prostate carcinogenesis, focusing on the activity of enzymes involved in androgen biosynthesis (steroid 17α-hydroxylase / 17,20-lyase [*CYP17*], 17β-hydroxysteroid dehydrogenase [*HSD17B*], and 3β-hydroxysteroid dehydrogenase [*HSD3B*]), androgen activation (5α-reductase [*SRD5A2* and *SRD5A1*]) and androgen catabolism / clearance (3β- and 3α-hydroxysteroid dehydrogenase [*HSD3A* and *HSD3*] eliminating DHT and cytochrome P450 3A [*CYP3A4* and *CYP3A* 5] clearing testosterone).[14-17] However, despite considerable effort in examining the genetic variation in these genes which affects their activity, in several studies (some of which were large and included haplotype analyses), no convincing

evidence emerged that functional polymorphisms in the *CYP17*, *HSD17B1*, *HSD3B*, *SRD5A2*, and *CYP3A* genes are associated with risk of prostate cancer.[16,18-25] However, in some studies significant associations with prostate cancer risk were found. For example, in one study an association was found between prostate cancer risk and polymorphisms in the *SRD5A1* and *HSD3B1* genes that are of uncertain functional significance.[26] In a meta-analysis of the V89L polymorphism in the *SRD5A2* gene an association was found between elevated risk and the L allele, but only for men with a European heritage and men younger than 65 years,[27] even though the L allele confers lower enzyme activity.[28] A *CYP17* polymorphism was associated with the risk of prostate cancer, but only in African–American men.

Thus, age and race are probably important factors, but have not always been addressed, as is also the case with the critical issue of functionality of polymorphisms. Although some studies have found significant associations with risk, overall the studies reported to date all suffer, to some degree, from issues related to insufficiently large sample sizes, study population differences, insufficient across-laboratory standardization, and quality control of the methods used for genotyping.[9,21] Of course these studies cannot address potentially important gene-environment and intraprostatic factors affecting androgen metabolism and gene–gene interactions have hardly been addressed.[9]

The androgen receptor (AR) gene contains a polymorphic region in exon 1 that consists of variable CAG microsatellite repeats that are associated with differences in AR activity. The normal range of these repeats is between eight and thirty-five and the mean is about twenty CAG repeats. The shorter the CAG repeat length, the higher the activity of the AR.[29,30] Several initial studies have suggested an association between shorter CAG repeat lengths and increased risk of prostate cancer.[2] However, larger, more recent studies do not confirm this.[31-33] Furthermore, interactions between genes and the stage (early versus advanced stage) or aggressiveness of the disease may be important as suggested, for example, by a study of polymorphisms in the *AR* and *PSA* genes.[34]

CLINICAL TRIALS WITH 5α-REDUCTASE INHIBITORS

Indirect evidence that androgens are involved in prostate carcinogenesis is derived from human studies with 5α-reductase inhibitors, which reduce the formation of DHT from testosterone via this enzyme in the prostate and the periphery, mainly the fat tissue. The 5α-reductase-type 2 inhibitor, finasteride, and dual 5α-reductase-type 1 and 2 inhibitor, dutasteride, have been studied in large clinical trials for their ability to reduce the risk of prostate cancer.[35,36] A reduced risk of developing prostate cancer by 23 – 24%, over a four-to-seven-year intervention period, was found in both of these studies, in men at average risk for prostate cancer[37] or high-risk men.[38] Both agents exerted the strongest preventive effect for low-grade prostate cancer, but for more clinically significant high-grade cancer there was no protective effect in the dutasteride trial, for cancers with a Gleason score of 7 or higher, and a small but significantly increased risk in the finasteride study for tumors with a Gleason score of 8 or higher. These studies provide evidence in support of androgen action as an important factor for prostate cancer development. However, the duration of the intervention in these two trials was short, in view of the known slow growth of prostate cancer. Moreover, the study subjects were middle-aged men who are known to have a high frequency of small cancers in their prostates.[39] Thus, results of these studies are unlikely to provide much insight into whether androgens are involved in the process of carcinogenesis or only influence the growth and progression of pre-existing cancers.

TESTOSTERONE TREATMENT, ANABOLIC STEROIDS, AND RISK OF PROSTATE CANCER

There has been a marked increase in recent years of treatment of aging men with testosterone, to ameliorate the effects of declining androgen levels with aging.[40] Whether this treatment increases the risk of prostate cancer has been subject to much discussion.[41,42] Recent meta-analyses of the effect of testosterone treatment on prostate cancer development did not indicate elevated risk,[43,44] although there was a significant increased risk of any prostate-related problems identified in one of these studies.[44] However, the sample sizes in the studies involved in these meta-analyses were low and the treatment duration short, and the lack of elevated risk of prostate cancer should be considered very preliminary and studies including many more subjects and much longer treatment periods are needed.[6,43,44] Studies relying on the effects of testosterone treatment of men on their serum PSA levels are not relevant to assess the risk of prostate cancer.[6]

Anabolic steroid abuse has become almost epidemic in the US and is not limited to athletes.[45-47] Although increased risk of prostate cancer has been suggested, no epidemiological studies have been conducted, and there are only some case reports of prostate cancer in anabolic steroid users.[48]

ANDROGENS AND PROSTATE CANCER PROGRESSION

The vast majority of prostate cancers initially respond to androgen ablation therapy with regression and reduction of PSA, but in virtually all cases, the tumors become hormone refractory and are currently referred to as castrate-resistant prostate cancer.[49,50] In most castrate-resistant prostate cancers, the androgen receptor (AR) remains strongly expressed and active in the absence of androgens.[50,51] The mechanisms identified for this phenomenon are AR gene amplification, altered expression and function of AR co-activators, and ligand-independent AR activation through stimulation of alternate signal transduction pathways,[49,52,53] as well as local production of androgen within the castration-resistant tumor,[54,55] although this has not been observed in all studies.[56] The AR can also acquire mutations that make the receptor either hypersensitive to androgen, facilitate AR function because of altered interactions with AR co-regulators, or expand AR ligand specificity when these mutations occur in the ligand-binding domain, so that the receptor can be promiscuously activated by a broad group of steroids, including estrogens, progestins, adrenal steroids, and even anti-androgens.[57-59] The AR of the commonly used LNCaP cell line contains such a mutation (T877A).[60] Most of these mutations do not appear to affect the receptor-binding affinity for androgens, such as DHT, but can still affect the transcriptional activity of the receptor, in response to these androgens. AR mutations appear to be rare in the early stages of prostate cancer (0 – 4%), but become more frequent in more advanced tumors or recurrent tumors.[59,61-63] AR mutations have been detected in 10 to well over 30% of patients with castrate-resistant tumors which have failed anti-androgen therapy, suggesting that the anti-androgen therapy causes a natural selection of cells that have acquired mutations.[64,65] The fact that the AR remains active, and probably essential, during prostate cancer progression and in the absence of circulating androgens puts further emphasis on the central role of androgen action in prostate carcinogenesis.

ANIMAL STUDIES OF ANDROGENS AND PROSTATE CARCINOGENESIS

The most direct and convincing evidence that androgens can cause prostate cancer comes from experiments with rats treated with testosterone. Robert Noble treated an inbred rat strain (designated NBL or Nb), which was probably of Long Evans origin,[66] with subcutaneously implanted cholesterol pellets containing testosterone propionate at six-to-eight-week intervals and found that 16 of the 85 treated rats (19%) developed grossly visible prostate adenocarcinomas.[67] We extended this observation with an experiment with NBL rats in which we subcutaneously placed Silastic tubing implants containing testosterone (not testosterone propionate), which hardly elevated circulating testosterone, and found that 11 out of 30 rats (37%) developed histologically confirmed adenocarcinomas in the dorsolateral prostate.[68] The same treatment of outbred Wistar Cpb:WU rats caused an 18% incidence of prostate cancer.[68] Morris Pollard applied subcutaneous Silastic tubing implants containing testosterone propionate (not testosterone) to a nearly inbred Wistar rat strain he maintained at Notre Dame, the Lobund Wistar (LW) rat, and reported an incidence of grossly visible prostate carcinomas of 0,[69] 14,[70] and 15%.[71] This was essentially reproduced by Hoover *et al*.,[72] who reported three prostate carcinomas in 42 LW rats (7%). Previously Pollard found a prostate tumor in one of twenty-five (4%) similarly treated Sprague Dawley rats.[73] Parviz Pour treated Wistar rats (MRC) maintained at the Eppley Institute with testosterone propionate in subcutaneous Silastic tubing implants, and induced prostate adenocarcinomas in two of the sixteen (13%) treated rats.[74] Testosterone propionate is fairly rapidly released from Silastic tubing implants,[72] while for unknown reasons testosterone is far less rapidly released and a sustained stable marginal elevation in circulating testosterone is possible.[68] Thus, chronic testosterone treatment results in the development of prostate adenocarcinomas in five different rat strains in incidences ranging from 4 to 37%.

If androgen administration described earlier is preceded by treatment with a chemical carcinogen, high prostate cancer incidences can be induced in rats, demonstrating that testosterone is a strong tumor promoter, which may be a factor in the carcinogenic activity of testosterone in the rat prostate summarized earlier. Carcinogens that are targeted to the prostate because of prostate-specific activation of a pro-carcinogen or stimulation of cell proliferation in the prostate at the time of administration of a chemical carcinogen, such as methylnitrosourea, appear to be most effective.[62,74-76] In the LW rat strain, an injection of methylnitrosourea that is not targeted to the prostate also functions as a very effective tumor initiating factor when followed by chronic androgen treatment .[18,71] This tumor promoting effect of testosterone in rats is evident even at circulating androgen concentrations that are well within the physiological range.[62,70,77]

Treatment of rats with the 5α-reductase inhibitor finasteride or the antiandrogen casodex concomitant with administration of testosterone propionate via Silastic implants, after treatment with the prostate-targeted carcinogen 3,2'-dimethyl-4-aminobiphenyl (DMAB), inhibited carcinogenesis in the dorsolateral prostate.[77] In contrast, when DMBA was given without testosterone propionate treatment, these

antiandrogens enhanced rather than inhibited the induction of ventral prostatic neoplasms.[78] Another 5α-reductase inhibitor inhibited the development of spontaneous carcinomas in the ventral prostate of the ACI rat, but only at low and not high doses.[79] Other studies with agents interfering with androgen action, particularly the androgen receptor blocker flutamide, have also been very effective in preventing prostate cancer development in rats treated sequentially with methylnitrosourea targeted to the prostate, followed by chronic low-dose testosterone administration via Silastic implants.[80]

These studies appear to be consistent with the results of the clinical trials with finasteride or dutasteride summarized earlier in the text and strongly support the idea that androgens are causatively involved in prostate carcinogenesis. The precise mechanisms by which androgens act in this fashion are, however, not very clear and may differ depending on which phase of carcinogenesis the androgens are involved in and may be influenced by their interactions with other potentially important factors, such as prostatic inflammation, diet, and genetic predisposition. One emerging mechanism is related to the discovery that androgen can induce topoisomerase-2B-mediated double-strand breaks in the DNA, resulting in gene rearrangements leading to *TMPRSS2 : ERG* gene fusions in prostate cancer cells (LNCaP and LAPC-4) and SV40-immortalized prostate epithelial cells.[81,82] This fusion of the androgen-regulated TMPRSS2 gene to ERG, which encodes an ETS transcription factor, is the most frequent gene fusion in prostate cancers, found in approximately 50% of cases; upregulation of this fusion gene by androgen is postulated to be involved in prostate carcinogenesis.[83] The studies of androgen induction of this fusion gene have been conducted in cell cultures and it remains to be seen whether this occurs *in vivo* in the human prostate.

Two studies of genetically modified mice demonstrate the importance of AR activity in prostate carcinogenesis. Transgenic mice that overexpress AR in the prostate by targeting additional AR cDNA under control of the probasin promoter, developed dysplastic lesions in 45% of the mice that had morphological similarities with human prostatic intraepithelial neoplasia or PIN, but no cancer was observed.[84] Transgenic mice (n = 5) with a mutation in the AR (E231G) that caused a ligand-independent activity of the receptor developed metastatic adenocarcinomas in the ventral prostate lobe.[85] Although these studies clearly suggest that just increased AR activity may lead to prostate cancer, there are no publications, using these two models, after the initial reports.

ROLE OF ESTROGENS IN PROSTATE CARCINOGENESIS: ANIMAL, AND HUMAN STUDIES

Testosterone can be converted to 17β-estradiol by the enzyme aromatase, which is expressed in the fat tissue and in human and rodent prostates.[86] Therefore, estrogen may be involved in the induction of prostate cancer by testosterone in rat models (see earlier text). When estradiol is combined with the testosterone treatment of these NBL rats, prostate cancer incidence is increased from 35 – 40% with androgen alone [68] to 90 – 100%.[87] Even a short course of estrogen treatment is sufficient to result in a high incidence of prostate cancer in NBL rats, if chronic low-dose testosterone treatment is given, while the testosterone metabolite DHT which cannot be aromatized to estrogen does not induce prostate cancer.[68] These data indicate that estrogen plays a critical role in prostate carcinogenesis. Of note, estrogen treatment alone results in the shutdown of LH production and endogenous androgen production, resulting in prostatic atrophy. Aromatase knockout mice[88] and aromatase overexpressing mice [89,90] suffer from androgen metabolism abnormalities which limits their potentially interesting use for carcinogenesis studies.[91] Aromatase knockout mice lack estrogen production and have elevated circulating testosterone levels and their prostates are enlarged, but they do not develop cancer.[88] In aromatase-overexpressing mice, estrogen production is elevated, while testosterone levels are considerably reduced, but no neoplastic or preneoplastic prostate lesions develop.[26,42] These observations are consistent with the idea that both hormones are necessary for prostate carcinogenesis. In humans, however, there is no evidence of an association between circulating estrogens levels and risk of prostate cancer,[8,9,92] with the possible exception of African–American men, in whom the serum estrogen level and the ratio of estradiol-to-testosterone has been positively associated with risk in a large NHANES III-based study.[93] There has also been no evidence of an association of risk with single nucleotide polymorphisms (SNPs) in the aromatase (*CYP19A1*) gene that are associated with altered serum levels of total and free estradiol and even free (but not total) testosterone.[94] On the other hand, evidence of an association between risk and TTTA repeat length polymorphisms in the estrogen receptor has been found,[95] but is not biologically plausible.[96] The low number of cases in several of these studies may account for inconsistencies in their results.

Both estrogen receptors-α and -β are expressed in the rat and human prostate, and they may mediate some or all the prostatic effects of estrogens.[97-99] When NBL rats are treated with estradiol plus testosterone in combination with the antiestrogen ICI182,780, development of prostatic dysplasia (a

putative preneoplastic lesion comparable to human prostatic intraepithelial neoplasia or PIN) is inhibited.[65] In contrast, the antiestrogen tamoxifen does not affect prostate cancer yield in rats treated with low-dose testosterone, after exposure to a prostate-targeted carcinogen.[80] Of note, the dysplasia in NBL rats, treated with estradiol plus testosterone, occur in a different region of the prostate (dorsolateral prostate) than carcinomas all of which originate from the periurethral prostatic ducts[87] and this dysplasia rarely progresses to cancer.[68] Mice lacking the estrogen receptor-β have been reported to develop enlargement and focal hyperplasia of the ventral prostate,[100,101] but this has not been confirmed in other studies,[91,102,103] and prostate enlargement by itself is not of significance in relation to carcinogenesis.[5] Overall, these data suggest that estrogen receptors do not play a major role in the induction of prostate cancer in rats, but conclusive studies are lacking at present. In humans, in contrast, it has been suggested that the prostatic estrogen receptor-β, which is selectively expressed in epithelial cells, may mediate inhibition of the progression of prostate cancer,[44,64] but this is not a generally accepted or validated concept at present. Haplotype analysis indicated that SNPs in the estrogen receptor-β gene were not or only very weakly associated with the risk of prostate cancer in a large nested case-control study.[104] A repeat length polymorphism in the estrogen receptor-α gene was associated with risk of prostate cancer, but limited to low grade and late onset tumors, and thus, of uncertain clinical significance.[105] An association was found limited to African–American men, between the risk of prostate cancer and a SNP in the estrogen receptor-α gene that may confer reduced activity.[106,107]

In the rodent[108] and human prostate [E. Cavalieri and E. Rogan, personal communication] and in analysis of urinary levels of estrogen metabolites and adducts in men with or without prostate cancer,[109] evidence has been found of conversion of estradiol and estrone to 2- and 4-hydroxyestradiol and -estrone. These catecholestrogens can be converted to estrogen semiquinones and estrogen quinones by the process of redox cycling. These reactive intermediates can adduct to DNA and redox cycling, causing the generation of reactive oxygen species, which can also damage the DNA.[110] The 4-hydroxyestrogen-quinone-DNA adducts rapidly depurinate, resulting in apurinic sites in the DNA, which when repaired by error-prone DNA repair mechanisms can potentially lead to the mutations.[111] Estradiol can indeed be a weak DNA damaging (genotoxic) carcinogen, as demonstrated in experiments with other tissues.[112] We have shown that these reactions can take place in the rat prostate[108] and conceivably also occur in the human prostate. There is evidence indicating that estrogen treatment causes DNA damage in the NBL rat prostate and that this occurs prior to cancer development and at the exact same site within the rat prostate, where carcinomas develop after treatment with estradiol plus testosterone.[108,110,113] We have also developed evidence that enzymes that provide protection against reactive estrogen metabolites, such as, catechol-*O*-methyltransferase and glutathione reductase, are more active in the ventral prostate region, which does not develop cancer in NBL rats treated with estradiol plus testosterone, and less active in the periurethral prostate area, where carcinomas do develop.[108]

CONCLUDING REMARKS

It is attractive and biologically plausible to postulate that endogenous factors present in every man, namely androgens, are responsible for the high frequency of prostate cancer in aging men. However, the data summarized here indicate that the human evidence for this is weak at best, and limited by the fact that adequate access to the tissue of interest, for detailed studies of intraprostatic factors and mechanisms, is extremely difficult if not impossible to attain. In contrast, animal model data indicate that testosterone is carcinogenic for the rat prostate and acts as a strong tumor promoter. The presence of weak genotoxic factors within the prostate can then conceivably result in carcinogenesis promoted by even moderate levels of androgens. One such genotoxic factor may be 17β-estradiol, the aromatase metabolite of testosterone. Other carcinogens may also be involved, as suggested by animal studies with a range of carcinogens that target or are made to target the prostate.[74,76,114] Such exposures to genotoxic carcinogens may be sufficient to cause prostate cancer at high prevalence in humans, just as 17β-estradiol appears to do in the testosterone-treated NBL rat[87] and other carcinogens in androgen-treated rat models.[71,72,74-76] The increase in estrogen-to-androgen ratio that occurs in aging men[115] can be viewed as support for the notion that estrogens, in addition to androgens, are critical factors in prostate carcinogenesis. This hypothesis that estrogens, which are ubiquitously and continuously present in the prostate, can induce mutations may explain why prostate cancer is so common. However, this hypothesis does not explain why some tumors progress to be clinically evident and aggressive, while others remain apparently indolent. It also does not explain why this process of progression appears to be far more common in Western countries, particularly among African–American men, than in most Asian countries, while migrants from low-risk to high-risk countries acquire the risk of their new environment.[2,116] Clearly, there are other factors than hormones *per se* that play a critically decisive role. There is no doubt that there are environmental factors, which are critical determinants of risk of clinically evident prostate cancer,

explaining the changes in prostate cancer risk in migrants from low- to high-risk countries, but these factors have not been identified. It is likely that there are genetic, hereditary factors as well as environmental factors that determine (i) the sensitivity of the androgen receptor for DHT, (ii) critical steps in the metabolism of androgens and estrogens, and (iii) the activity of enzymes involved in the generation of and protection against reactive estrogen metabolites and DNA repair. These various genetic and non-genetic, hormonal and non-hormonal factors probably interact in highly complex and poorly understood ways, to modify risk of prostate cancer. The notion of such a complexity of prostate carcinogenesis is consistent with the great complexity in the molecular alterations in prostate cancers that has emerged over the past decade. Nonetheless, the idea that androgens are central to prostate carcinogenesis remains fully viable, even though epidemiological studies have not provided support for this, and the precise mechanisms by which they may act in the initial stages of this process are unclear. This lack of understanding impedes the development of better preventive approaches than those provided by 5α-reductase inhibitors. The critical role of the androgen receptor and androgen metabolism during prostate cancer progression, on the other hand, is better understood and has resulted in improved treatments.

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REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
2. Bosland MC. The role of steroid hormones in prostate carcinogenesis. J Natl Cancer Inst Monogr 2000;27:39-66.
3. Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000;21:427-33.
4. Tuohimaa P. Control of cell prolifation in male accessory sex glands. Male Accessory Sex Glands. In: Spring-Mills E, Hafez ES, editors. Amsterdam: Elsevier / North-Holland Biomedical Press; 1980. p. 131-53.
5. Milman HA, Bosland MC, Walden PD, Heinze JE. Evaluation of the adequacy of published studies of low-dose effects of bisphenol A on the rodent prostate for use in human risk assessment. Regul Toxicol Pharmacol 2002;35:338-46.
6. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009;55:310-20.
7. Laitinen S, Martikainen PM, Tammela TL, Visakorpi T. Cellular changes in prostate cancer cells induced by intermittent androgen suppression. Eur Urol 2007;52:725-32.
8. Eaton NE, Reeves GK, Appleby PN, Key TJ. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. Br J Cancer 1999;80:930-4.
9. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170-83.
10. Cunha GR. Mesenchymal-epithelial interactions: past, present, and future. Differentiation 2008;76:578-86.
11. Berry PA, Maitland NJ, Collins AT. Androgen receptor signalling in prostate: effects of stromal factors on normal and cancer stem cells. Mol Cell Endocrinol 2008;288:30-7.
12. Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, Henderson BE. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. Lancet 1992;339:887-9.
13. Dondi D, Piccolella M, Biserni A, Della Torre S, Ramachandran B, Locatelli A,, *et al*. Estrogen receptor beta and the progression of prostate cancer: role of 5alpha-androstane-3beta,17beta-diol. Endocrine-related cancer 2010;17:731-42.
14. Ross RK, Coetzee GA, Pearce CL, Reichardt JK, Bretsky P, Kolonel LN, *et al*. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. Eur Urol 1999;35:355-61.
15. Ross RK, Pike MC, Coetzee GA, Reichardt JK, Yu MC, Feigelson H, *et al*. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. Cancer Res 1998;58:4497-504.
16. Chu LW, Reichardt JK, Hsing AW. Androgens and the molecular epidemiology of prostate cancer. Curr Opin Endocrinol Diabetes Obes 2008;15:261-70.
17. Platz EA, Giovannucci E. The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer. J Steroid Biochem Mol Biol 2004;92:237-53.
18. Setiawan VW, Schumacher FR, Haiman CA, Stram DO, Albanes D, Altshuler D, *et al*. CYP17 genetic variation and risk of breast and prostate cancer from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Cancer Epidemiol Biomarkers Prev 2007;16:2237-46.
19. Kraft P, Pharoah P, Chanock SJ, Albanes D, Kolonel LN, Hayes RB, *et al*. Genetic variation in the HSD17B1 gene and risk of prostate cancer. PLoS genetics 2005;1:e68.
20. Pearce CL, Makridakis NM, Ross RK, Pike MC, Kolonel LN, Henderson BE, *et al*. Steroid 5-alpha reductase type II V89L substitution is not associated with risk of prostate cancer in a multiethnic population study. Cancer Epidemiol Biomarkers Prev 2002;11:417-8.
21. Pearce CL, Van Den Berg DJ, Makridakis N, Reichardt JK, Ross RK, Pike MC, *et al*. No association between the SRD5A2 gene A49T missense variant and prostate cancer risk: lessons learned. Hum Mol Genet 2008;17:2456-61.
22. Beuten J, Gelfond JA, Franke JL, Weldon KS, Crandall AC, Johnson-Pais TL, et al. Single and multigenic analysis of the association between variants in 12 steroid hormone metabolism genes and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2009;18:1869-80.
23. Li J, Coates RJ, Gwinn M, Khoury MJ. Steroid 5-{alpha}-reductase Type 2 (SRD5a2) gene polymorphisms and risk of prostate cancer: a HuGE review. Am J Epidemiol 2010;171:1-13.
24. Keshava C, McCanlies EC, Weston A. CYP3A4 polymorphisms--potential risk factors for breast and prostate cancer: a HuGE review. Am J Epidemiol 2004;160:825-41.
25. Schleutker J. Polymorphisms in androgen signaling pathway predisposing to prostate cancer. Mol Cell Endocrinol 2011. [In Press].
26. Setlur SR, Chen CX, Hossain RR, Ha JS, Van Doren VE, Stenzel B, *et al*. Genetic variation of genes involved in dihydrotestosterone metabolism and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2010;19:229-39.
27. Wang C, Tao W, Chen Q, Hu H, Wen XY, Han R. SRD5A2V89L polymorphism and prostate cancer risk: a meta-analysis. Prostate 2010;70:170-8.
28. Makridakis N, Ross RK, Pike MC, Chang L, Stanczyk FZ, Kolonel LN, *et al*. A prevalent missense substitution that modulates activity of prostatic steroid 5alpha-reductase. Cancer Res 1997;57:1020-2.
29. Beilin J, Ball EM, Favaloro JM, Zajac JD. Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. J Mol Endocrinol 2000;25:85-96.
30. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res 1994;22:3181-86.
31. Price DK, Chau CH, Till C, Goodman PJ, Baum CE, Ockers SB, *et al*. Androgen receptor CAG repeat length and association with prostate cancer risk: results from the prostate cancer prevention trial. J Urol 2010;184:2297-302.

32. Lindström S, Ma J, Altshuler D, Giovannucci E, Riboli E, Albanes D, *et al*. A large study of androgen receptor germline variants and their relation to sex hormone levels and prostate cancer risk. Results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. J Clin Endocrinol Metab 2010;95:E121-7.
33. Freedman ML, Pearce CL, Penney KL, Hirschhorn JN, Kolonel LN, Henderson BE, *et al*. Systematic evaluation of genetic variation at the androgen receptor locus and risk of prostate cancer in a multiethnic cohort study. Am J Hum Genet 2005;76:82-90.
34. Xue W, Irvine RA, Yu MC, Ross RK, Coetzee GA, Ingles SA. Susceptibility to prostate cancer: interaction between genotypes at the androgen receptor and prostate-specific antigen loci. Cancer Res 2000;60:839-41.
35. Goodman PJ, Tangen CM, Crowley JJ, Carlin SM, Ryan A, Coltman CA Jr, *et al*. Implementation of the Prostate Cancer Prevention Trial (PCPT). Control Clin Trials 2004;25:203-22.
36. Andriole G, Bostwick D, Brawley O, Gomella L, Marberger M, Tindall D, *et al*. Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial. J Urol 2004;172:1314-7.
37. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, *et al*. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215-24.
38. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, *et al*. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192-202.
39. Sakr WA, Grignon DJ, Crissman JD, Heilbrun LK, Cassin BJ, Pontes JJ, *et al*. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. In Vivo 1994;8:439-43.
40. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. Am J Med 2011;124:578-87.
41. Morgentaler A. Testosterone and prostate cancer: what are the risks for middle-aged men? Urol Clin North Am 2011;38:119-24.
42. Schultheiss D, Machtens S, Jonas U. Testosterone therapy in the ageing male: what about the prostate? Andrologia 2004;36:355-65.
43. Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, *et al*. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560-75.
44. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, *et al*. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005;60:1451-7.
45. Kanayama G, Hudson JI, Pope HG Jr. Illicit anabolic-androgenic steroid use. Horm Behav 2010;58:111-21.
46. Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG Jr. Anabolic-androgenic steroid dependence: an emerging disorder. Addiction 2009;104:1966-78.
47. van Amsterdam J, Opperhuizen A, Hartgens F. Adverse health effects of anabolic-androgenic steroids. Regul Toxicol Pharmacol 2010;57:117-23.
48. Tentori L, Graziani G. Doping with growth hormone / IGF-1, anabolic steroids or erythropoietin: is there a cancer risk? Pharmacol Res 2007;55:359-69.
49. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005;23:8253-61.
50. Yuan X, Balk SP. Mechanisms mediating androgen receptor reactivation after castration. Urol Oncol 2009;27:36-41.
51. Ruizeveld de Winter JA, Janssen PJ, Sleddens HM, Verleun-Mooijman MC, Trapman J, Brinkmann AO, *et al*. Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. Am J Pathol 1994;144:735-46.
52. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer 2011;18:R175-82.
53. Knudsen KE, Penning TM. Partners in crime: deregulation of AR activity and androgen synthesis in prostate cancer. Trends Endocrinol Metab 2010;21:315-24.
54. Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, *et al*. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res 2008;68:6407-15.
55. Chang KH, Li R, Papari-Zareei M, Watumull L, Zhao YD, Auchus RJ, *et al*. Dihydrotestosterone synthesis bypasses testosterone to drive castration-resistant prostate cancer. Proc Natl Acad Sci U S A 2011;108:13728-33.
56. Hofland J, van Weerden WM, Dits NF, Steenbergen J, van Leenders GJ, Jenster G, *et al*. Evidence of limited contributions for intratumoral steroidogenesis in prostate cancer. Cancer Res 2010;70:1256-64.
57. Buchanan G, Greenberg NM, Scher HI, Harris JM, Marshall VR, Tilley WD. Collocation of androgen receptor gene mutations in prostate cancer. Clin Cancer Res 2001;7:1273-81.
58. Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. Endocr Relat Cancer 2004; 11:459-76.
59. Tilley WD, Buchanan G, Hickey TE, Bentel JM. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. Clin Cancer Res 1996;2:277-85.
60. Veldscholte J, Berrevoets CA, Ris-Stalpers C, Kuiper GG, Jenster G, Trapman J, *et al*. The androgen receptor in LNCaP cells contains a mutation in the ligand binding domain which affects steroid binding characteristics and response to antiandrogens. J Steroid Biochem Mol Biol 1992;41:665-9.
61. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, *et al*. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 1995;332:1393-8.
62. Bosland MC, Dreef-Van Der Meulen HC, Sukumar S, Ofner P, Leav I, Han X, *et al*. Multistage prostate carcinogenesis: the role of hormones. Princess Takamatsu Symp 1991; 22:109-23.
63. Marcelli M, Ittmann M, Mariani S, Sutherland R, Nigam R, Murthy L, *et al*. Androgen receptor mutations in prostate cancer. Cancer Res 2000;60:944-9.
64. Horvath LG, Henshall SM, Lee CS, Head DR, Quinn DI, Makela S, *et al*. Frequent loss of estrogen receptor-beta expression in prostate cancer. Cancer Res 2001;61:5331-5.
65. Thompson CJ, Tam NN, Joyce JM, Leav I, Ho SM. Gene expression profiling of testosterone and estradiol-17 beta-induced prostatic dysplasia in Noble rats and response to the antiestrogen ICI 182,780. Endocrinology 2002;143:2093-105.
66. Noble RL, Hochachka BC, King D. Spontaneous and estrogen-produced tumors in Nb rats and their behavior after transplantation. Cancer Res 1975;35:766-80.
67. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. Cancer Res 1977;37:1929-33.
68. Bosland MC. Unpublished data.
69. Pollard M, Luckert PH. Production of autochthonous prostate cancer in Lobund-Wistar rats by treatments with N-nitroso-N-methylurea and testosterone. J Natl Cancer Inst 1986;77:583-7.
70. Pollard M, Luckert PH. Autochthonous prostate adenocarcinomas in Lobund-Wistar rats: a model system. Prostate 1987;11:219-27.
71. Pollard M, Luckert PH, Snyder DL. The promotional effect of testosterone on induction of prostate-cancer in MNU-sensitized L-W rats. Cancer Lett 1989;45:209-12.
72. Hoover DM, Best KL, McKenney BK, Tamura RN, Neubauer BL. Experimental induction of neoplasia in the accessory sex organs of male Lobund-Wistar rats. Cancer Res 1990;50:142-6.
73. Pollard M, Luckert PH. Prostate cancer in a Sprague-Dawley rat. Prostate 1985;6:389-93.
74. Pour PM, Stepan K. Induction of prostatic carcinomas and lower urinary tract neoplasms by combined treatment of intact and castrated rats with testosterone propionate and N-nitrosobis(2-oxopropyl)amine. Cancer Res 1987;47:5699-706.
75. McCormick DL, Rao KV, Dooley L, Steele VE, Lubet RA, Kelloff GJ, *et al*. Influence of N-methyl-N-nitrosourea, testosterone, and N-(4-hydroxyphenyl)-all-trans-retinamide on prostate cancer induction in Wistar-Unilever rats. Cancer Res 1998;58:3282-8.
76. Shirai T, Tamano S, Kato T, Iwasaki S, Takahashi S, Ito N. Induction of invasive carcinomas in the accessory sex organs other than the ventral prostate of rats given 3,2'-dimethyl-4-aminobiphenyl and testosterone propionate. Cancer Res 1991;51:1264-9.
77. Tsukamoto S, Akaza H, Onozawa M, Shirai T, Ideyama Y. A five-alpha reductase inhibitor or an antiandrogen prevents the progression of microscopic prostate carcinoma to macroscopic carcinoma in rats. Cancer 1998;82:531-7.

78. Akaza H, Tsukamoto S, Morita T, Yamauchi A, Onozawa M, Shimazui T, *et al*. Promoting effects of antiandrogenic agents on rat ventral prostate carcinogenesis induced by 3,2'-dimethyl-4-aminobiphenyl (DMAB). Prostate Cancer Prostatic Dis 2000;3:115-9.
79. Homma Y, Kaneko M, Kondo Y, Kawabe K, Kakizoe T. Inhibition of rat prostate carcinogenesis by a 5alpha-reductase inhibitor, FK143. J Natl Cancer Inst 1997;89:803-7.
80. McCormick DL, Johnson WD, Lubet RA, Steele VE, Bosland MC. Differential chemopreventive activity of the antiandrogen, flutamide, and the antiestrogen, tamoxifen, in the rat prostate. Proc Am Assoc Cancer Res 2002;43:640.
81. Haffner MC, Aryee MJ, Toubaji A, Esopi DM, Albadine R, Gurel B, *et al*. Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. Nat Genet 2010;42:668-75.
82. Bastus NC, Boyd LK, Mao X, Stankiewicz E, Kudahetti SC, Oliver RT, *et al*. Androgen-induced TMPRSS2:ERG fusion in nonmalignant prostate epithelial cells. Cancer Res 2010;70:9544-8.
83. Clark JP, Cooper CS. ETS gene fusions in prostate cancer. Nat Rev Urol 2009;6:429-39.
84. Stanbrough M, Leav I, Kwan PW, Bubley GJ, Balk SP. Prostatic intraepithelial neoplasia in mice expressing an androgen receptor transgene in prostate epithelium. Proc Natl Acad Sci U S A 2001;98:10823-8.
85. Han G, Buchanan G, Ittmann M, Harris JM, Yu X, Demayo FJ, *et al*. Mutation of the androgen receptor causes oncogenic transformation of the prostate. Proc Natl Acad Sci U S A 2005;102:1151-6.
86. Ellem SJ, Schmitt JF, Pedersen JS, Frydenberg M, Risbridger GP. Local aromatase expression in human prostate is altered in malignancy. J Clin Endocrinol Metab 2004;89:2434-41.
87. Bosland MC, Ford H, Horton L. Induction at high incidence of ductal prostate adenocarcinomas in NBL / Cr and Sprague-Dawley Hsd:SD rats treated with a combination of testosterone and estradiol-17 beta or diethylstilbestrol. Carcinogenesis 1995;16:1311-7.
88. McPherson SJ, Wang H, Jones ME, Pedersen J, Iismaa TP, Wreford N, *et al*. Elevated androgens and prolactin in aromatase-deficient mice cause enlargement, but not malignancy, of the prostate gland. Endocrinology 2001;142:2458-67.
89. Fowler KA, Gill K, Kirma N, Dillehay DL, Tekmal RR. Overexpression of aromatase leads to development of testicular leydig cell tumors: an in vivo model for hormone-mediated TesticularCancer. Am J Pathol 2000;156: 347-53.
90. Li X, Nokkala E, Yan W, Streng T, Saarinen N, Wärri A, *et al*. Altered structure and function of reproductive organs in transgenic male mice overexpressing human aromatase. Endocrinology 2001;142:2435-42.
91. Jarred RA, McPherson SJ, Bianco JJ, Couse JF, Korach KS, Risbridger GP. Prostate phenotypes in estrogen-modulated transgenic mice. Trends Endocrinol Metab 2002;13:163-8.
92. Yao S, Till C, Kristal AR, Goodman PJ, Hsing AW, Tangen CM, *et al*. Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case-control study. Cancer Causes Control 2011;22:1121-31.
93. Rohrmann S, Nelson WG, Rifai N, Brown TR, Dobs A, Kanarek N, *et al*. Serum estrogen, but not testosterone, levels differ between black and white men in a nationally representative sample of Americans. J Clin Endocrinol Metab 2007;92:2519-25.
94. Travis RC, Schumacher F, Hirschhorn JN, Kraft P, Allen NE, Albanes D, *et al*. CYP19A1 genetic variation in relation to prostate cancer risk and circulating sex hormone concentrations in men from the Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiol Biomarkers Prev 2009;18:2734-44.
95. Cussenot O, Azzouzi AR, Nicolaiew N, Fromont G, Mangin P, Cormier L, *et al*. Combination of polymorphisms from genes related to estrogen metabolism and risk of prostate cancers: the hidden face of estrogens. J Clin Oncol 2007;25:3596-3602.
96. Tang L, Yao S, Till C, Goodman PJ, Tangen CM, Wu Y, *et al*. Repeat polymorphisms in estrogen metabolism genes and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Carcinogenesis 2011;32:1500-6.
97. Latil A, Bièche I, Vidaud D, Lidereau R, Berthon P, Cussenot O, *et al*. Evaluation of androgen, estrogen (ER alpha and ER beta), and progesterone receptor expression in human prostate cancer by real-time quantitative reverse transcription-polymerase chain reaction assays. Cancer Res 2001;61:1919-26.
98. Lau KM, Leav I, Ho SM. Rat estrogen receptor-alpha and -beta, and progesterone receptor mRNA expression in various prostatic lobes and microdissected normal and dysplastic epithelial tissues of the Noble rats. Endocrinology 1998;139:424-7.
99. Leav I, Lau KM, Adams JY, McNeal JE, Taplin ME, Wang J, *et al*. Comparative studies of the estrogen receptors beta and alpha and the androgen receptor in normal human prostate glands, dysplasia, and in primary and metastatic carcinoma. Am J Pathol 2001;159:79-92.
100. Krege JH, Hodgin JB, Couse JF, Enmark E, Warner M, Mahler JF, *et al*. Generation and reproductive phenotypes of mice lacking estrogen receptor beta. Proc Natl Acad Sci U S A 1998;95:15677-82.
101. Weihua Z, Makela S, Andersson LC, Salmi S, Saji S, Webster JI, *et al*. A role for estrogen receptor beta in the regulation of growth of the ventral prostate. Proc Natl Acad Sci U S A 2001;98:6330-5.
102. Couse JF, Curtis Hewitt S, Korach KS. Receptor null mice reveal contrasting roles for estrogen receptor alpha and beta in reproductive tissues. J Steroid Biochem Mol Biol 2000; 74:287-96.
103. Dupont S, Krust A, Gansmuller A, Dierich A, Chambon P, Mark M. Effect of single and compound knockouts of estrogen receptors alpha (ERalpha) and beta (ERbeta) on mouse reproductive phenotypes. Development 2000;127:4277-91.
104. Chen YC, Kraft P, Bretsky P, Ketkar S, Hunter DJ, Albanes D, *et al*. Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiol Biomarkers Prev 2007;16:1973-81.
105. Nicolaiew N, Cancel-Tassin G, Azzouzi AR, Grand BL, Mangin P, Cormier L, *et al*. Association between estrogen and androgen receptor genes and prostate cancer risk. Eur J Endocrinol 2009;160:101-6.
106. Maruyama H, Toji H, Harrington CR, Sasaki K, Izumi Y, Ohnuma T, *et al*. Lack of an association of estrogen receptor alpha gene polymorphisms and transcriptional activity with Alzheimer disease. Arch Neurol 2000;57:236-40.
107. Hernández J, Balic I, Johnson-Pais TL, Higgins BA, Torkko KC, Thompson IM, *et al*. Association between an estrogen receptor alpha gene polymorphism and the risk of prostate cancer in black men. J Urol 2006;175:523-7.
108. Cavalieri EL, Devanesan P, Bosland MC, Badawi AF, Rogan EG. Catechol estrogen metabolites and conjugates in different regions of the prostate of Noble rats treated with 4-hydroxyestradiol: implications for estrogen-induced initiation of prostate cancer. Carcinogenesis 2002;23:329-33.
109. Yang L, Gaikwad NW, Meza J, Cavalieri EL, Muti P, Trock B, *et al*. Novel biomarkers for risk of prostate cancer: results from a case-control study. Prostate 2009;69:41-8.
110. Cavalieri E, Frenkel K, Liehr JG, Rogan E, Roy D. Estrogens as endogenous genotoxic agents--DNA adducts and mutations. J Natl Cancer Inst Monogr 2000:75-93.
111. Mailander PC, Meza JL, Higginbotham S, Chakravarti D. Induction of A.T to G.C mutations by erroneous repair of depurinated DNA following estrogen treatment of the mammary gland of ACI rats. J Steroid Biochem Mol Biol 2006;101:204-15.
112. Liehr JG. Role of DNA adducts in hormonal carcinogenesis. Regul Toxicol Pharmacol 2000;32:276-82.
113. Han X, Liehr JG, Bosland MC. Induction of a DNA adduct detectable by 32P-postlabeling in the dorsolateral prostate of NBL / Cr rats treated with estradiol-17 beta and testosterone. Carcinogenesis 1995;16:951-4.
114. Bosland MC, Prinsen MK. Induction of dorsolateral prostate adenocarcinomas and other accessory sex gland lesions in male Wistar rats by a single administration of N-methyl-N-nitrosourea, 7,12-dimethylbenz(a)anthracene, and 3,2'-dimethyl-4-aminobiphenyl after sequential treatment with cyproterone acetate and testosterone propionate. Cancer Res 1990;50: 691-9.
115. Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. T Aging Male 2002;5:98-102.
116. Gann PH. Risk factors for prostate cancer. Rev Urol 2002;4 Suppl 5:S3-10.

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