Transcription factors and hormone receptors: Sex-specific targets for cancer therapy (Review)

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Abstract. Despite advancements in diagnostic and therapeutic technologies, cancer continues to pose a challenge to disease-free longevity in humans. Numerous factors contribute to the onset and progression of cancer, among which sex differences, as an intrinsic biological condition, warrant further attention. The present review summarizes the roles of hormone receptors estrogen receptor α (ERα), estrogen receptor β (ERβ) and androgen receptor (AR) in seven types of cancer: Breast, prostate, ovarian, lung, gastric, colon and liver cancer. Key cancer-related transcription factors known to be activated through interactions with these hormone receptors have also been discussed. To assess the impact of sex hormone receptors on different cancer types, hormone-related transcription factors were analyzed using the SignaLink 3.0 database. Further analysis focused on six key transcription factors: CCCTC-binding factor, forkhead box A1, retinoic acid receptor α, PBX homeobox 1, GATA binding protein 2 and CDK inhibitor 1A. The present review demonstrates that these transcription factors significantly influence hormone receptor activity across various types of cancer, and elucidates the complex interactions between these transcription factors and hormone receptors, offering new insights into their roles in cancer progression. The findings suggest that targeting these common transcription factors could improve the efficacy of hormone therapy and provide a unified approach to treating various types of cancer. Understanding the dual and context-dependent roles of these transcription factors deepens the current understanding of the molecular mechanisms underlying hormone-driven tumor progression and could lead to more effective targeted therapeutic strategies.

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Abbreviations: ADT, androgen deprivation therapy; AF, activation functions; AKT, protein kinase B; AP-1, activator protein 1; AR, androgen receptor; ASCL1, Achaete-Scute homolog 1; CTCF, CCCTC-binding factor; CRPC, castration-resistant prostate cancer; DBD, DNA-binding domain; DHT, dihydrotestosterone; EMT, epithelial-mesenchymal transition; EOC, epithelial ovarian cancer; ER, estrogen receptor; ERG, ETS-related gene; E1, estrone; E2, estradiol; EZH2, enhancer of zeste homolog 2; FOXA1, forkhead box A; GATA2, GATA binding protein 2; GR, glucocorticoid receptor; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor 1-α; LBD, ligand-binding domain; NSCLC, non-small cell lung cancer; NTD, N-terminal domain; PBX1, PBX homeobox 1; PI3K, phosphoinositide 3-kinase; PLK3, polo-like kinase 3; CDKN1A, cyclin-dependent kinase inhibitor 1A; p27, cyclin dependent kinase inhibitor 1B; PPARα, peroxisome proliferator-activated Receptor A; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; RARA, retinoic acid receptor A; ROS, reactive oxygen species; SP1, specificity protein 1; STAT3, signal transducer and activator of transcription 3; TNBC, triple-negative breast cancer; TMPRSS2, transmembrane serine protease 2

Key words: estrogen receptor, androgen receptor, hormone, transcription factor, tumor progression, sex-specificity

Contents

1. Introduction

The Global Cancer Observatory reported that the top seven types of cancer according to incidence rates in 2022 were breast (23.8%), lung (9.4%), colorectal (8.9%) cervix uteri (6.9%), thyroid (6.4%), corpus uteri (4.3%) and stomach (3.5%) cancer for females. For males, the top seven by incidence were lung (15.2%), prostate (14.2%), colorectal (10.4%), stomach (6.1%), liver (5.8%), bladder (4.6%) and esophagus (3.5%) cancers. Similarly, the top seven types of cancer according to mortality rates in 2022 were breast (15.4%), lung (13.5%), colorectal (9.4%), cervix uteri (8.1%), liver (5.5%), stomach (5.4%) and pancreas (5.1%) cancers for females. For males the top seven by mortality rate were llung (22.7%), liver (9.6%), colorectal (9.2%), stomach (7.9%), prostate (7.3%), esophagus (5.9%) and pancreas (4.6%) cancer (1). These statistics demonstrate sex

differences in cancer incidence and mortality rates that can be attributed to varying expression levels of hormone receptors and associated genes involved in cancer occurrence and malignancy mechanisms (2,3).

Estrogen, commonly recognized as a female hormone, also significantly impacts males. Among the four types of estrogen, estrone (E1), estradiol (E2), estriol and estetrol, E2 is the most predominant in both males and premenopausal females. While E2 levels in males are lower compared with in premenopausal females, they are comparable to or exceed those in postmenopausal females (4,5). In males, E2 is primarily produced in extragonadal tissues, particularly increasing in individuals with a higher BMI (4-7). Estrogen inhibits bone resorption and provides cardiovascular protection, essential for maintaining health in premenopausal women. However, after menopause, ovarian estrogen production ceases, diminishing these protective effects and increasing the risk of developing diseases, such as cardiovascular disease and osteoporosis (8-12). Additionally, in postmenopausal women, estrogen is mainly produced in peripheral tissues, heightening the risk of developing breast cancer (13,14).

Androgens, commonly known as male hormones, notably impact females as well. In males, androgens are secreted by the testes and adrenal glands; whereas in females, androgens are produced by the ovaries and adrenal glands (15). Androgens bind to androgen receptors (AR) in various tissues, including the prostate, seminal vesicles and skeletal muscle, to regulate physiological activities, sperm production and cancer growth in males (16,17). In females, precursor substances of androgen, such as androstenedione, are more likely to convert to estrogen compared with androgens and act on estrogen receptors (ER) (18). Excessive androgen secretion in females can worsen endocrine disorders such as polycystic ovary syndrome and congenital adrenal hyperplasia (19,20).

The expression and activation of sex hormone receptors serve a significant role in the progression and malignancy of breast and prostate cancer, influencing tumor growth, metastasis and response to treatment (21). While a direct linear correlation between cancer stage and hormone receptor expression is not consistently observed (22,23), sex hormone receptor status serves a key role in determining treatment options and prognosis at various stages of cancer (24). In the early stages of cancer (stage 1 or 2, according to the AJCC Cancer Staging Manual), cancer cell growth is mainly promoted in a sex hormone-dependent manner, so that it may be treated with hormone therapy. However, in the advanced stages of cancer (stage 3 or 4), hormone receptor expression levels often diminish or become less predictive of treatment efficacy, requiring more aggressive therapies, such as chemotherapy or targeted therapy (25,26). ER-low or ER-negative (-) patients with breast cancer have a higher recurrence rate and show distinct clinicopathological findings compared with ER-high patients. The 5-year recurrence rates are 5.1% for ER-high, 7.4% for ER-low and 9.7% for ER-negative patients, with ER-negative cases showing significantly worse outcomes ($P<0.001$). ER-high patients typically have lower tumor grades, lower Ki-67 proliferation indices, and are associated with the luminal A subtype, which responds well to hormone therapy. By contrast, ER-negative patients present with higher tumor grades, significantly elevated Ki-67 indices, and a higher prevalence of triple-negative breast cancer, often leading to a poorer prognosis (24). Furthermore, hormone receptor-positive types of cancer, such as luminal A and B, respond well to hormone therapies, while HER2-positive and triple-negative breast cancer (TNBC) subtypes often require more aggressive treatments, such as targeted therapy or chemotherapy (27-29). Among these subtypes, both luminal subtypes typically show positive ER and progesterone receptor (PR) expression, while luminal B breast cancer generally displays increased HER2 expression levels compared with luminal A. Luminal B breast cancer is also associated with higher proliferation rates (e.g., Ki-67 index), increased HER2 expression and a poor prognosis, indicating more aggressive clinical characteristics (27-30).

Prostate cancer is similarly categorized by its dependence on AR signaling, with advanced cases evolving into castration-resistant prostate cancer (CRPC), which requires more intensive treatments. Hormone-sensitive prostate cancer, which typically describes most early-stage cases, is commonly treated with androgen deprivation therapy (ADT) (31). However, CRPC requires more aggressive treatments, such as second-line hormonal therapies, such as enzalutamide or chemotherapy (32). Thus, the expression levels of hormone receptors in the early stages of cancer are a major factor in treatment decisions. However, in advanced stages, their predictive value for treatment decreases due to reduced dependence on hormones.

Recent studies have reported that AR and ER signaling pathways are closely associated, particularly in breast cancer, where AR can either suppress or enhance estrogen receptor α (ERα) activity depending on the context (33,34). In ER-positive (+) breast cancer, ARs often act as a tumor suppressor by inhibiting ERα-driven tumorigenesis, with AR activation showing significant anti-tumor effects, even in cases of resistance to ER and CDK4/6 inhibitors (35). AR redistributes ER and its co-activators on chromatin, suppressing ER-regulated genes and upregulating AR target genes, which correlates with improved survival in patients with ER(+) breast cancer (36). However, AR can also promote oncogenic functions in the context of androgen excess, where androgens act as precursors to estrogen (37). This leads to overstimulation of estrogen-regulated gene expression, driving tumor proliferation and progression in ER-positive breast cancer (34). In CRPC, estrogen receptor β (ERβ) activation reduces AR expression, inducing apoptosis and acting as a tumor suppressor. These findings highlight the key role of AR and ER interactions in cancer progression and present opportunities for targeted therapies (38).

While cancer research spans numerous fields of research, studies focusing on sex-specific differences are currently limited. Addressing these differences may lead to significant breakthroughs in cancer prevention and treatment. Specifically, hormones can act on their receptors to influence the expression of hormone-related transcription factors, which in turn can affect the expression of oncogenes or tumor suppressors (39). Understanding how sex hormone receptors interact with common transcription factors in different types of cancer may serve to identify novel therapeutic targets, which could aid in the development of personalized treatment strategies and thereby maximize the efficacy of cancer therapies.

2. Roles of ERs and ARs in tumor progression

ERα. ERα was first discovered in 1958 by Jensen *et al* (40). Subsequently, ERα was found to regulate gene transcription through interactions with estrogen, resulting in extensive research into its role in various diseases. ERα is encoded by the ESR1 gene on chromosome 6, and consists of several domains in the following structure: NH_2-A/B-C-D-E-F-COOH. The N-terminal domain (NTD; A/B) contributes to transcriptional activation and provides receptor specificity. The DNA-binding domain (DBD; C) enhances DNA binding, whereas the D domain stabilizes the C domain through binding to heat shock proteins. The ligand-binding domain (LBD; E/F) facilitates regulation via activation functions (AF)-1 and AF-2, thus aiding in transcriptional control. The AF1 domain, a ligand-independent region, is typically regulated through phosphorylation by kinases such as mitogen-activated protein kinase (MAPK), enhancing its capacity to recruit coactivators and stimulate transcription, even in the absence of hormone binding (41-44). By contrast, the AF2 domain is ligand-dependent, undergoing a conformational change upon estrogen binding to the LBD, particularly in helix 12 (45). This shift facilitates the recruitment of coactivators, such as nuclear receptor coactivator 1 and p300/CBP, via their LxxLL motifs (46). These coactivators, once bound, modify chromatin through histone acetylation, which enables transcription (47). These regulatory mechanisms are functionally conserved in ERβ and ARs (48,49).

ERα is a pivotal molecule in the development and progression of various types of cancer. In breast cancer, ERα is associated with tumor progression and is upregulated in ~75% of breast cancer tissues, in contrast to ~10% in healthy tissues (50). ERα is more prevalent in the luminal A type, compared with the basal type of breast cancer. ERα interacts with estrogen to promote tumor growth (51). Given these properties, anti-hormone therapies that target ERα, such as aromatase inhibitors, tamoxifen and fulvestrant, have proven to be effective in breast cancer (52,53).

Aromatase inhibitors reduce estrogen levels by inhibiting the enzyme aromatase, which is responsible for converting the androgen hormone androstenedione and androstenediol into E1 and E2, respectively. As a result, these inhibitors are used in the treatment of ER(+) breast cancer to lower estrogen levels, thus suppressing cell proliferation and invasion (54). By contrast, tamoxifen is an anti-estrogen drug that blocks the activity of estrogen in breast cancer. Tamoxifen directly binds to ERα, which prevents estrogen from exerting its effects, thereby inhibiting cell proliferation and tumor growth (55). The clinical study by Arpino *et al* (56) on patients with breast cancer demonstrated that the ER(+)/PR(-) breast cancer group is less sensitive to tamoxifen, which targets ER, compared with the ER(+)/PR(-) breast cancer group. This is because tamoxifen inhibits the estrogen effect, which influences the expression of the PR gene (57). As a result, PR(-) patients experience reduced efficacy from tamoxifen treatment. Moreover, these patients tend to exhibit increased expression levels of other receptors, such as HER-1 and HER-2, which contributes to more aggressive tumor characteristics, including therapy resistance, faster proliferation and a higher probability of metastasis. Specifically, HER-2 positive tumors are known to exhibit resistance to tamoxifen therapy, while HER-1 expression is predominantly observed in ER-negative tumors, which are associated with poor prognosis (58). Therefore, tamoxifen and fulvestrant are specifically used in ER(+) breast cancer, regardless of PR status, but their efficacy may vary depending on the presence or absence of PR. Additionally, ERα is comprised of 595 amino acids with a molecular weight of 66 kDa, and alternative splicing results in several isoforms such as ERα46 and ERα36, with the ERα46 isoform acting as a competitive inhibitor when co-expressed with ERα66 (59-61).

In prostate cancer, ERα promotes cell proliferation and inhibits apoptosis, thereby facilitating tumor growth (62). Notably, ERα expressed in stromal tissue has been shown to stimulate the growth of prostatic epithelium through growth factors (63). An *in vivo* study has demonstrated that knocking down ERα suppresses tumor growth (64), and research indicates that patients with high ERα expression levels have poor prognoses (65). In the majority of prostate cancer subtypes, ERα activation is associated with tumorigenesis and cancer progression (66-68). ERα typically promotes cancer cell proliferation by activating pathways such as IL-6 signaling, which supports cell survival and resistance to ADT. This is particularly relevant in CRPC, where androgen-independent mechanisms serve a pivotal role in sustaining tumor growth (66,67). In aggressive prostate cancer subtypes, including neuroendocrine prostate cancer and CRPC, elevated ERα levels contribute to increased malignancy and facilitate cancer cell survival and invasiveness, often through interactions with AR-mediated pathways (68).

Ovarian cancer exhibits ERα expression in ~80% of patients (69). ERα significantly promotes cell migration and the epithelial-mesenchymal transition (EMT) process by upregulating EMT-associated transcription factors such as Snail and Slug, and by downregulating the epithelial marker E-cadherin (70). Furthermore, a study by Chan *et al* (71) demonstrated that cell growth induced by E2 treatment was reduced when ERα was knocked down using siRNA, confirming its role in cell proliferation. The aforementioned anti-estrogen treatments, such as aromatase inhibitors, tamoxifen and fulvestrant, are generally less effective due to the modest response rate in patients with ovarian cancer compared with patients with breast cancer, and are thus not commonly used (52,72).

Non-small cell lung cancer (NSCLC), the most common type of lung cancer, is characterized by ERα promoting tumor progression by enhancing macrophage infiltration, which alters the tumor microenvironment to favor cancer growth and increases cell invasion (73). Clinical data also demonstrates that within the same elderly cancer patient group, women have a higher survival rate compared with men. Lung adenocarcinoma, a common subtype of NSCLC, commonly occurs in non-smokers, with a higher incidence rate in women (19.6%) compared with men (11.8%) (74). Premenopausal women with lung adenocarcinoma had a median survival of 643 days compared with 735 days for postmenopausal women (P=0.01). Additionally, premenopausal women presented with more advanced stages of the disease, with 66% in stage IV compared with 53% in postmenopausal women. This highlights the significant impact of menopausal status on disease progression and survival outcomes. A study by Hsu *et al* (75) indicated that

E2 stimulates cancer cell migration, while ER antagonists such as tamoxifen, targeting the estrogen signaling pathway, inhibit lung cancer cell growth. Another study reported that women >60 years have a survival advantage compared with younger women, though this age effect is not observed in men (76).

Meanwhile, research on gastric cancer suggests that ERα may have a dual role. A study showed that transfection-induced overexpression of ERα decreases β-catenin expression, thus inhibiting cell proliferation and invasion (77). Additionally, ERα and ERβ mRNA levels in tumors, compared with normal tissues, have been associated with increased metastatic potential in gastric cancer (78). By contrast, it has also been suggested that knockdown of ERα inhibits the proliferation, migration and invasion of gastric cancer cells by regulating the expression of factors such as p53 and CDK inhibitor 1A (CDKN1A), associated with poor prognosis in patients (79).

Colon cancer is significantly influenced by estrogen and exhibits varying effects depending on which estrogen receptor it interacts with. ERα promotes the development and proliferation of colon cancer cells (80,81). The type of ERs interacting with estrogen varies with colon cancer stage, with ERα predominantly driving tumor progression in late stages. Conversely, the isoform ERα36 shows lower expression in tumor tissue compared with healthy colorectal tissue and decreases with advancing Dukes' stage (A+B>C+D, P=0.017) and lymph node metastasis stage (N0>N1/N2, P=0.049), suggesting a function opposite to full-length ERα66 (82).

In hepatocellular carcinoma (HCC), the most common type of liver cancer, ERα is expressed at lower levels compared with adjacent normal tissue, and its promoter is hypermethylated (83). Hou *et al* (84) reported that ERα acts as a tumor suppressor by upregulating the expression of tyrosine phosphatase receptor type O, which promotes apoptosis and inhibits cell proliferation. However, in HCV-related HCC, ERα mRNA and protein expression levels are elevated, and increased ERα expression is associated with increased levels of inflammatory and oncogenic genes, such as NF-κB and cyclin D1, suggesting a role in promoting liver cancer progression (85).

ERβ. ERβ, discovered in 1996 (86), interacts with various molecules across different types of cancer and serves a significant role in tumor progression. Recognized as a crucial hormone receptor, ERβ functions as a tumor suppressor (87). ERβ is composed of AF-1, AF-2, DBD and LBD domains (88). The transcriptional activation domains, AF-1 and AF-2, are situated in the NTD and C-terminal domain (CTD), respectively. ERβ has several isoforms due to alternative splicing, with the primary ones being ERβ1, ERβ2, ERβ3, ERβ4 and ERβ5 (89). Among them, ERβ1, the full-length protein, is commonly referred to as ERβ (90).

In breast cancer, ERβ generally exhibits lower expression levels and has a weak negative correlation with ERα (Spearman $R=-0.18$, $P=2.2\times10^{-16}$) (91). ERβ is more abundantly expressed in basal-like or normal-like breast cancer subtypes (91). In ERα(+) breast cancer, ERβ suppresses ERα and thus inhibits tumor growth. Conversely, ERβ can act as a carcinogen in ERα(-) breast cancer (89). Moreover, ERβ interacts with various signaling pathway molecules including AR, p53, E-cadherin, cell cycle arrest molecules, phosphatase and PTEN, PI3K and AKT, all of which contribute to either inhibiting or promoting cancer growth (92). Notably, stable expression of ERβ in the ERα(+) cell line MCF7 results in decreased cell proliferation. Of the 921 differentially expressed genes after E2 treatment in ERβ(+) compared with ERβ(-) breast cancer cells, 424 had ERβ binding sites within 10 kb. These target genes are crucial in regulating cell proliferation, death, differentiation, motility, adhesion, signal transduction and transcription (93).

In the prostate gland, ERβ isoforms range from ERβ1 to ERβ5 (94), each having distinct functions that can act either as tumor suppressors or oncogenes. Typically, ERβ acts as a tumor suppressor contrary to ERα in prostate cancer (95), upregulating E-cadherin to inhibit EMT (96). Furthermore, ERβ enhances prolyl hydroxylase domain 2 expression, which hydroxylates hypoxia-inducible factor 1-α (HIF-1α), marking it for degradation by the Von Hippel-Lindau tumor suppressor (97,98). ERβ also upregulates forkhead box O3, subsequently increasing the expression of the apoptotic gene p53 upregulated modulator of apoptosis (PUMA) and the cell cycle arrest genes p21 and p27, thereby inhibiting tumor cell proliferation (68). When activated by ligands such estradiol or the selective ERβ agonist LY3201, ERβ functions as a tumor suppressor by inhibiting AR activation and the response of AR target genes (99). ERβ activation induces cellular differentiation and inhibits proliferation, particularly in early-stage or low-grade prostate cancer. ERβ exerts these effects by promoting the degradation of pro-tumorigenic factors such as HIF-1α, which helps maintain a differentiated, non-invasive state in the prostate (68). However, in advanced or high-grade prostate cancer, including CRPC, ERβ expression is frequently downregulated, leading to the loss of its protective effects and contributing to tumor progression (68,100). However, when ERβ1 forms heterodimers with ERβ2 or ERβ5, it correlates with poorer patient outcomes, promoting increased cell migration and invasion (101).

In the context of ovarian cancer, it has been hypothesized that ERβ serves as a tumor suppressor. Indeed, studies have demonstrated that in epithelial ovarian cancer (EOC), comprising 90% of ovarian cancer, the expression of ERβ is diminished in tumor tissues compared with normal tissues (102). Overexpression of ERβ has been observed to suppress the expression and activity of ERα, and to decrease levels of pAKT, cyclin D1 and cyclin A2. An *in vivo* study employing orthotopic xenograft mouse models showed that overexpression of ERβ curbs tumor growth (103). In EOC, ERβ interacts with an indole derivative (3-{[2-chloro-1-(4-chlorobenzyl)-5-methoxy-6-methyl-1H-indol-3-yl]methylene}-5-hydroxy-6-methyl-1,3-dihydro-2H-indol-2-one) to inhibit ovarian cancer cell proliferation (104).

Lung cancer studies, particularly in NSCLC, suggest that ERβ facilitates tumor progression and adversely affects patient prognosis (95,105). ERβ expression positively correlates with tumor size, lymph node metastasis, clinical stage and differentiation. Silencing ERβ *in vitro* reduces cell invasion and colony formation (105). Overexpression of ERβ in *in vivo* mouse models has been shown to accelerate tumor progression via the ERβ/circ-TMX4/miR-622/CXCR4 signaling pathway (106).

In gastric cancer, ERβ operates as a tumor suppressor and manifests at reduced levels in gastric cancer tissues compared with normal gastric mucosa (107,108). Knockdown of ERβ in gastric cancer cell lines AGS and MKN45 activates growth

arrest and DNA damage inducible α, leading to increased apoptosis and autophagy through inhibition of the MAPK pathway. Furthermore, ERβ knockdown results in fewer colonies formed (109). Clinical studies have reported a negative correlation between ERβ expression levels, tumor grade and Lauren type in gastric cancer (110).

In colon cancer, ERβ is recognized as a tumor suppressor (111-115). When expressed in the colon cancer cell line SW480, ERβ reduces cell proliferation, induces cell cycle arrest in the G_1 phase, increases tp21 and p53 expression levels and decreases the expression levels of c-Myc (112). Treatment with the ERβ-selective agonist ERB-041 has shown anticancer effects in colorectal cancer, including reduced metastasis and tumorigenesis in zebrafish xenograft and mouse models, as well as decreased migration and survival in colorectal cancer cell lines (113). During the transition from healthy tissue to cancer, the expression of ERβ decreases (114), and negatively correlates with survival rates in patients (115).

In liver cancer, ERβ also acts as a tumor suppressor, notably in HCC, where ERβ interacts with E2 to exert anti-proliferative and anti-inflammatory effects (116). It has been reported that ERβ induces the expression of suppressor of cytokine signaling 1 and inhibits the JAK1-STAT6 pathway, preventing the polarization of tumor-associated macrophages to the M2 phenotype, thereby inhibiting HCC growth (117). Intrahepatic cholangiocarcinoma treatment with the ERβ antagonist KB9520 has shown to increase apoptosis and reduce cell proliferation *in vitro* using HuH-28 cells and *in vivo* in a thioacetamide-induced experimental model of intrahepatic cholangiocarcinoma (118). These findings collectively affirm that ERβ functions as a tumor suppressor in liver cancer.

ARs. AR was discovered in the 1960s, and since then, its structural functions and mechanisms have been extensively studied (119-122). AR consists of several domains: NTD, DBD, hinge region, LBD and CTD. Similar to ERβ, AF-1 is located in the NTD and AF-2 is in the LBD. The hinge region, positioned between the DBD and LBD, contains the nuclear localization signal, facilitating the translocation of AR from the cytoplasm to the nucleus (120-122). Although the functions of AR are well documented in prostate cancer, its roles in other cancer types are less clearly understood.

In prostate cancer, AR promotes tumor progression. A previous study reported that IL-6 activates the NTD of AR in LNCaP cells, enhancing cell proliferation via MAPK and signal transducer and activator of STAT3 signaling pathways (123). Consequently, primary cancer therapy for prostate cancer frequently utilizes ADT, which aims to inhibit androgens or block their binding to AR, thus suppressing tumor growth (124). However, as the cancer advances, it may evolve into CRPC, which resists both ADT and drugs such as abiraterone and enzalutamide (125-127). Due to this resistance, extensive research on ADT therapy continues to explore mechanisms of resistance and develop novel therapeutic strategies (128,129). Shiota *et al* (130) investigated organelles generating reactive oxygen species (ROS) following AR inhibition and reported that ROS are primarily induced in peroxisomes through peroxisome proliferator-activated receptor α (PPARα) activation. Additionally, inhibiting PPARα reduced cell proliferation and restored sensitivity to enzalutamide. Inhibition of enhancer of zeste homolog 2 (EZH2) or achaete-scute homolog 1 (ASCL1) have been shown to re-sensitize prostate cancer cells to enzalutamide. EZH2, a component of the polycomb repressive complex 2, functions as a histone methyltransferase. In CRPC, EZH2 can promote AR signaling independent of its histone modification role, even in the absence of androgens (100,131). ASCL1, a transcription factor involved in neuroendocrine differentiation, is linked to resistance against AR-targeted therapies, including enzalutamide, due to its role in promoting neuroendocrine-like characteristics in prostate cancer. Inhibiting either EZH2 or ASCL1 shifts the cancer cells back to a phenotype more reliant on AR signaling, thereby restoring sensitivity to enzalutamide (66).

In breast cancer, multiple studies have investigated the antitumor activity of AR, highlighting its potential to suppress estrogen-regulated tumorigenesis and improve clinical outcomes, particularly in ER(+) breast cancer (36,132-135). AR activation displaces ER and key co-activators such as p300 and SRC-3 from chromatin, leading to the downregulation of ER-regulated genes and the upregulation of tumor suppressor genes and AR target genes. This antitumor activity remains effective even in ER(+) breast cancer resistant to CDK4/6 inhibitors (36,132). Conversely, in ER(-) breast cancer, AR promotes tumor progression. Treatment with the AR agonist dihydrotestosterone (DHT) has been shown to increase cell proliferation, migration, invasion and metastasis, as confirmed using *in vivo* mouse models (133). Additionally, AR is activated by various signaling pathways, including the PI3K, MAPK and mTOR pathways, further contributing to tumor progression (134,135).

In ovarian cancer, ARs are known to promote tumor progression (136). Research has demonstrated that ARs are upregulated in >50% of EOC cases, leading to extensive investigations into its role (137,138). Treating EOC with DHT has been shown to decrease the expression levels of TGF-β1 receptors (TGFBR1-TGFBR2) and CDKN1A (139). Moreover, androgen treatment in OVCAR-3 and SKOV-3 cell lines, using androgen-supplemented medium, increased cell proliferation and invasion, a process mediated by the androgen receptor coactivator p44 (140). Martins *et al* (141) reported that in high-grade serous ovarian cancer, AR overexpression suppresses the tumor suppressor PTEN, thereby facilitating tumor progression.

Whether ARs act as a tumor suppressor or an oncogene in lung cancer remains unresolved. Liu *et al* (142) reported that ARs impede cell invasion in NSCLC and diminishes the expression of the oncogene tumor protein D52 via the circular-SLCO1B7/microRNA (miR)-139-5p axis, thereby impeding tumor progression. Additionally, miR-224-5p, which hampers apoptosis and accelerates tumor growth, directly targets ARs and patients with NSCLC with high AR expression levels have a significantly longer overall survival rate [hazard ratio (HR)=0.5, log rank $P=8.9x10^{-16}$] (143). By contrast, Li *et al* (144) demonstrated that treating the NSCLC cell line A549 with luteolin suppressed AR expression and subsequently reduced cell proliferation. Additionally, Recchia *et al* (145) reported that the interaction between AR and the EGFR-enhanced A549 cell proliferation via the

Table I. Function of hormone receptors in different types of cancer.

Hormone receptor	Type of cancer							
	Breast	Prostate	Ovarian	Lung	Gastric	Colon	Liver	(Refs.)
ERα	Oncogene	Oncogene	Oncogene	Oncogene	Dual function	Oncogene	Oncogene	(50-85)
ERβ	Dual function	Dual function	Tumor suppressor	Oncogene	Tumor suppressor	Tumor suppressor	Tumor suppressor	(68,91-118)
AR	Dual function	Oncogene	Oncogene	NC	NC	NC	NC	(36,123-153)

NC, not classified; ER, estrogen receptor; AR, androgen receptor.

mTOR/CD1 pathway. Thus, further research into the detailed mechanism of AR is essential.

In regards to gastric cancer, similar to lung cancer, the precise role of AR is not well defined, but the majority of studies suggest that AR promotes tumor progression. Liu *et al* (146) reported that AR upregulates the oncogenic miR-125b in gastric cancer, which inhibits apoptosis and promotes proliferation. Conversely, treatment with the AR antagonist bicalutamide induces apoptosis and inhibits proliferation. Furthermore, Xia *et al* (147) found that the AR splice variant AR-v12 is more highly expressed in tumor tissues compared with normal tissues and upregulates myosin light chain kinase, enhancing cell migration and invasion. Soleymani Fard *et al* (148) reported that >50% of the 60 patients with gastric cancer exhibited upregulated ARs, which were significantly associated with the upregulation of EMT-related genes, including Snail, β-catenin, Twist1 and STAT3. AR upregulation is associated with poor survival outcomes (HR=3.478, P=0.001), and treatment with enzalutamide has been found to inhibit tumor progression.

The role of AR in colon cancer remains unclear. Studies suggest that the activation of membrane-associated AR inhibits the PI3K/AKT pathway, induces apoptosis and subsequently suppresses tumor growth in colorectal cancer (149,150). Conversely, Rodríguez-Santiago *et al* (151) reported that ARs promote tumor progression, noting that their upregulation in tumor tissues is associated with increased tumor size, differentiation and metastasis. AR activation not only diminishes antitumor immune activity but also increases the secretion of tumor-promoting factors from the nervous system, thereby facilitating tumor growth.

In liver cancer, similarly to colon cancer, the role of AR is not well-defined. Acosta-Lopez *et al* (152) observed increased expression levels of AR in tumor tissues compared with normal tissues in HCC, associating increased AR activity with poorer prognosis in advanced HCC. Furthermore, Ren *et al* (153) suggested that mTORC1 phosphorylates AR at serine residue 96, which promotes tumor progression. Meanwhile, Ren *et al* (154) reported that treatment with DHT escalates cell proliferation, invasion and migration in the HepG2 cell line, while Ouyang *et al* (155) determined that AR inhibits cell migration and invasion in HCC cell lines HA22T and SK-HEP-1 via the miR-325/ACP5 signaling pathway.

The present review investigated the effects of three hormone receptors across seven major types of cancer. The impact of sex hormone receptors on each type of cancer is summarized in Table I. Studies on the influence of these receptors on tumor progression have advanced considerably in hormone-responsive organs, although their effects in non-responsive organs remain less understood.

3. Role of key transcription factors in mediating hormone receptor-driven tumor progression

Key cancer-related transcription factors activated through interactions with hormone receptors. The sex hormones examined in the present study activate mechanisms of cancer malignancy or suppression through their respective receptors. In this process, various transcription factors are known to regulate the expression of key molecules involved in these mechanisms via sex hormone signaling. Prominent transcription factors include specificity protein 1 (SP1), ETS-related gene (ERG), β-catenin, activator protein 1 (AP-1), c-Myc, NF-κB and STAT3. Table II provides a summary of how these key transcription factors influence cancer progression through their interactions with sex hormone receptors.

SP1 is a transcription factor that binds to specific promoter regions containing GC-rich sequences and serves a key role in activating the expression of various genes. SP1 is known to function as an oncogene through the three sex hormone receptors examined in this study. In breast cancer, the ER/SP1 complex binds to DNA, promoting the expression of estrogen-induced genes such as c-Myc, creatine kinase B-type (CKB), cathepsin D, retinoic acid receptor α (RARα) and heat shock protein 27 (Hsp27), thereby facilitating tumor progression (156). In ovarian cancer, estrogen stimulates the expression of genes related to angiogenesis in the endometrium and endothelial cells through the SP1/ERβ complex, with this abnormal angiogenesis promoting tumor growth and invasion (157). Furthermore, in prostate cancer, the AR/SP1 complex binds to the VEGF core promoter in chromatin, and androgen increases VEGF expression via the SP1 binding site, driving angiogenesis and tumor progression (158).

ERG is a key transcription factor belonging to the ETS family that serves a key role in various biological processes such as angiogenesis, cell differentiation, migration and

Table II. Key cancer-related transcription factors activated by hormone receptor interactions.

Transcription factor	ERα	ERβ	AR	(Refs.)
SP1	Oncogene	Oncogene	Oncogene	(156-158)
ERG	Oncogene	Tumor suppressor	Oncogene	(159,160)
β-catenin	Tumor suppressor	Oncogene	Oncogene	(77,161,162)
AP-1	Oncogene	Tumor suppressor	Tumor suppressor	(87,163-165)
c-Myc	Oncogene	Tumor suppressor	Oncogene	(112,166-168)
NF-κB	Oncogene	Tumor suppressor	Oncogene	(169-171)
STAT3	Oncogene	Oncogene	Oncogene	(172-174)

SP1, specificity protein 1; ERG, ETS-related gene; AP-1, activator protein 1.

metastasis (159,160). In prostate cancer, ERG is notably upregulated due to gene fusion with transmembrane serine protease 2 (TMPRSS2), and this upregulation has been associated with aggressive prostate cancer (159). Setlur *et al* (159) demonstrated that TMPRSS2-ERG expression increased following ERα agonist treatment, which also led to increased prostate cancer cell viability. Conversely, ERβ agonist treatment resulted in a decrease in both TMPRSS2-ERG expression and cancer cell viability, indicating that the impact on cancer progression varies depending on whether ERα or ERβ is activated by estrogen stimulation. Moreover, an *in vitro* study by Kohvakka *et al* (160) demonstrated that the abnormal expression of prostate cancer-specific long non-coding RNAs (lncRNAs) further promotes tumor development and progression.

β-catenin, a key molecule in the Wnt signaling pathway, exerts varying effects on cancer malignancy depending on the type of sex hormone receptor involved. Experimental overexpression of ERα via vector-based transfection inhibits β-catenin, thereby suppressing the growth, proliferation and invasion of gastric cancer cells, halting their entry into the G_1/G_0 phase and promoting apoptosis (77). Meanwhile, in prostate cancer, androgen interacts with AR to promote tumor progression, whereas estrogen stimulates cell proliferation specifically in androgen-responsive prostate cancer (63,126). Increased expression levels of β-catenin via ERβ increases the incorporation of [methyl-3H]thymidine and upregulates cyclin D2 expression, promoting cell cycle progression (161). Furthermore, β-catenin stimulates AR transcriptional activity through transcriptional intermediary factor 2 and glucocorticoid receptor-interacting protein 1, thereby activating AR signaling. This activation increases androgen affinity, reduces the efficacy of anti-androgen therapies and accelerates tumor progression in prostate cancer (162).

The AP-1 family of transcription factors, including c-Fos and c-Jun, increases cell proliferation in breast cancer via E2-ERα signaling. However, through ERβ signaling, AP-1-mediated transcription is suppressed by the recruitment of the transcriptional repressor C-terminal binding protein, which counteracts the proliferation driven by ERα (87,163). In prostate cancer, AR not only mediates androgen-induced cancer progression but also interacts with AP-1 to form a complex, wherein they mutually inhibit each other's binding affinity to DNA-binding sites (164,165).

Estrogen stimulation enhances the interaction between c-Myc and ERα, with both binding closely to the VEGF promoter. A study by Dadiani *et al* (166) demonstrated that estrogen activates c-Myc expression via ERα in ERα(+) breast cancer cells, promoting cell growth and proliferation while inhibiting differentiation. Additionally, estrogen transiently induces the transcription of VEGF, a key factor in angiogenesis, thereby facilitating cell migration (166). By contrast, ERβ signaling suppresses c-Myc transcription, modulating the expression levels of proliferation-related genes. For instance, ERβ increases the production of antiproliferative genes such as p21 and p27, leading to G_1 or G_2 cell cycle arrest and inhibiting the proliferation of breast and colorectal cancer cells (112,167). Moreover, c-Myc is a major target gene of AR signaling, with AR enhancing the transcription and expression levels of c-Myc, thereby promoting prostate cancer cell growth and progression. Consequently, c-Myc upregulation is associated with the development and progression of prostate cancer (168).

NF-κB is known to mutually inhibit ERα, yet when co-activated, NF-κB modifies ERα function, leading to endocrine resistance and promoting breast cancer metastasis and recurrence, making ER(+) tumors more aggressive (169). In prostate cancer, the effects of NF-κB vary depending on the receptor involved. Estrogen-activated ERβ mediates the proteasomal degradation of HIF-1α, which suppresses NF-κB activation, thereby reducing inflammation and potentially inhibiting the development of malignant tumors (170). Conversely, Zhang *et al* (171) reported that NF-κB expression activates AR promoter transcription, increasing AR expression levels and cell proliferation while inhibiting apoptosis. This ultimately promotes metastasis and angiogenesis, thereby accelerating tumor progression.

STAT3 functions as a key transcription factor involved in various cancer progression pathways, including cellular transformation, proliferation, survival and angiogenesis, often through its interaction with sex hormone receptors (172-174). In breast cancer cells, leptin signaling increases ERα expression, which in turn enhances STAT3 activity, improving ERα-dependent cell viability and promoting tumor progression (172-174). In lung cancer cells, STAT3 activation upregulates ERβ signaling, leading to increased cell proliferation (173). In prostate cancer, AR directly interacts with STAT3, enhancing its activity. Yamamoto *et al* (174), reported

that AR activation neutralizes the inhibitory effects of the STAT3 protein inhibitor PIAS3, thus protecting STAT3 from inhibition. Since STAT3 is an oncogene that mediates cellular transformation and promotes prostate cancer, its interaction with AR further accelerates tumor progression.

Cancer-related transcription factors linked to hormone receptor interactions: Insights from database analysis. To identify sex-specific key transcription factors involved in hormone receptor-driven cancer progression across seven major types of cancer (breast, prostate, ovarian, colon, lung, liver and gastric cancer), a comprehensive data analysis approach using the SignaLink 3.0 database (http://signalink.org) was employed. The SignaLink database integrates experimentally validated and curator-inferred protein-protein interactions (PPIs) and regulatory mechanisms from multiple sources, focusing on *homo sapiens* to ensure human-specific relevance. The dataset includes curated data from OmniPath (https://www.omnipathdb.org), BioGRID (https://thebiogrid.org), Reactome (https://reactome.org) and ComPPI (https://comppi.linkgroup.hu/) (175).

The initial analysis of SignaLink 3.0 identified 6,738 transcription factors associated with ERα, ERβ and AR. This set was filtered to focus on transcription factors that either regulate or are regulated by all three hormone receptors (ERα, ERβ and AR). Through this process, 31 transcription factors were identified that are regulated by all three hormone receptors and 10 transcription factors that regulate these receptors (Fig. 1; Table III) (176-219). Notably, there was no overlap between the two groups.

To further refine the selection, a text mining approach was conducted by combining data from GeneCards (https://www.genecards.org/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/). GeneCards is a comprehensive database that provides detailed information on human genes, including their functions, interactions and involvement in diseases (220). GeneCards was used to explore the biological roles of each transcription factor and utilized PubMed to analyze how they interact with hormone receptors. The selection criteria focused on transcription factors that, as evidenced in the literature, both regulate and are regulated by at least two of the three hormone receptors and have demonstrated significant roles in cancer progression. Through this process, studies were identified that demonstrated the critical roles of these transcription factors in modulating hormonal signaling pathways, which are implicated in sex-specific tumor biology. These interactions were further analyzed to assess their impact on tumor progression, with a focus on understanding the mechanisms by which these transcription factors regulate hormone receptor activity across various types of cancer.

These transcription factors are primarily known to influence hormone-related cancer progression through various pathways, including the PI3K/AKT/mTOR signaling pathway and the Hippo-YAP/TAZ pathway. PI3K/AKT/mTOR signaling is a common pathway modulated by multiple transcription factors such as PPARG and AR, leading to enhanced tumor growth and survival, especially in prostate cancer (191,207,208). SMARCA4 and the Hippo-YAP/TAZ signaling pathway are implicated in lung cancer, where they promote tumorigenicity by regulating gene transcription involved in cell proliferation and metastasis (213). Consequently, six key transcription factors were identified: CCCTC-binding factor (CTCF), forkhead box A1 (FOXA1), retinoic acid receptor α (RARA), PBX homeobox 1 (PBX1), GATA binding protein 2 (GATA2) and CDKN1A, as candidate hormone-related transcription factors. It was then investigated how interactions between these transcription factors and hormone receptors affect tumor progression, summarizing the pathways influenced by these interactions (Fig. 2).

The CTCF has been extensively studied in breast cancer. Montes-de-Oca-Fuentes *et al* (221) revealed that in the ER(+) breast cancer cell line MCF7, CTCF binds with ERα and regulates its gene expression. By contrast, in the ER(-) cell line MDA-MB-231, this binding site is methylated, which prevents binding. Additionally, Rossi *et al* (222) reported that CTCF influences the transcriptional activity of both ERα and ERβ. In a mouse model overexpressing HER2/neu, CTCF binds to both ERα and ERβ, supporting their transcriptional activity and indirectly contributing to tumor progression. Moreover, in prostate cancer, CTCF is known to interact with AR and tends to suppress the expression of AR target genes (219).

FOXA1 has been extensively researched in breast cancer and is known to interact with ERα, regulating estrogen responses and transcription activity and activating oncogene expression (223-226). Additionally, FOXA1 has a positive correlation with AR (r=0.8975, P<0.001) (227,228). Tsirigoti *et al* (229) reported that FOXA1 regulates AR expression levels in TNBC and is inversely correlated with Snail Family Transcriptional Repressor 1 (SNAI1) (Spearman's R=-0.377, $P<2.2x10^{-16}$), and suggested that in SNAI1-knockout TNBC, FOXA1 induces AR expression, fostering basal-luminal plasticity. In prostate cancer, FOXA1 is positively correlated with ERβ (epithelial, ρ=0.41, P<0.001; stromal, ρ=0.354, P<0.001), and FOXA1 knockdown via siRNA inhibits cell proliferation and migration in LNCaP and PC-3 cell lines (230). FOXA1 is also implicated in promoting tumor progression in prostate cancer and HCC through AR-mediated signaling (231,232).

RARA has gained substantial attention in breast cancer. It binds ERα to mediate transcription of ERα target genes (233). Salvatori *et al* (234) reported that, once activated by retinoic acid, RARA suppresses EGFR expression, while ERα, activated by E2, enhances EGFR expression. Nevertheless, in the absence of ligands, ERα interacts with RARA to augment its ability to suppress EGFR expression, functioning as a tumor suppressor. RARA also participates in the AR-related transcription network in prostate cancer, inversely regulating the expression of target genes such as polo-like kinase 3 (PLK3). Specifically, RARA increases PLK3 expression, while AR reduces it, contributing to tumor progression (235). Notably, in the HepG2 HCC cell line, ERβ does not interact with the RARA promoter in the presence of estrogen, but upon 4-hydroxytamoxifen (4-OHT) treatment, ERβ activates transcription of RARA (236).

PBX1 is predominantly studied in breast cancer, specifically for its interaction with ERα compared with other hormone receptors. PBX1 serves as both a transcription and pioneer factor in the estrogen signaling pathway, binding to chromatin before ERα to enhance its accessibility and elevate the expression of estrogen-responsive genes linked to aggressive tumor behavior. This mechanism supports PBX1 as a poor prognostic

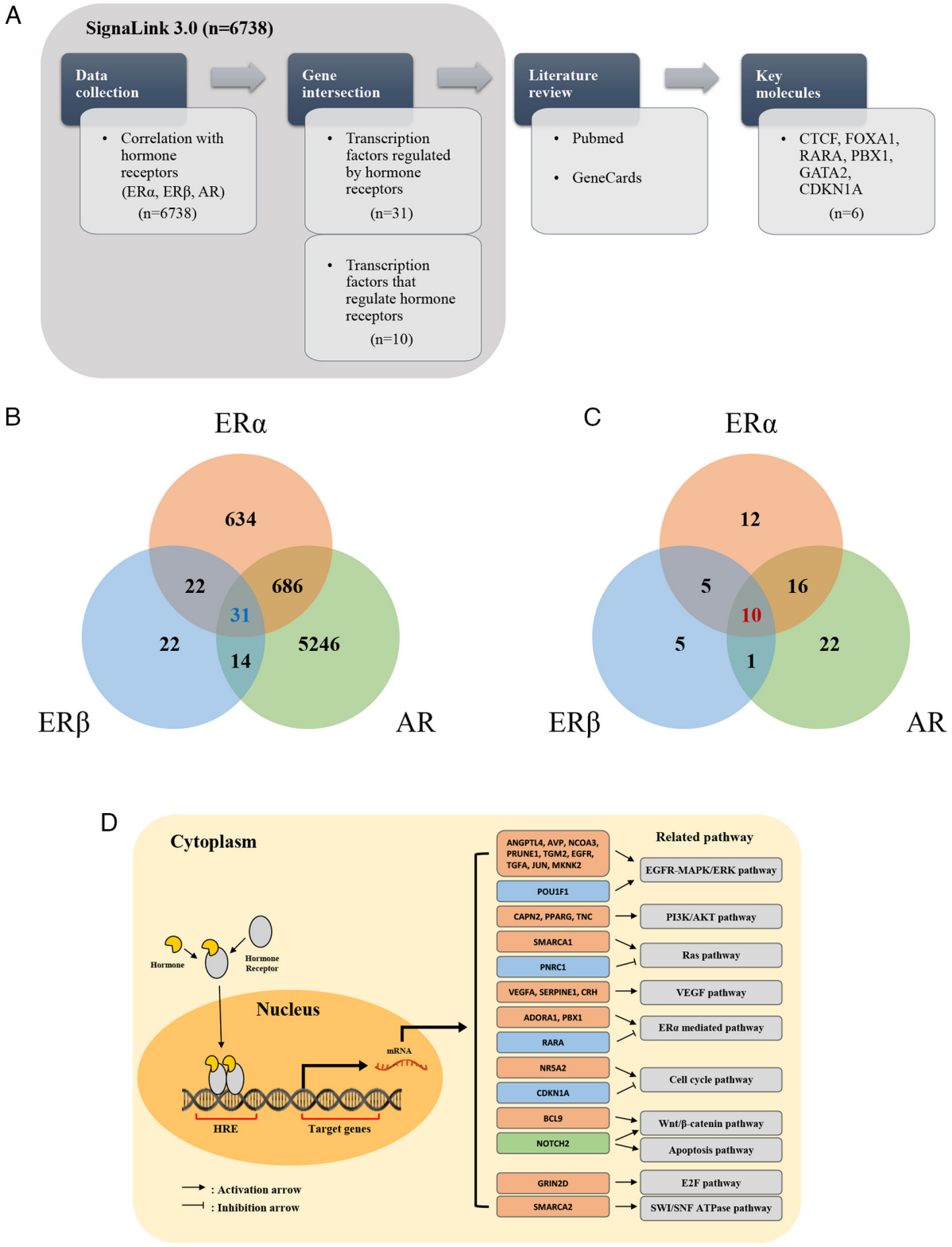

Figure 1. Transcription factors related to hormone receptors. (A) Workflow of identification of sex-specific key transcription factors. (B) Transcription factors regulated by hormone receptors. (C) Transcription factors that regulate hormone receptors. (D) Schematic of hormone regulation of 31 transcription factors and their related pathways in cancer. Transcription factors in the red box promote cancer progression. Transcription factors in the blue box suppress cancer progression. Transcription factors in the green box can function as both. ER, estrogen receptor; AR, androgen receptor; HRE, hormone response element; CTCF, CCCTC-binding factor; FOXA1, forkhead box A1; RARA, retinoic acid receptor α; PB1, PBX homeobox 1; GATA2, GATA binding protein 2; CDKN1A, CDK inhibitor 1A.

biomarker for breast cancer (237,238). Although direct interactions between PBX1 and AR are not documented, evidence suggests an indirect regulatory pathway. Kikugawa *et al* (239) demonstrated that promyelocytic leukemia zinc finger (PLZF), an AR-regulated tumor suppressor gene, inhibits PBX1 expression. Thus, when androgen interacts with AR, PLZF

Table III. Key cancer-related transcription factors associated with hormone receptor interactions from database analysis.

A, Regulated by hormone receptors (n=31)

Function in cancer progression	Transcription factors	Regulatory mechanism	Type of cancer	(Refs.)
Promotion	ADORA1	Promotes transcriptional activity of ERα	Breast	(176)
	ANGPTL4	Activates ERK1/2 pathway	Ovarian	(177)
	AVP	AVPR1A/ERK/CREB pathway	Prostate	(178)
	BCL9	Enhances the Wnt/β-catenin signaling	Gastric and TNBC	(179,180)
	CAPN2	AKT/mTOR signaling pathway	Prostate	(181)
	CRH	IL-6/JAK2/STAT3 signaling pathway and VEGF-induced tumor angiogenesis	Colon	(182)
	EGFR	Activates the MEK/pERK signaling pathway	HCC	(183)
	GRIN2D	Enhances glycolysis, gluconeogenesis and the E2F signaling pathway	LUAD	(184)
	JUN	Activates the MAPK/AP-1 signaling pathway	Various	(185)
	MKNK2	Enhances the phosphorylation of eIF4E	NSCLC	(186)
	NCOA3	Activates the PERK-ATF4 pathway	Breast	(187)
	NR5A2	Increases the resistance of endocrine therapy	Breast	(188,189)
	PBX1	Controls the TGFβ, ERα, NOTCH3 signaling pathway	Various	(190)
	PPARG	Activates the PI3K/AKT pathway	Prostate	(191)
	PRUNE1	Enhances the canonical Wnt/β-catenin signaling	NSCLC	(192)
	SERPINE1	Activates the VEGFR-2 signaling pathway	Gastric	(193)
	SMARCA1	Activate the Ras signaling, Rap1 signaling and the cGMP-PKG signaling pathway	Breast	(194)
	TGFA	Activates the EGFR signaling pathway	Breast	(195)
	TGM2	Activates the Erk activity and EGFR signaling pathway and the NF-κB survival pathway	Colorectal, breast and ovarian	(196,197)
	TNC	Activate the PI3K/AKT/NF-κB pathways	Prostate	(198)
	VEGFA	Activates the AKT signaling pathway	Colon	(199)
	SMARCA2	Deactivates AR through SWI/SNF ATPase degradation via SMARCA2 loss	Prostate	(200)
Suppression	CDKN1A	Inhibits the activity of cyclin-CDK complexes, cyclin D-CDK4/6 and cyclin E-CDK2	Prostate	(201)
	PNRC1	Suppresses Grb2-mediated Ras/MAP-kinase activation	Breast	(202)
	POU1F1	Phosphorylation by MEK/ERK signaling pathways sensitizes cancer cells to chemotherapy.	Breast	(203)
	RARA	Modulates retinoic acid and estrogen signaling	Breast	(204)
Dual function	NOTCH2	Promotes the apoptosis in ER(-) breast cancer Induced biliary differentiation and stem-like maintenance Enhances EMT and contributes to chemoresistance via Wnt/β-catenin signaling	Breast, HCC and gastric	(205,206)
Unknown	CHAT	-	-	-
	CRYZ	-	-	-
	NBPF15	-	-	-
	NOTCH2NLA	-	-	-

Table III. Continued.

B, Regulators of hormone receptors (n=10)

Function in cancer progression	Transcription factors	Regulatory mechanism	Type of cancer	(Refs.)
Promotion	AR	Activates the PI3K/AKT/mTOR signaling pathway	Prostate	(207,208)
	EGR1	Activates the AR signaling pathway	Prostate	(209)
	ESR1	Crosstalk with the PI3K/AKT/mTOR signaling pathway	Various	(210)
	FOXA1	Promotes the binding the other transcription factors Activates the glycolysis pathway	Prostate, LUAD	(211,212)
	GATA2	Activates the AR signaling	Prostate	(208)
	SMARCA4	Activates the Hippo-YAP/TAZ signaling pathway	Lung	(213)
	STAT3	Activated the STAT3 transactivation activity	Breast	(172,214)
	YBX1	Promotes the PI3K/AKT pathway	Various	(215)
Suppression	SPI1	Promotes the apoptotic pathway	LUAD	(216)
Dual function	CTCF	Regulates estrogen-responsive genes, cell cycle and epigenetic regulation Interacts with AR and suppresses AR target gene expression	Breast and prostate	(217-219)

ADORA1, adenosine A1 receptor; ANGPTL4, angiopoietin like 4; AVP, arginine vasopressin; BCL9, B-cell CLL/lymphoma 9; CAPN2, calpain 2; CRH, corticotropin-releasing hormone; EGFR, epidermal growth factor receptor; GRIN2D, Glutamate Ionotropic Receptor NMDA Type Subunit 2D; JUN, Jun proto-oncogene; MKNK2, MAP kinase interacting serine/threonine kinase 2; NCOA3, nuclear receptor coactivator 3; NR5A2, nuclear receptor subfamily 5 group A member 2; PBX1, PBX homeobox 1; PPARG, peroxisome proliferator-activated receptor gamma; PRUNE1, prune homolog 1; SERPINE1, serpin family E member 1; SMARCA1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 1; TGFA, transforming growth factor alpha; TGM2, transglutaminase 2; TNC, tenascin C; VEGFA, vascular endothelial growth factor A; SMARCA2, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 2; CDKN1A, cyclin-dependent kinase inhibitor 1A; PNRC1, proline-rich nuclear receptor coactivator 1; POU1F1, POU class 1 homeobox 1; RARA, retinoic acid receptor alpha; NOTCH2, Notch receptor 2; CHAT, choline O-acetyltransferase; CRYZ, crystallin zeta; NBPF15, neuroblastoma breakpoint family member 15; NOTCH2NLA, Notch 2 N-terminal like A; AR, androgen receptor; EGR1, early growth response 1; ESR1, estrogen receptor 1; FOXA1, forkhead box A1; GATA2, GATA binding protein 2; SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4; STAT3, signal transducer and activator of transcription 3; YBX1, Y-box binding protein 1; SPI1, Spi-1 proto-oncogene; CTCF, CCCTC-binding factor; ER, estrogen receptor; CRPC, castration-resistant prostate cancer; TNBC, triple negative breast cancer; HCC, hepatocellular carcinoma; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; SWI/SNF, switch/sucrose non-fermenting.

expression increases, which subsequently suppresses PBX1 expression and inhibits tumor progression.

GATA2 has been extensively studied in relation to AR, particularly in prostate cancer, where it significantly affects AR. GATA2 activates AR and the AR signaling pathway, which promotes tumor progression. GATA2 also enhances the expression of TGFβ1, further driving tumor progression through interaction with the AR signaling pathway (240-242). In breast cancer, GATA2 inhibits AR translocation from the cytoplasm to the nucleus, thereby suppressing the expression of the tumor suppressor PTEN (243). Treeck *et al* (244) showed that in the ovarian cancer cell line HEC-1A, a three-fold increase in GATA2 expression occurred following ERβ knockdown. Additionally, GATA2 closely interacts with TP53.

CDKN1A, also known as p21, is a key transcription factor in various types of cancer. CDKN1A acts as a tumor suppressor in breast cancer. The presence of estrogen leads to ERα inhibiting p53 transcriptional activity, which reduces CDKN1A expression and promotes tumor progression (245,246). Conversely, treatment with tamoxifen or ERα inhibitors elevates CDKN1A expression and decreases cell proliferation (245-247). ERβ also regulates CDKN1A indirectly; in breast cancer, ERβ suppresses CDKN1A expression in the presence of wild-type p53, but increases CDKN1A expression levels in cases with mutant p53, as demonstrated *in vitro* (248). The effects of ERβ have been explored in ovarian cancer; He *et al* (249) concluded that LY500307, an ERβ agonist, increases CDKN1A levels and apoptosis in ovarian cancer stem cells. Kim *et al* (201) showed that the interplay between AR and CDKN1A in prostate

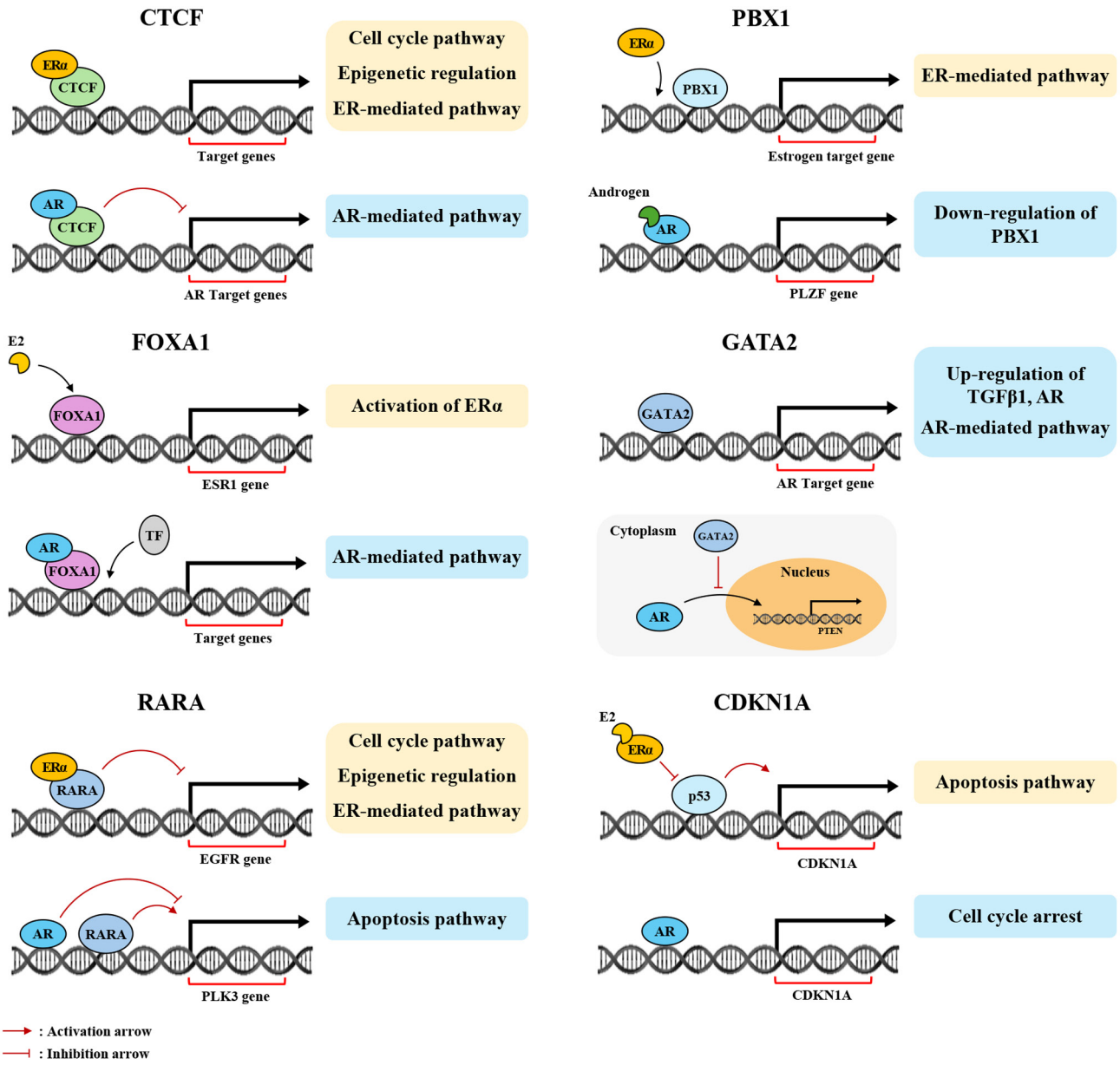

Figure 2. Graphical representation of how different hormone receptors, ERα, ERβ and AR, influence the activity or expression of the key transcription factors: CTCF, FOXA1, RARA, PB1, GATA2 and CDKN1A. ER, estrogen receptor; AR, androgen receptor; E2, estradiol; CTCF, CCCTC-binding factor; FOXA1, forkhead box A1; RARA, retinoic acid receptor α; PB1, PBX homeobox 1; GATA2, GATA binding protein 2; CDKN1A, CDK inhibitor 1A; PLZF, promyelocytic leukemia zinc finger; ESR1, estrogen receptor 1; PLK3 polo like kinase 3.

cancer demonstrates AR inhibiting cyclin D1/2 and CDK4/6 transcription while increasing CDKN1A transcription, leading to cell cycle arrest and reduced cell proliferation.

Studies on the interaction between hormone receptors and their transcription factors in cancer are limited and mainly focused on breast cancer. This focus is due to the high hormone dependency of breast cancer, with the majority of cases expressing hormone receptors, especially estrogen receptors, crucial for cancer cell growth and progression (250). Prostate cancer, also sensitive to hormones, shows significant influence from androgen receptors in its development and progression (251,252). By contrast, cancers such as gastric and lung cancer are less dependent on hormone signaling, resulting in fewer studies and less evidence on the impact of hormone receptor interactions. The established role of hormone therapy in treating breast and prostate cancer further stimulates research in these areas, while the absence of similar therapeutic approaches in other types of cancer restricts research on hormone receptor interactions.

4. Conclusions

In hormone-dependent types of cancer such as breast and prostate cancer, the interplay between AR, ER and other hormone receptors serves a key role in tumor progression and therapy resistance. In ER(+) breast cancer, when ER signaling is inhibited, AR can compensate by becoming more active, potentially driving tumor progression or resistance to treatment (253). Similarly, ER may assume a more prominent role when AR activity is diminished. This

compensatory relationship also extends to other types of cancer such as prostate cancer, where AR is the main driver of tumor growth, but ER can contribute to cancer progression under certain conditions (254). The compensatory dynamics between AR and ER underscore the need for therapies that target both receptors simultaneously to prevent one from compensating for the inhibition of the other (255). The interactions between these hormone receptors are important in understanding cancer malignancy and developing more effective, comprehensive therapeutic strategies.

The present study underscores the roles of sex-specific hormone receptors ERα, ERβ and AR across seven types of pan-cancer, highlighting their interactions with key transcription factors such as CTCF, FOXA1, RARA, PBX1, GATA2 and CDKN1A, and their impact on tumor progression. In conclusion, sex hormone receptors can either function as oncogenes or tumor suppressors depending on the type of cancer, and may exhibit both roles within a single tumor. Moreover, key transcription factors that interact with these hormone receptors serve crucial roles in regulating cancer prognosis and tumor progression. In certain types of cancer closely associated with sex hormones, such as breast and prostate cancer, hormone receptors significantly influence cancer prognosis and progression. Utilizing these sex-specific characteristics in cancer treatments enables precision medicine tailored to the unique characteristics of each patient, and transcription factors that interact with sex hormone receptors in pan-cancer may serve as novel anticancer therapeutic targets. To advance therapeutic strategies, further in-depth studies are essential in several areas: The molecular mechanisms that underlie the dual roles of sex hormone receptors as oncogenes and tumor suppressors, the specific interactions between hormone receptors and transcription factors in various types of cancer, and the development of targeted therapies that exploit these interactions. Additionally, further research is required to explore the sex-specific differences in cancer biology and their implications for treatment, as well as the potential for personalized medicine approaches based on hormone receptor status and transcription factor profiles.

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Authors' contributions

Conceptualization was conducted by JK and SYK. Formal analysis and data interpretation were conducted by JK, HB, CS, EK and SYK. Literature analysis was conducted by JK, HB and CS. Writing of the original draft was conducted by JK, HB, CS and SYK. Reviewing and editing of the manuscript was conducted by JK, HB, CS, EK and SYK. Visualization was conducted by JK and SYK. Supervision was conducted by JK, EK and SYK. Project administration was conducted by EK and SYK. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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