Endocrinology. 2023 Jun; 164(6): bqad071. PMCID: PMC10413436
Published online 2023 May 8. doi: 10.1210/endocr/bqad071: 10.1210/endocr/bqad071 PMID: 37154098

Stranger Things: New Roles and Opportunities for Androgen Receptor in Oncology Beyond Prostate Cancer

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Received 2023 Feb 17

Abstract

The androgen receptor (AR) is one of the oldest therapeutic targets in oncology and continues to dominate the treatment landscape for advanced prostate cancer, where nearly all treatment regimens include some form of AR modulation. In this regard, AR remains the central driver of prostate cancer cell biology. Emerging preclinical and clinical data implicate key roles for AR in additional cancer types, thereby expanding the importance of this drug target beyond prostate cancer. In this mini-review, new roles for AR in other cancer types are discussed as well as their potential for treatment with AR-targeted agents. Our understanding of these additional functions for AR in oncology expand this receptor's potential as a therapeutic target and will help guide the development of new treatment approaches.

Keywords: androgen receptor, prostate cancer, breast cancer, endometrial cancer, adrenal cancer, melanoma, bladder cancer, liver cancer

While androgen receptor (AR) signaling is the major therapeutic target for the treatment of prostate cancer, recent studies have highlighted causal roles for AR in other cancer types. These functional studies importantly distinguish direct roles for AR in tumor biology from indirect hormone actions and/or potential noncausal correlations. With cancers that present sexually dimorphic patterns, a key distinction is whether the differences in incidence and/or severity are due to environmental factors or underlying biological differences. Cancers such as gastric, lung, and mesothelioma are more common in men, but it remains uncertain whether these sex-specific differences are due to direct androgen/AR actions within these tumor types or caused by differences in environmental factors such as diet, smoking, and occupational hazards (1-3). For instance, the increased incidence of mesothelioma in men compared with women is thought to be attributable to men being more often employed in jobs exposing them to asbestos (4, 5). Additional environmental factors such as diet and smoking could also influence how many males and females develop cancer (6). The incidence of other sexually dimorphic cancers such as Kaposi's sarcoma, while occurring 2.3 times to 50 times more often in men than in women, likely reflects the higher transmission rate of Kaposi's sarcoma–associated herpesvirus in men, and hence indirectly skews the cancer incidence sex ratio (7-9). In contrast, several cancer types exhibit sex disparities even when accounting for environmental variables. For instance, some mouse models of hepatocellular carcinoma (HCC) can disproportionately occur in male mice compared with their genetically similar female counterparts when other factors are equal (eg, housing conditions, diet, etc.), mirroring what is observed in male and female patients where men are 2 to 3 times more likely to get HCC than women (10-12). While sex steroid hormone signaling is often proposed as a causative factor, the systemic effects of hormones and their metabolism have made it challenging to delineate the exact molecular mechanism of action. However, recent advances in preclinical modeling, combined with clinical data, have begun to clarify functional new roles for long-suspected players like the AR in previously underexplored cancers. In this mini-review, we examine mounting evidence that supports testing AR-targeting agents (both agonists and antagonists) in tumor types beyond prostate cancer.

Bladder Cancer

Urothelial carcinoma has a nearly 4:1 male:female predominance (13). Sex differences persist even after correcting for other known risk factors for bladder cancer including smoking, urinary tract infection, occupation, and environmental hazards (14). These observations suggest that sex is a critical biological variable in urothelial carcinoma biology. The sex disparity is possibly explained by the interplay of the promoting effect from testosterone (15), the protective effect of estrogen (16, 17), and sex hormone modulation of the liver's ability to metabolize bladder carcinogens (18).

AR signaling has been proposed to play a role in the pathogenesis of urothelial carcinoma, and may represent an advantageous therapeutic target (19). Through sex chromosome–independent mechanisms, androgens promote a CD8+ T cell exhaustion program and contribute to sex bias in urothelial carcinoma. Mechanistically, AR transcriptionally transactivates Tcf7/TCF1, which can drive a novel sex-specific regulon in progenitor exhausted CD8+ T cells. Ablation of the androgen–AR axis rewires the tumor microenvironment to favor effector T cell differentiation and potenti-

ates the efficacy of anti-PD-1 immune checkpoint blockade in preclinical mouse models (20). Within bladder cancer cells, AR signaling may also crosstalk with other oncogenic proteins (eg, ERBB2, EGFR, NF-κB, ELK1, ATF2), regulate CD44 (biomarker associated with progressive tumorigenesis), downregulate uridine diphosphate (UDP) glucuronosyltransferases (carcinogen detoxification), and activate an epithelial–mesenchymal transition (associated with metastasis) (18, 21-27). Alternatively, in a sex chromosome–dependent fashion, key sex chromosome–based epigenomic genes have been reported to suppress bladder tumorigenesis in females. A recent report demonstrated that *KDM6A* and its murine ortholog *Kdm6a* are encoded by the X chromosome but escape X chromosome inactivation. KDM6A expression is twice as high in females compared with males (28). Urothelium-specific conditional knockout of *Kdm6a* in mice significantly increased urothelial carcinoma risk in females, but not in males, suggesting that KDM6A is a female-biased tumor suppressor.

In urothelial carcinoma patients, high AR expression has been associated with tumor progression, recurrence, and metastasis, as well as resistance to radiotherapy and certain chemotherapies including cisplatin, gemcitabine, and doxorubicin (29-36). However, a contrasting clinical study reports decreased AR expression in urothelial carcinoma compared with benign bladder, and low AR being associated with higher grade and more invasive tumors (37). Despite this discrepancy, use of 5-alpha reductase inhibitors and AR suppression alone or in combination with chemotherapy or immunotherapy have been associated with diminished urothelial carcinoma tumor progression and decreased disease recurrence (38-46) (Table 1).

Tissue analysis of patients in the LAMB trial (NCT00949455) found that ~30% of urothelial carcinoma tumors overexpressed AR, which correlated with worse prognosis (66). This work provided rationale to test the benefit of androgen deprivation therapy with enzalutamide in ATLANTIS (EudraCT number 2015-003249-25. ISRCTN25859465), an ongoing multi-arm phase II trial of maintenance therapy in metastatic urothelial carcinoma. In patients with positive AR expression by immunohistochemistry, ATLANTIS randomizes between enzalutamide and placebo maintenance, using progression-free survival (PFS) as a primary outcome (67). Such studies will be helpful to prospectively assess the efficacy of targeting AR in patients with urothelial carcinoma. Future studies should include the use of AR antagonism in both maintenance and frontline combination therapy settings for patients with urothelial carcinoma, as well as in combination with immune checkpoint inhibition given the potential for synergistic effect of anti-PD1 therapy with AR inhibition observed in preclinical studies (20).

Melanoma

Differences in outcomes by sex have been noted in melanoma for decades, with male sex being independently associated with worse prognosis both in terms of relapse from early-stage disease and survival in late-stage disease (68-71). The biology behind this dimorphic outcome is likely complex and may involve hormone-dependent and -independent effects on both tumor-intrinsic and -extrinsic pathways (72-76). Androgens may play a role in melanoma metastasis via the modulation of miRNA signaling and subsequent microphthalmia-associated transcription factor (MITF) degradation and an altered MITF–AXL ratio (77, 78). Alternatively, inhibition of AR can decrease melanoma cell growth in cell lines and xenograft tumor growth in both immunocompromised and

immune-intact mice by a proposed cancer cell–intrinsic mechanism of induced dsDNA breakage, cytoplasmic leakage, and STING activation (79). Recently, androgen signaling in melanoma has also been implicated in resistance to targeted therapy possibly through a similar melanoma cell–intrinsic mechanism (80).

Fifty percent of melanomas have a BRAF mutation that activates the MAPK signaling pathway (69). In these patients, BRAF-directed targeted therapy with combined BRAF and MEK inhibition is a highly effective therapy for many patients; however, outcomes are heterogeneous and strategies to improve response are urgently needed (69). Robert et al (69) and Vellano and colleagues (80) noted significant differences in outcome by sex in patients treated with BRAF- and MEK-directed targeted therapy (n = 664) . Importantly, the investigators had access to paired tumor specimens in a subset of patients treated with BRAF/MEKi in the neoadjuvant setting (n = 23). Analysis of pretreatment tumor biopsies demonstrated that AR staining was minimal at baseline. However, post-treatment resected specimens showed increased AR staining, particularly in males, as well as expression of AR signaling genes noted in patients who failed to achieve a pathological response, suggesting an association between AR activity and response (Fig. 1). Murine models of *BRAF*-mutated melanoma demonstrated a similar sexual dimorphism with female mice showing improved control compared with males in both immunocompetent and immunocompromised (CD-1 nude) preclinical models. Intriguingly, administration of testosterone in male and female mice upregulated AR expression and led to diminished tumor control while treatment with enzalutamide improved tumor control in both male *and* female mice. CRISPR-mediated AR knockout in melanoma cells abrogated the differences by mouse sex in animals receiving BRAF/MEKi both with and without hormonal modulation. Although additional cancer cell extrinsic roles for AR cannot be fully ruled out, these data support the concept of AR as a melanoma cell autonomous driver of targeted therapy resistance. Importantly, hormonal modulation represents a potential druggable target to augment current standard of care therapies in melanoma.

The first clinical trial targeting AR in melanoma (Debio 8200-IMM-101) was reported in March 2023 (49). In this phase I, single-arm, open-label study, the safety and efficacy of ADT (triptorelin) plus bicalutamide and anti-PD-1 (nivolumab) was evaluated in male melanoma patients (n = 14) who were refractory to anti-PD-1. No grade 4 or 5 adverse effects were observed. Disease control was observed in 6 patients, but objective responses were seen in only 1 (RECIST) and 2 (iRECIST) patients. Whether the responses were due to the AR-targeted therapy needs to be tested in randomized controlled trials.

Endometrial Cancer

Hormonal signaling is well known to be important in endometrial cancer, particularly in tumors with low grade histology. Although most work has focused on estrogen and progesterone signaling and blockade (81), there is mounting evidence that AR is relevant in this disease. Epidemiologic and translational studies have highlighted the importance of circulating androgens in patients with endometrial cancer (82, 83), and androgens have a known link with obesity (84), which one of the primary predisposing factors for development of endometrial cancer (85, 86). When primary endometrial tumors are evaluated, AR expression has ranged from 20% to 86% depending on the cohort studied (87-90). Highest expression has been found in lower grade tu-

mors (87, 88), but notably, even some nonendometrioid (higher risk) tumors had AR expression (91, 92). Although most cases that were AR+ were also estrogen receptor α (ERα+), a smaller subset of patients had AR+/ERα− tumors (92). From a prognostic standpoint, most tumors with increased hormone receptor expression (namely, ERα and progesterone receptor [PR]) are lower grade and have a better prognosis than higher-grade tumors, which are more frequently hormone receptor negative (93, 94). As such, patients whose tumors demonstrate AR positivity will often have an improved survival relative to those with AR-negative tumors ($P < .0001$; n = 85) (91). However, 1 study demonstrated that while AR expression was correlated with favorable outcomes overall, patients with AR+/ERα− tumors (ie, a high AR to ERα ratio) had shorter survival outcomes ($P < .001$; n = 142) (88). Thus, the role of AR signaling in endometrial cancer may be more complicated than initially thought.

Data are limited regarding the use of AR blockade in the treatment of endometrial cancer. Preclinical data evaluating enzalutamide have been mixed (95). Although short-term there was evidence of increased local control in vivo, long-term there was a paradoxical increase in the amount of invasive and metastatic lesions. This suggests a more complex role of androgen blockade within the context of endometrial tumor biology relative to other hormone signaling pathways, as progesterone modulation and estrogen modulation have both been successful in endometrial cancer (96-98). More recently, however, a phase II study evaluating enzalutamide in combination with paclitaxel and carboplatin (the standard first-line treatment for metastatic endometrial cancer) in patients with untreated advanced or recurrent endometrioid, endometrial cancer found an impressive overall response rate (ORR) of 71% and a median PFS of 14 months (NCT02684227; n = 35) (47). Multiple translational endpoints were included. Once available, these data may inform which patients are most likely to benefit from AR blockade alone or in combination with standard chemotherapy.

Adrenal Cancer

Adrenocortical carcinoma (ACC) is a rare, yet highly aggressive cancer that originates in the outer portion of the adrenal gland (99, 100). The overall 5-year survival rate for ACC is <50%, and there are currently no available targeted therapies (101). In contrast to most other nonreproductive cancers (6), ACC is more common in women than in men (~2.5:1) (102, 103). This unique sex bias in ACC may provide important clues about the etiology of adrenal cancer and provide new opportunities for therapeutic intervention. A protective role for androgens, which is mediated by both tumor cell–intrinsic and –extrinsic mechanisms, has recently emerged.

The potential for AR to play a beneficial role in adrenal cancer was first suggested by clinical observations of androgen-producing tumors. Although adrenal tumors that purely secrete excess androgens are extremely rare, they are known to have a more favorable prognosis. In one of the largest cohorts available (104), ~50% of cases were benign. Of the malignant ACC cases, 80% of patients showed durable, long-term survival and remained disease free following treatment with a mean follow-up of more than 10 years. Consistent with these findings, analysis of The Cancer Genome Atlas project on ACC (105) reveals that pure androgen-secreting tumors are predomi-

nately found within the least aggressive subtype (Table 2). Moreover, high *AR* expression is associated with significantly longer PFS and overall survival (OS). Together, these data suggest that contrary to other cancer types like prostate, high androgen levels are clinically favorable in ACC.

Building on these clinical correlates, recent preclinical studies have uncovered tumor cell–intrinsic and –extrinsic mechanisms through which androgens can suppress the growth of adrenal tumors. Studies in mice demonstrate that circulating androgens regulate homeostatic renewal of the adrenal cortex by suppressing the recruitment and proliferation of stem cells (106), and enhancing apoptotic turnover of differentiated cortex cells (107). In human ACC cells, dihydrotestosterone (DHT) treatment reduces proliferation as well as anchorage-independent growth, effects that can be rescued by antiandrogens, indicating a tumor suppressive role for AR in ACC cells (108). Beyond these ACC cell-autonomous roles, androgen signaling has more recently been found to promote antitumor immunity in a mouse model of ACC. This newly developed transgenic model is based on targeted loss of *ZNRF3*, a Wnt pathway inhibitor (109, 110) that is frequently deleted in human ACC (105, 111). Despite initial hyperplasia in both males and females (112), *Znrf3* conditional knockout mice only develop adrenal tumors with advanced aging, in a sex-dimorphic manner (113, 114). Specifically, females predominately develop metastatic adrenal tumors while males primarily develop benign tumors. This striking sex difference in tumor formation is linked to a differential immune response whereby males exhibit significantly higher recruitment of CD68-positive myeloid cells, including phagocytic macrophages and antigen-presenting dendritic cells. In females, DHT treatment enhances phagocytic macrophages (113). Conversely, androgen deprivation in males through surgical castration potently blocks this response by suppressing recruitment of monocyte-derived Cd11c- as well as Cd11b-positive cells (114). Notably, T cell infiltration is also reduced with castration (114), suggesting impaired adaptive immunity from the loss of antigen-presenting cells. This work supports a new role for androgens in promoting antitumor immunity in the adrenal, and importantly translates to ACC patients. Analysis of The Cancer Genome Atlas revealed that men have a higher Adrenal Myeloid Response Score than women, which is associated with better OS and PFS even when patients are stratified by sex (114). These findings may have significant clinical implications, particularly with respect to hypogonadism that is prevalent in aging men (115) and a known side effect of mitotane (116)—the only available frontline therapy for ACC.

Liver Cancer

The development and progression of HCCs manifest more in men than in women (1). Previous research indicates that differences between sexes in occupational roles, smoking habits, and diet account for higher incidence and mortality rates in men vs women (117). Prior studies also suggest that the disproportionate manifestation of HCCs in men compared with women can be explained by sex hormones rather than environmental factors (117). To that end, preclinical models recapitulate the sexual dimorphism observed in humans with HCC, supporting the notion that there are fundamental biological differences that underly the observed HCC sex disparities. These mechanistic studies have begun to demonstrate how sex hormones crosstalk with pathways involved in cell proliferation, survival, and migration to promote HCC (11, 118-127). Moreover, a recent study un-

veiled AR-dependent molecular mechanisms primarily driven by neutrophils promoting male-driven liver metastasis by creating a protumorigenic milieu for tumor cells residing in this organ (128). Importantly, these steroid hormone studies may yield tractable treatment approaches.

Overexpression of AR in HCCs has been linked to protumorigenic states, worse prognosis, and worse OS according to database/genomic results, in vitro studies, in vivo experiments, and emerging clinical trials (11, 123-127). Paradoxically, loss of function or low expression of AR has also been linked to the development and progression of HCC, suggesting that AR can also function as a tumor suppressor (118-122). Thus, both agonists and antagonists of AR signaling have been proposed for the treatment of HCC.

Oncogenic roles for AR in HCC

Liver-specific deletion of the pioneer factors *Foxa1* and *Foxa2* in a diethylnitrosamine-induced mouse model of hepatocarcinogenesis that recapitulates the sexual dimorphism observed in humans completely reversed the oncogenic effects of androgens as well as the tumor suppressive effects of estrogens (11). Chromatin immunoprecipitation (ChIP)-Seq analysis revealed that AR/FOXA1/2 complexes drive hepatocarcinogenesis while ERα/FOXA1/2 complexes impair HCC. In a separate study, high AR expression in human HCC tissues (n = 142) correlated with advanced disease stage and poor OS (123). Cell culture and xenograft mouse model studies using AR+ HCC cells demonstrated that these cells have intact AR transcriptional activity and AR-mediated cell growth that could be blocked with enzalutamide. However, AR inhibition led to feedback activation of AKT–mTOR signaling to alternatively promote HCC progression by increasing nuclear AR expression. Combined targeting of AR and mTOR had dramatic anti-HCC activity in vivo. Thus, treatment of AR-driven HCC may require drug combination approaches to overcome AR reactivation mechanisms.

Tumor-suppressive roles for AR in HCC

Despite the higher incidence of HCC in men, several studies suggest that AR can have tumor-suppressive roles in liver cancer. For example, AR inhibited the expression of the RAS oncogene family member RABL6 by increasing the expression of the RABL6-targeting miRNA miR-122-5p (118). These functional studies were supported by clinical correlates derived from the UALCAN, GEPIA, and ENCORI databases that demonstrated that AR signaling decreases as HCCs progress to later stages and is negatively correlated with RABL6 expression. Further, preclinical studies using orthotopic HCC xenograft models demonstrated that silencing of AR using shRNAs promoted tumor growth and increased RABL6 expression (118). In a separate study, AR loss of function, via lowered miR-325 expression, increased ACP5-mediated HCC cell migration and invasion (120). Accordingly, AR knockdown in HA22T human HCC cell xenograft models increased ACP5 expression and metastasis. Similarly, the loss of AR signaling in HCC cells due to hypoxia also increases the circular RNA circ-LNPEP, which indirectly increases RAB9A expression, leading to the subsequent progression of HCC (119). Here, expression of circ-LNPEP, AR, or the combination was modulated in SK-HEP-1 cells and injected orthotopically into nude mice. AR signaling suppressed metastasis of HCC, an effect that could be reversed by circ-LNPEP.

The multifaceted roles of AR in HCC suggest a mixed role for the receptor in liver cancer that complicates the use of AR modulators for treatment (Fig. 2). An example of this is a phase II, double-blind, 2-arm study (NCT02528643, n = 165) testing the efficacy of enzalutamide alone in advanced HCC in men and women that demonstrated no significant effect on OS or PFS (48). The existence of both procancer and anticancer roles of AR in HCC suggests that an improved understanding of the downstream effects of AR signaling may yield better therapies that can block the AR's oncogenic signaling while sparing its tumor-suppressive effects.

Gastric/Lung/Kidney/Esophageal Cancer

The sexual dimorphism observed in several cancer types or subtypes has been linked to environmental and occupational factors. For instance, increased rates of gastric, lung, kidney, and esophageal cancers in men may be attributed to the higher rates of smoking in men and differences in diet (129-132). Despite the numerous reports of environmental, recreational, and occupational factors driving sexual dimorphisms in these cancers, less is known about the potential roles and mechanisms of sex hormones in these malignancies. Reports of AR signaling in gastric and esophageal cancers suggest oncogenic roles where AR overexpression is negatively correlated with prognosis and enables the expression of other oncogenes such as CCRK via transcriptional activation (133-141). In lung cancer, there are mixed reports on the AR's function, suggesting AR may play contradictory roles in carcinogenesis (142, 143). Likewise, AR has been reported to have differential effects in renal cell carcinoma metastasis depending on the metastatic site (144, 145). Hence, targeting AR signaling in these cancers has not been a major clinical focus.

Breast Cancer

AR is expressed in ~70% of breast cancers but varies between subtype with the highest expression (~70-90%) in ERα+ tumors and the lowest (~10-30%) in triple-negative breast cancers (TNBCs) (Fig. 3) (55, 146, 147). Clinical studies have correlated altered AR expression with disease progression and therapy relapse (148-156). However, there are conflicting data with regards to whether AR is marker of favorable or poor prognosis (149-152, 154-156). Further, attempts to link serum androgen levels with prognosis have also yielded unclear answers, in part due to the challenges with measuring available/free intratumoral androgen levels (157). Likewise, a series of preclinical studies suggest that both AR agonists and antagonists can impair breast cancer in cellular, ex vivo, and in vivo models (149-151, 154, 158-176). Importantly, early phase (I/II) clinical trials reinforce the paradoxical preclinical findings that both activation and inhibition of AR may benefit breast cancer patients (50, 52, 54, 55, 57-60). What is becoming clear is that the AR's role in breast cancer depends on the subtype as well as host factors (eg, hormonal status—premenopausal vs postmenopausal—body composition).

Triple-Negative Breast Cancer

TNBCs are characterized by the absence of ERα, PR, and HER2 staining. TNBC represents an extremely aggressive subtype of breast cancer with limited treatment options. As such, there is great interest in identifying new therapeutic targets for TNBC. Interestingly, a series of microarray stud-

ies found that TNBCs can be further subdivided (152, 170, 177, 178). Within TNBCs, there is a population of AR+ tumors commonly referred to as molecular apocrine or the related luminal AR TNBC that does not express ERα, but demonstrates paradoxical expression of genes typically associated with ERα+ luminal breast cancers. Consensus suggests that these apocrine TNBCs are driven in part by AR and as such, are good candidates for AR signaling inhibitors.

Preclinical studies using AR+ TNBC cell lines (eg, MDA-MB-453) and xenograft (cell line and patient-derived [eg, HCI-009]) mouse models indicate that AR signaling inhibitors such as enzalutamide and seviteronel have antitumor efficacy alone and in combination with other mechanistically distinct agents such as radiotherapy or CDK4/6, mTOR, and/or PARP inhibitors (160, 163, 165, 166, 168). Conversely, androgens increase the growth AR+ TNBC cells and tumors (149, 160, 171, 172). For these molecular apocrine TNBCs, AR signaling appears to compensate for the lack of procancer signaling normally provided by other nuclear receptors such as ERα. AR promotes a gene expression signature resembling that of an ERα-mediated signature, despite the lack of ERα protein in these cells (152, 170, 171). In addition, AR signaling can increase the phosphorylation and activity of HER2 and/or HER3 signaling (163, 179, 180), and enhance the transcriptional activity of MYC (181). Similar to prostate cancer (182), AR inhibition decreases the expression of DNA repair machinery, thereby sensitizing breast cancers to PARP inhibitors or radiotherapy (166, 168).

Clinical studies suggest a potential role for AR signaling inhibitors in the treatment of a subset of TNBC. A multicenter, single-arm, phase II trial (NCT01842321) of abiraterone acetate plus prednisone in patients with AR+ locally advanced or metastatic TNBC (n = 30) reported that after 6 months of treatment, patients had a clinical benefit rate (CBR) of 20% (below its primary endpoint goal of 25%) with 1 patient having a complete response and 5 patients having stable disease (50). Here, the ORR was 6.7% (95% CI 0.8-22.1%) and the median PFS was 2.8 months (95% CI 1.7-5.4%). These data suggest that some patients selected for the molecular apocrine subtype had a beneficial response to abiraterone. Likewise, early results from a phase II trial (NCT02580448) testing seviteronel, another CYP17 lyase inhibitor with partial AR inhibitory activity, in women with advanced AR+ TNBC or ERα+ breast cancer suggest benefit from seviteronel with 33% CPR at 16 weeks (albeit only 6 evaluable patients) for TNBC (51). Since TNBC lacks the ER, it is probable that any beneficial effects of CYP17 lyase inhibitors are due to their ability to lower androgens rather than effects on estrogen levels.

Multiple antiandrogens have also been tested in patients with TNBC. In a single-arm, open-label, phase II study (NCT01889238) evaluating the safety and efficacy of enzalutamide in women with locally advanced or metastatic AR+ TNBC (n = 78), the primary endpoint of CBR at 4 months was 33% (95% CI 23%-45%) in the evaluable (defined as at least 10% AR+ cells by immunohistochemistry (IHC) and 1 or more postbaseline tumor assessments) group compared with the intent-to-treat population (25% CBR; 95% CI 17-33%) (52). Secondary endpoints such as median PFS and OS also suggested enzalutamide-mediated efficacy. PFS was 2.9 months (95% CI 1.9-3.7 months) in the intent-to-treat group and 3.3 months (95% CI 1.9-4.1 months) in the evaluable group. Likewise, OS was 12.7 months (95% CI 8.5-16.5 months) in the intent-to-treat population compared with 16.5 months (95% CI 12.7-20.0 months) in the evaluable group. These data support the notion that enzalutamide has efficacy in women with AR+ TNBC. These data are supported by

another single-arm study of adjuvant enzalutamide in early-stage AR+ TNBC (n = 50) that reported enzalutamide was well-tolerated and exhibited a 3-year disease-free survival of 80% (95% CI 67-94%) with adjuvant endocrine therapy (53). Further, interim analysis of NCT03383679, a randomized, phase II trial of darolutamide or capecitabine, an inhibitor of de novo nucleotide synthesis, in patients with advanced AR+ TNBC revealed that 5 of 19 evaluable patients had a 26.3% CBR (95% CI 9.2%-51.2%) after 16 weeks of darolutamide treatment (54). An open-label, single-arm, multisite, phase II study (NCT00468715) testing bicalutamide in patients with AR+ERα/PR– breast cancer (n = 26) (55) (the majority of these patients also had normal HER2 levels and, hence, fit TNBC criteria) reported that patients had a 19% CBR (95% CI 7-39%) after 6 months of bicalutamide treatment and a median PFS of 12 weeks (95% CI 11-22 weeks), the latter being comparable with single agent or combination chemotherapy in similar trials. In addition, a nonrandomized phase I/II trial (n = 46) testing the CDK4/6 inhibitor palbociclib in combination with bicalutamide in patients with AR(+) TNBC (NCT02605486) met its initial primary endpoint, with the combination therapy having ~24% PFS at 6 months (56). An important consideration for all these trials is that, at present, it is unclear whether screening for AR+ tumors selected for a more indolent form of TNBC. Future, randomized trials should help address this issue.

A single trial (NCT02971761) has also been reported that tested the initial efficacy of the selective AR modulator (SARM) GTx-024 (enobosarm) in combination with anti-PD-1 therapy (pembrolizumab) in patients (n = 16 evaluable) with AR+ TNBC (63). Although the combination of enobosarm and pembrolizumab had a modest clinical benefit of 25% at 16 weeks, the trial was stopped because of the withdrawal of the enobosarm drug supply.

HER2+ Breast Cancer

HER2+ breast cancers overexpress HER2, often as a result of *HER2* gene amplifications and/or dysregulation (183). While ~70% of HER2+ breast cancers are ERα negative, this subtype does express AR more often than other ERα-negative breast cancer types (eg, TNBC) (157). As noted above for TNBC, some studies suggest crosstalk between AR and HER2 in ERα–/HER2+ breast cancers (163, 164, 179). This pathway could be further enhanced by AR-mediated expression of WNT7B and subsequent coactivation of AR by β-catenin (179). Hence, AR signaling may promote a HER2+ phenotype in a subset of ER-negative breast cancers. These preclinical findings are supported by a clinical study (NCT02091960; n = 89) testing the safety and efficacy of enzalutamide in an open-label, single-arm, phase II study of women with advanced HER2+/AR+ breast cancer previously treated with the anti-HER2 agent trastuzumab (57). In this study, CBR at 24 weeks was 24% but was not related to AR expression levels or hormone receptor status. Collectively, these data suggest that while some HER2+ patients benefit from the addition of enzalutamide, there is a need to identify biomarkers predictive of response.

ERα+ Breast Cancer

A long-standing debate in the hormone-dependent cancer field is regarding the role of AR in ERα+ breast cancer. Without a full understanding of their mechanism of action, androgens were first used for the treatment of breast cancer in the 1940s (157). However, their use was discontinued in the 1980s due to the discovery of more effective treatments that exhibited fewer masculinizing

side effects, such as chemotherapy and, later, tamoxifen. Genomic analyses from large clinical cohorts including METABRIC indicate that *AR* is rarely deleted in breast cancer and is instead, more often amplified (184, 185). However, decreased copy number variations are observed in many breast cancers and track with poor prognosis (184, 185). Consistent with these findings, the AR was demonstrated to counter ERα-mediated transformation, and thus have a protective role in normal breast (186-190). In the past decade, a series of preclinical studies and clinical trials have explored the use of both activators and inhibitors of the AR to treat ERα+ breast cancer, with both seemingly opposing strategies capable of inducing anticancer effects.

The case for AR signaling inhibitors in ERα+ breast cancer Enzalutamide blocks 17β-estradiol (E2)-mediated MCF-7 cell and tumor growth, mainly by decreasing proliferation (149, 162). Similar results were observed following shRNA-mediated knockdown of *AR* (162). Enzalutamide also inhibited the DHT-mediated growth of ER+ MCF-7 and BCK4 cells as well as MCF-7 orthotopic xenografts but did so by also inducing apoptosis (149). Interestingly, while DHT promoted MCF-7 cell growth, combined DHT+ enzalutamide inhibited MCF-7 cell growth greater than enzalutamide alone, suggesting potential divergent mechanisms of action. It is not known if this phenomenon would be observed in vivo since enzalutamide alone control groups were not included in the xenograft experiment.

Mechanistic studies suggest that ER and AR can cooperate, and that the AR is required for maximum ER DNA binding (162). E2-induced AR binding at novel sites not observed in the presence of DHT alone. Rather these new AR binding sites were enriched for ER binding sites and estrogen response elements. Of note, cell type–specific effects suggest that other factors beyond ER status such as FOXA1 likely also play key roles in modulating AR activity. Inhibition of the AR using the antiandrogen enzalutamide or MJC13, which inhibits AR nuclear localization via disruption of the AR with its cochaperone FKBP52 (191), inhibited E2-mediated growth. Here, AR inhibition sensitized ER+ breast cancer cells to tamoxifen and fulvestrant. Enzalutamide also decreased the growth of ER+ tamoxifen-resistant MCF-7 cell and orthotopic patient-derived (PT12) xenograft models, as well as metastatic burden in a PT12 intracardiac injection model of metastasis. As observed in a prior study (149), enzalutamide decreased proliferation in the context of E2-mediated tumor growth, while in vivo enzalutamide increased tumor cell death in DHT-treated mice.

Interestingly, noncanonical AR activity was also shown to enable endocrine therapy resistance in ER+ breast cancer (159). In MCF-7 models of endocrine-resistance, knockdown of *AR* inhibited cell growth and growth signaling pathways commonly upregulated in recurrent tumors. Notably, knockdown of AR, but not enzalutamide, increased a subset of ER-mediated signaling cascades and restored tamoxifen sensitivity to tamoxifen-resistant MCF-7 cells. Accordingly, enzalutamide did not alter the growth of an ERα+, aromatase inhibitor–resistant PDX model (Gar15-13). Androgens were not tested in this model. Similar effects were observed in ERα+ MCF-7 and ZR-75-B cells where overexpression of AR promoted the ER agonist activity of tamoxifen (154, 161). This switch of tamoxifen's pharmacological activity was proposed to occur via AR-mediated activation of EGFR-extracellular signal-regulated kinase. Likewise, the synthetic androgen R1881 increased ERα+ breast cancer cell growth, but only when levels of the Rho guanine nucleotide dissociation

inhibitor (Rho GDI), a potential suppressor of tamoxifen resistance, were low. Likewise, overexpression of AR also promoted resistance to aromatase inhibitors in MCF-7 cells, an effect that could be reversed with antiandrogens (167).

A drawback of many preclinical studies is that they do not evaluate the AR's role in the context of important host variables such as menopausal status and obesity (Fig. 4), which are factors that have known effects on ERα+ breast cancer. For instance, in an ovariectomized rat model of postmenopausal breast cancer, AR promoted tumorigenesis in obese, but not lean rats (169), an effect that could be blocked by enzalutamide. This study went on to suggest that circulating factors unique to the obese host such as increased interleukin 6, could fine-tune the tumor's response to sex steroid hormones like testosterone. These data suggest that future clinical trials targeting AR in ERα+ breast cancer will need to account for these additional host factors.

Clinical trials testing the efficacy of AR signaling inhibition in ERα+ breast cancer have yielded equivocal results. In a randomized phase II study (NCT01381874) testing the safety and efficacy of abiraterone acetate plus prednisone ± the steroidal aromatase inhibitor exemestane vs exemestane alone in postmenopausal women with ERα+ metastatic breast cancer pretreated with nonsteroidal aromatase inhibitors (letrozole or anastrozole) (n = 297), the addition of abiraterone to exemestane did not improve PFS compared with exemestane alone (4.5 vs 3.7 months; HR 0.96; 95% CI 0.70-1.32; *P* = .794) (58). In the AR+ subpopulation (n = 227) of this cohort, there was also no significant benefit with abiraterone treatment. While there was a trend toward abiraterone-mediated benefit, there were no significant differences between arms observed for the secondary endpoints of ORR (12.1% abiraterone acetate plus exemestane vs 6.3% exemestane alone; *P* = .366) and CBR (22.7% abiraterone acetate plus exemestane vs 12.7%; *P* = .137). It is unclear whether an abiraterone-mediated buildup of progesterone, observed in abiraterone-treated patients, contributed to the lack of clinical efficacy. While subgroup analyses suggested a possible response to enzalutamide in patients with luminal A, the addition of enzalutamide did not improve exemestane inhibition of proliferation in a phase II study (n = 194) of preoperative treatment with enzalutamide in ER+ breast cancer (NCT02676986) (59). Similarly, the addition of enzalutamide to exemestane did not improve PFS compared with exemestane alone regardless of previous exposure to an endocrine therapy in a phase II, randomized, double-blind, placebo-controlled, multicenter study (n = 247) of enzalutamide in combination with exemestane in women with advanced ERα+ or PR+, HER2-normal breast cancer (NCT02007512) (60). However, retrospective analysis revealed that patients who had not previously received any endocrine therapy (n = 127) and whose tumors expressed high *AR* mRNA levels and possibly low *ESR1* levels may have benefitted from enzalutamide (HR 0.24; 95% CI 0.10-0.60; *P* = .0011). These results are consistent with a small (n = 18) phase 2 trial of bicalutamide in combination with aromatase inhibition in ERα+/AR+ breast cancer that was terminated early due to futility (192).

Finally, in a single-arm, open-label, phase II trial (n = 32) of fulvestrant plus enzalutamide in women with ER+/HER2 normal metastatic breast cancer (NCT02953860), PFS >24 weeks was observed in 22% of patients (61). These findings included 42% of women who had received prior fulvestrant, suggesting that the addition of enzalutamide benefitted patients. Here, the best responders expressed higher levels of AR and ER, whereas the poorest responders had evidence of

increase PI3K–AKT–mTOR signaling in their tumors. Increased programmed death-ligand 1 levels were also observed in the treated patients, suggesting that the addition of immune checkpoint therapy may benefit these patients.

The case for AR activators in ERα+ breast cancer While the above-described studies advocate for the use of AR signaling inhibitors in the treatment of ERα+ breast cancers, there are also compelling data indicating that AR agonists could benefit these patients. This work began with early studies demonstrating that androgens inhibited the growth of ERα+/AR+ breast cancer cell lines such as T47D and ZR-75-1, an effect that could be reversed by co-treatment with antiandrogens (172, 176). Both basal and estrogen-induced breast cancer cell growth was impaired by androgens (176). A caveat to studies relying exclusively on androgens, such as testosterone and DHT, is that they can be further metabolized to strong and weak estrogens, respectively (193). Hence, some effects observed in ER+ cells may be indirect, underscoring the need for complementary approaches (190, 193). Using mutant expression constructs, AR's DNA-binding domain was shown to be required for its regulation of ERα activity (151). Accordingly, electrophoretic mobility shift, ChIP, and ChIP-Seq data indicate that the AR can interact with estrogen response elements in luminal breast cancer cells and disrupt >25% of ERα-mediated transcription (174). In contrast to the cooperativity observed in MCF-7 cells (162), ChIP-Seq and microarray expression profiling in ZR-75-1 cells demonstrated a mutual interference between the ligand-activated receptors (AR and ERα) on transcriptional activity (174). Androgens suppressed estrogen-induced survival and proliferative pathways. Androgen response elements and AR-binding sites were enriched at ERα binding sites and vice versa. The net impact on transcription when both AR and ER were present depended on the genome locus. In addition to endogenous androgens, SARMs can also inhibit the growth of ERα+ breast cancer cell and PDX models (175). Ligand-activated AR reprogrammed the ER and FOXA1 cistrome, inhibiting the growth of breast cancer models driven by wildtype or mutant ERα, the latter being commonly observed in refractory metastatic breast cancers (173, 175). In the context of mutant ERα, androgens could also inhibit distant metastasis in PDX models (173). In contrast, enzalutamide had minimal effects in these studies on the growth or spread of the same ERα+ PDX models (173, 175). The AR-mediated inhibition of ERα genomic signaling and antitumor activity was explored further in a large study using ERα+ cell lines, estrogen-treated, primary patient-derived explants (n = 17), cell line xenografts, PDX models (n = 4 different models) derived from metastatic breast cancers expressing wildtype or mutant ERα, and an intraductal injection model of reported tamoxifen-resistant breast cancer (150). Robust antitumor effects of androgens (DHT or the SARM enobosarm) were observed across multiple disease contexts including resistance to hormone therapy and CDK4/6 inhibitors (150). It was not tested if the androgen-mediated tumor suppressive effects could be reversed by co-treatment with antiandrogens. Notably, androgens were able to improve the efficacy of current standard-of-care agents. Conversely, enzalutamide had no effect when tested in 2 of the PDX models. Mechanistically, activated AR could sequester ER and shared coactivators such as p300 and SRC-3 away from ER target genes controlling proliferation and survival (150, 194). Conversely, activated AR increased the expression of tumor suppressors encoded by known AR target genes.

Recent clinical studies provide preliminary support for additional testing of AR agonists in ERα+ breast cancer. In a small (n = 22) phase II study (NCT01616758) examining the initial safety and efficacy of enobosarm in postmenopausal women with AR+/ERα+ metastatic breast cancer who

previously responded to adjuvant and/or salvage endocrine therapy, 3/15 patients who made it 6 months on therapy and confirmed AR+ cancers had stable diseases (64). A phase II, open label, multicenter, randomized study (NCT02463032; n = 136) investigating the safety and efficacy of enobosarm in postmenopausal women with metastatic or locally advanced ERα+/AR+ breast cancer further demonstrated that enobosarm was well tolerated and had positive effects on quality of life (65). Importantly, a higher percent tumor AR staining correlated with greater enobosarm antitumor activity such that enobosarm-treated patients exhibited a CBR of 52% at 24 weeks when tumors were >40% AR+. These data provided the impetus for a larger randomized, open label, phase III ARTEST trial (NCT04869943) testing the efficacy of enobosarm monotherapy in AR+/ERα+/HER2− metastatic breast cancer (n = 210) (62).

Conclusions and Future Perspectives

Given the widespread expression of AR throughout the body in both men and women, it is perhaps not surprising that AR activity has been causally linked to other malignancies beyond prostate cancer. What is becoming increasingly clear is that AR expression alone is likely not sufficient to predict for response to AR-targeted therapy in many cancers. Hence, additional markers are needed to identify optimal patient populations. Moreover, systemic factors known to influence steroid hormone signaling such as menopausal status in women and obesity may also prove to be important variables when evaluating AR as a therapeutic target. Further refinement of these new patient subtypes will help oncologists leverage the arsenal of AR-targeting drugs already available and, therefore, expand treatment options for these additional cancers.

Acknowledgments

We thank Kelly Kage for assistance with preparing the figures. Figure 3 was created with BioRender.com. This work was supported by a grant from the National Institutes of Health (NIH P50CA140388 to D.E.F.) and support from the Mike Slive Foundation for Prostate Cancer Research (D.E.F.).

Abbreviations

ACC	adrenocortical carcinoma
AR	androgen receptor
CBR	clinical benefit rate
ChIP	chromatin immunoprecipitation
DHT	dihydrotestosterone
E2	17β-estradiol
HCC	hepatocellular carcinoma
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PR	progesterone receptor
SARM	selective androgen receptor modulator
TNBC	triple-negative breast cancer

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Disclosures

D.E.F. has received research funding from GTx, Inc. and has familial relationships with Hummingbird Bioscience, Maia Biotechnology, Alms Therapeutics, Hinova Pharmaceuticals, and Barricade Therapeutics. The other authors report no potential conflicts of interest. The funders had no role in the conceptualization of the study or writing of the manuscript, or in the decision to publish this article.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Figures and Tables

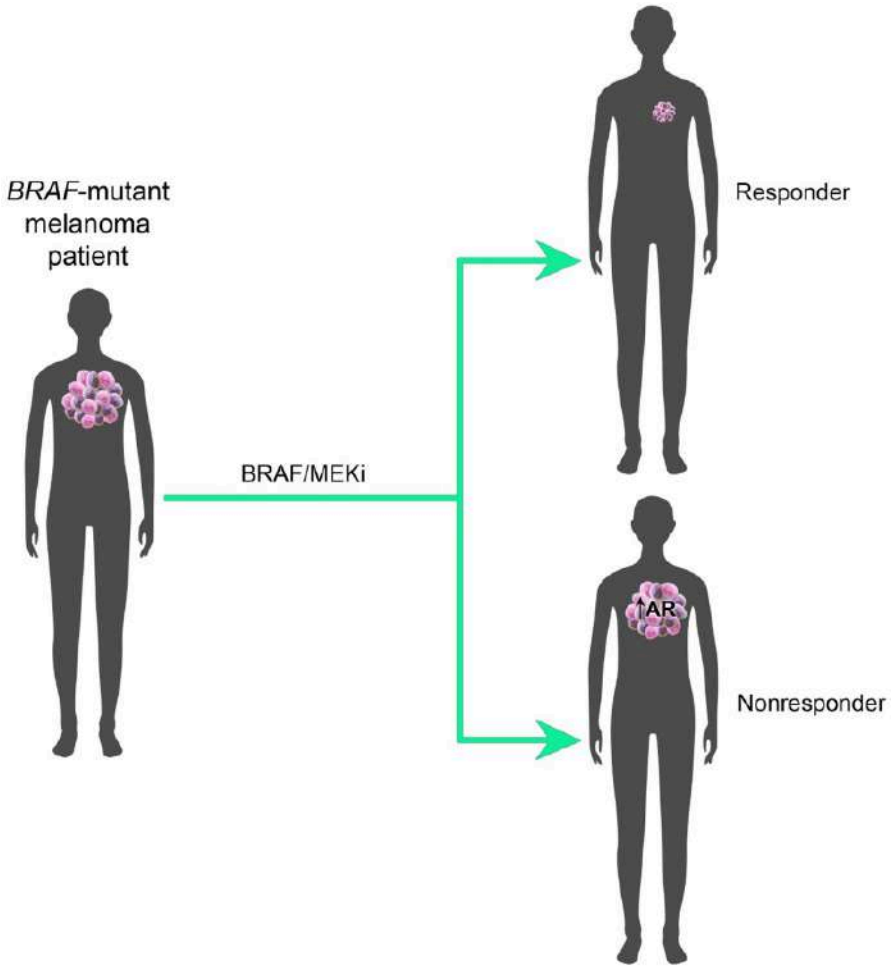
Table 1.

Notable nonprostate cancer clinical trials testing AR modulators

Clinical trials identifier	Phase	Population	Size	Treatment	Primary outcome measures	Results	Re
AR antagonists in endometrial, liver, bladder and melanoma clinical trials							
NCT02684227	II; single arm	Measurable stage III, stage IV, chemonaive recurrent endometrioid endometrial cancer	n = 52	Enzalutamide plus paclitaxel and carboplatin	ORR and proportion progression free at 6 months	ORR 71%; PFS at 6 months 79%	(4
NCT02528643	II; randomized	Progressive and advanced HCC; or nonresponsive HCC	n = 165	Enzalutamide	OS at 22 months; median follow-up at 14.65 months	No significant difference in OS	(4
NCT02642913	I/II; nonrandomized	Advanced HCC	n = 28	Enzalutamide ± sorafenib	PFS	Primary outcome results not reported	Ha al. no pu
NCT02197897	II; single-arm	Non–muscle invasive bladder cancer	n = 15	Tamoxifen citrate	Clinical response of the marker lesion over 2.5 years using RECIST combined with final biopsy	Primary outcome results not reported	Go Re pu
NCT02605863	II; nonrandomized	Non–muscle invasive bladder cancer	n = 1	Enzalutamide	Number of patients with recurrent disease at 1 year	Terminated; low enrollment; sponsor withdrew support	Me al no pu
NCT02300610	I/Ib; nonrandomized	Stage IV (locally advanced or metastatic) bladder	n = 10	Enzalutamide combined with gemcitabine	Dose escalation (all patients with mUC);	MTD: 160 mg in 6 participants.	(4

Abbreviations: AR, androgen receptor; CBR, clinical benefit rate; CR, complete response; DLT, dose-limiting toxicity; ER, estrogen receptor alpha; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; MTD, maximum tolerated dose; NCT, national clinical trial; ORR, overall response rate; OS, overall survival; PD, progressive disease; PF, progression-free; PFS, progression-free survival; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; TNBC, triple-negative breast cancer.

Figure 1.



AR promotes resistance to BRAF and MEK inhibitors in *BRAF*-mutant melanomas. Patients harboring *BRAF*-mutant melanoma are treated with BRAF and MEK inhibitors (BRAF/MEKi). Treatment-resistant *BRAF*-mutant melanomas exhibit increased expression and activity of the androgen receptor (AR).

Table 2.

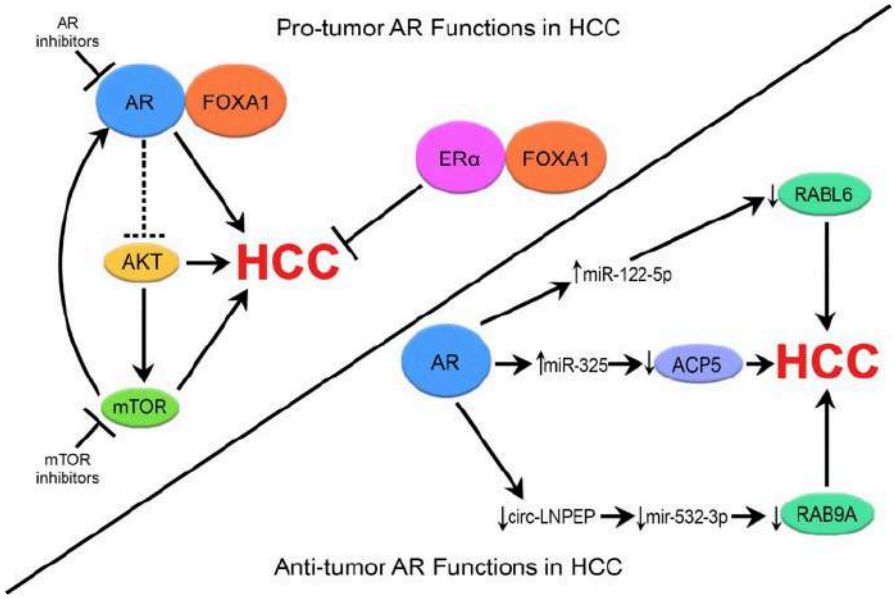
Steroid hormone production by adrenocortical carcinoma subtype

		Molecular subtype and prognosis				Total: n (%)
		CoC1: n (%) Good prognosis	CoC2: n (%) Intermediate prognosis	CoC3: n (%) Poor prognosis	Unknown: n (%)	
Adrenal hormone excess	Silent	16 (51.6%)	6 (19.4%)	4 (12.9%)	5 (16.1%)	31 (33.7%)
	Androgen	5 (62.5%)	2 (25%)	1 (12.5%)	—	8 (8.7%)
	Androgen + estrogen	1 (50%)	—	1 (50%)	—	2 (2.2%)
	Androgen + mineralcorticoid	—	—	—	1 (100%)	1 (1.1%)
	Cortisol	3 (17.6%)	6 (35.3%)	6 (35.3%)	2 (11.8%)	17 (18.4%)
	Cortisol + androgen	3 (15%)	4 (20%)	8 (40%)	5 (25%)	20 (21.7%)
	Cortisol + mineralcorticoid	1 (100%)	—	—	—	1 (1.1%)
	Mineralcorticoid	1 (33.3%)	1 (33.3%)	1 (33.3%)	—	3 (3.3%)
	Estrogen		2 (100%)	—	—	2 (2.2%)
	Unknown	1 (14.3%)	—	3 (42.9%)	3 (42.9%)	7 (7.6%)

Notably, androgen-producing tumors are enriched in the subtype with the best prognosis (CoC1). Data are derived from The Cancer Genome Atlas.

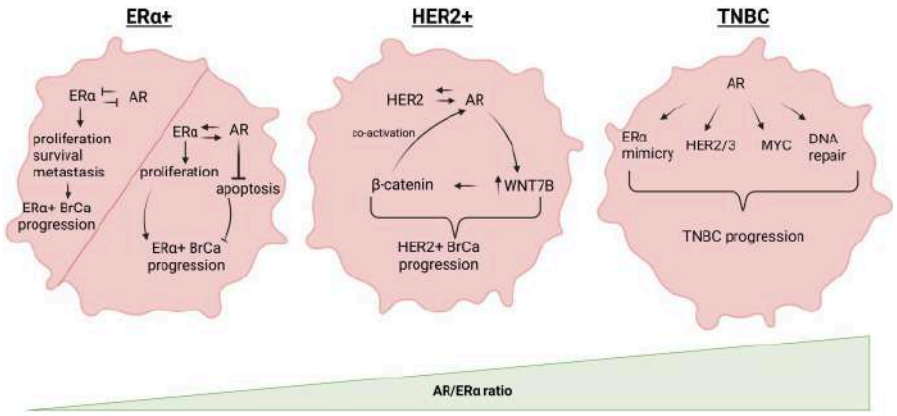
Abbreviation: CoC, Cluster of Cluster.

Figure 2.



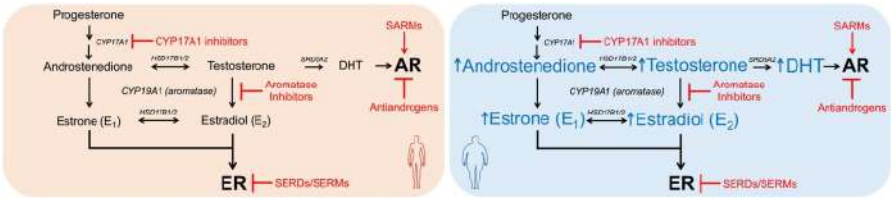
Procancer and anticancer roles for AR in HCC. Schematic of reported contrasting roles for AR in HCC. ACP5, tartrate-resistant acid phosphatase type 5; AR, androgen receptor; ERα, estrogen receptor α; FOXA1, forkhead box protein A1; HCC, hepatocellular carcinoma; mTOR, mammalian target of rapamycin; RABL6, Rab-like protein 6.

Figure 3.



Subtype-specific roles for AR in breast cancer. Schematic of reported roles for AR in ERα+, HER2+ and triple-negative breast cancer. AR, androgen receptor; BrCa, breast cancer; ERα, estrogen receptor α; TNBC. Triple-negative breast cancer. Figure created with BioRender.com.

Figure 4.



Effects of obesity of steroidogenesis. Indicated in blue on the right are the steroid metabolites that have been reported to be increased in obese individuals. Shown in *italics* are steroidogenic enzymes. AR, androgen receptor; ER, estrogen receptor; SARM, selective androgen receptor modulator; SERD, selective estrogen receptor degrader; SERMs, selective estrogen receptor modulator.