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Review

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Steroid Hormone Receptor Isoform Diversity in Gynecologic Oncogenesis: Mechanisms, Biomarker Evidence, and Implications for Precision Oncology

Apeksha Padakannaya[a], Chandrahas Koumar Ratnacaram[a, b, c]

Abstract

Aberrant regulation of steroid hormone receptors (SHRs) can alter transcriptional programs relevant to gynecologic tumor initiation, progression, and treatment response. Importantly, receptor diversity arises through biologically distinct mechanisms, including alternative pre-mRNA splicing, alternative promoter usage, alternative translation initiation, and post-translational modification; receptor subtypes encoded by different genes should not be considered splice variants. This narrative review focuses on estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) diversity in ovarian, endometrial, cervical, vulvar, and related gynecologic malignancies. Evidence is organized by tumor type and interpreted according to its level of support, distinguishing mechanistic preclinical observations from patient associations, candidate biomarkers, and clinically evaluated therapeutic strategies. Breast-cancer studies are used only as comparative mechanistic context when directly relevant to SHR isoform biology. Current evidence is strongest for ER- and PR-related receptor forms, whereas gynecologic data for AR, GR, and especially MR variants remain limited. Clarifying the molecular origin, tumor-specific function, and clinical validation of individual receptor forms will be essential before isoform-directed approaches can be incorporated into precision gynecologic oncology.

Keywords: Gynecologic cancers; Steroid hormone receptors; Alternative splicing; Receptor isoforms; Biomarkers; Precision oncology

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[a]Division of Cancer Research and Therapeutics, Yenepoya Research Centre, Yenepoya (Deemed to be University), Mangalore 575018, India
[b]Specialised Research Unit, Yenepoya Medical College, Mangalore 575018, India
[c]Corresponding Author: Chandrahas Koumar Ratnacaram, Division of Cancer Research and Therapeutics, Yenepoya Research Centre, Yenepoya (Deemed to be University), Mangalore 575018, India. Email: rckoumar@yenepoya.edu.in

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Introduction

Overview of gynecological cancers

Cancer remains one of the leading causes of death worldwide. According to Global Cancer Observatory incidence and mortality database (GLOBOCAN) estimates for 2022, approximately 20 million new cancer cases and 9.7 million cancer deaths occurred globally. Gynecologic cancers—malignancies of the cervix, uterine corpus, ovary, vulva, and vagina—accounted for approximately 1.47 million new cases and 680,000 deaths in the same period. Cervical cancer is the most frequently diagnosed of these, with an estimated 661,021 new cases and 348,189 deaths in 2022, followed by cancers of the uterine corpus (420,242 cases) and ovary (324,398 cases) [1]. Together these malignancies represent a substantial, and in many low- and middle-income settings rising, share of the cancer burden in women [2–4]. Despite advances in prevention, early detection, and treatment, the global burden of gynecologic cancers is projected to increase, underscoring the need for greater awareness, resource allocation, and continued research into innovative therapies and the underlying molecular mechanisms [5–7].

Importance of steroid hormone receptors (SHRs) in cancer

SHRs are intracellular transcription factors that regulate gene expression in response to steroid hormones [8]. In cancer cells, aberrant expression and regulation of SHRs have made them attractive targets for anti-cancer therapy [9, 10], and sex steroids and their receptors are directly implicated in the pathogenesis of malignancies of the female reproductive tract [11]. Although estrogen receptor (ER)-targeted therapies have been the most clinically successful, research on other SHRs, including the androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR), is ongoing. The complex nature of SHR function, involving post-translational modification, coregulator availability, and receptor-form diversity, makes a detailed mechanistic understanding essential for effective therapy development [12].

SHR signaling is highly tissue- and context-dependent; therefore, the same hormone or receptor form cannot be as-

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sumed to have equivalent biological or therapeutic effects across tumor types. This review focuses primarily on ovarian, endometrial, cervical, vulvar, and other gynecologic malignancies. Breast-cancer evidence is included only when it provides mechanistic or clinical context that helps interpret a receptor form also relevant to gynecologic disease. Throughout the review, findings are interpreted within the tumor type in which they were generated rather than extrapolated across cancers.

Methodology

This article is a narrative review of SHR diversity in gynecologic cancers. The literature search was performed in PubMed for English-language publications from January 2000 through 2025, with older seminal studies retained when required to establish the molecular origin of a receptor form. Search concepts combined receptor terms (estrogen receptor/ESR1/ESR2, progesterone receptor/PGR, androgen receptor/AR, glucocorticoid receptor/NR3C1, mineralocorticoid receptor/NR3C2) with terms describing molecular variation (alternative splicing, splice variant, isoform, alternative promoter, alternative translation, transcript variant) and disease terms (ovarian, fallopian tube, endometrial/uterine, cervical, vulvar, vaginal, and gynecologic cancer). Breast cancer was searched only for comparative evidence relevant to receptor-form biology.

Articles were prioritized when they (1) defined the molecular origin of a receptor form, (2) evaluated that form in a gynecologic tumor, model, or patient cohort, or (3) assessed prognostic, predictive, or therapeutic relevance. Publications were excluded when they were unrelated to steroid receptor diversity, lacked relevance to the cancers under review, or discussed receptor expression without information pertinent to receptor form or mechanism. Reference lists of key articles were also examined for seminal studies. Because this is a narrative rather than a systematic review, no formal risk-of-bias instrument or Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based study-selection workflow was applied; this is acknowledged as a limitation. Evidence is therefore described by study context (preclinical, observational patient evidence, candidate biomarker evidence, or clinical investigation) to avoid implying equivalent levels of validation. Two further limitations should be noted: only a single bibliographic database (PubMed) was searched, supplemented by reference-list screening, so relevant work indexed elsewhere may have been missed; and study selection was performed by the authors without independent duplicate screening. The review discusses 79 sources, and where a cited source is not a peer-reviewed primary report, this is stated at the point of use.

SHR Isoforms: Structure and Function

Overview of SHRs

SHRs comprise the receptors for glucocorticoids, androgens, estrogens, progestogens, and mineralocorticoids [13]. In canonical genomic signaling, lipophilic steroids diffuse across the plasma membrane and bind their cognate receptors; unliganded AR and GR reside predominantly in the cytoplasm, whereas ERα (encoded by estrogen receptor 1 gene (ESR1)) and ERβ (encoded by estrogen receptor 2 gene (ESR2)) are found largely in the nucleus. Ligand binding promotes receptor dimerization and nuclear translocation, after which the receptor engages specific hormone response elements in the regulatory regions of target genes to modulate transcription, with downstream consequences for cellular function [14]. Sequence and structural divergence among these receptors underlies their distinct ligand specificities and transcriptional programs [15]. SHRs also mediate non-genomic actions, activating rapid signaling cascades independently of transcriptional regulation.

SHRs perform several critical functions. One of their primary roles is gene regulation, in which they control the expression of thousands of genes and thereby influence key biological processes including growth, metabolism, and immune responses [16]. Crosstalk between SHRs and other signaling pathways contributes to hormone resistance and hormone independence in breast and prostate cancer [12, 17]. Understanding both the genomic and non-genomic actions of SHRs is essential for developing targeted therapies that improve patient outcomes and overcome treatment resistance.

Molecular origins of SHR diversity

The term "isoform" is used here as a broad protein-form descriptor, but the underlying molecular mechanism is specified wherever possible. True alternative splice variants arise from differential exon inclusion or splice-site use within a pre-mRNA; an early example in gynecologic tissue is the estrogen receptor exon 5 splicing variant (ER E5SV), whose mRNA was detected in gynecologic cancers and which arises by authentic exon skipping [18]. By contrast, ERα (ESR1) and ERβ (ESR2) are receptor subtypes encoded by different genes and are not splice variants of one another. PR-A and PR-B arise from the same PGR gene through distinct promoter/transcript usage and translation start sites rather than classical alternative splicing. ERα46 is generated by alternative splicing [19, 20], whereas ERα36 reflects alternative promoter usage together with alternative splicing. Post-translational modifications such as phosphorylation or SUMOylation modify an existing receptor protein and are discussed as regulatory mechanisms, not as splice variants. Genetic polymorphisms are likewise distinguished from transcript isoforms. Reliable assignment of these mechanisms depends on isoform-resolved transcript detection, for which long-read sequencing approaches offer particular advantages over short-read or probe-based methods [21]. This nomenclature is used throughout the review to prevent mechanistically different forms from being conflated.

Functional implications of SHR isoforms

ER and PR forms have the most developed literature in gynecologic oncology, whereas evidence for AR, GR, and MR transcript variants is substantially more limited. GR diversity

includes alternatively spliced GRα and GRβ as well as additional transcript and translational variants; their functional consequences are context-dependent, and evidence from reproductive physiology or non-gynecologic tumors should not be treated as direct evidence of gynecologic oncogenic function [22, 23]. AR splice variants are clinically established primarily in prostate cancer, but androgen receptor splice variant 7 (AR-V7) has been detected by targeted RNA sequencing in two reported gynecologic carcinomas, one arising in the lower uterine segment and one in the ovary; notably, DNA methylation profiling aligned these tumors with AR-V7-positive breast rather than prostate carcinomas [24]. This supports further investigation rather than current clinical use. In contrast, direct evidence linking specific MR splice variants to gynecologic cancer behavior or treatment response remains sparse. Accordingly, MR is retained as an important SHR family member but is not assigned an isoform-specific oncogenic or therapeutic role without gynecologic evidence.

Molecular Mechanisms of SHR Isoform-Driven Oncogenesis

Crosstalk between SHR isoforms and oncogenic pathways

Gynecologic cancer development and progression are shaped by oncogenic signaling pathways and by crosstalk between those pathways and SHR forms. Distinct forms of ER, PR, and AR can elicit different cellular responses to the same hormone, and they interact with multiple oncogenic pathways, including phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), and Wnt/β-catenin, adding further complexity to the signaling networks that drive tumor growth, therapy resistance, and metastasis [25]. Receptor-form diversity is not confined to steroid receptors: an intermediate isoform of the prolactin receptor, for example, promotes mammary oncogenesis through Ras/MAPK signaling [26], illustrating how an altered receptor N-terminus can rewire downstream pathway output.

Progesterone receptor A (PR-A; approximately 94–97 kDa) and progesterone receptor B (PR-B; approximately 114–120 kDa) are encoded by the same PGR gene but should not be classified as classical alternative splice variants. In humans, distinct estrogen-responsive promoters generate transcript classes that support expression of PR-A and PR-B, with PR-B containing an additional 164-amino-acid N-terminal B-upstream segment. The two receptor forms can have different transcriptional activities depending on cellular and promoter context [25]. This distinction is important when interpreting PR-A/PR-B ratios in cancer because altered abundance does not, by itself, demonstrate aberrant splicing.

Estrogen exerts its biological effects primarily through two nuclear receptors, ERα and ERβ. ERα is typically associated with oncogenic activity, whereas ERβ generally acts as a tumor suppressor; certain ERβ forms, however, such as ERβ5, may display oncogenic properties in specific contexts [27]. Among ERα forms, ERα36 has attracted particular attention. ERα36 mediates epidermal growth factor receptor (EGFR)-related extracellular signal-regulated kinase (ERK) activation, indicating a role in EGFR-linked signaling in endometrial cancer (EC) [28], and it also promotes E2-induced cyclin D1 (CCND1) expression through the protein kinase C delta (PKCδ)/ERK pathway, contributing to EC growth and progression [29, 30]. In cervical cancer, ERα36 is expressed in the CaSki and HeLa cell lines as well as in cervical tumor tissue [31] (Fig. 1).

Oncogenic pathways in ovarian cancer down-regulate ERα, suppressing estrogen-dependent signaling and limiting therapy effectiveness that targets ERα. In the inflammatory tumor microenvironment, chronic nuclear factor kappa-B (NF-κB) activation represses ERβ, blocking its anti-proliferative effects. However, inhibiting NF-κB restores ERβ's role in estradiol signaling and reactivates ERα pathways. ERβ can also signal through non-genomic pathways like Wnt/β-catenin. This pathway plays a role in certain ovarian cancer subtypes, such as endometrioid and granulosa cell tumors, further reducing the effectiveness of ER-targeted therapies [32].

Tumor-Specific Evidence for SHR Forms in Gynecologic Cancers

To address tissue-specific hormone biology, evidence is presented by tumor type before cross-cancer comparisons are made. Within each tumor type, mechanistic findings are separated conceptually from prognostic/predictive associations and therapeutic evidence.

Isoforms in ovarian cancer

Wetendorf et al demonstrated that constitutive PR-B expression led to ovarian neoplasia, with increased cell proliferation and reduced apoptosis. PR-B regulated key cell-cycle genes, including CCND1 and the G2/M transition regulators forkhead box protein M1 (FOXM1), Polo-like kinase 1 (PLK1), cell division cycle 25C (CDC25C), cyclin B1 (CCNB1), and cyclin-dependent kinase 1 (CDK1), thereby promoting proliferation. These progesterone-driven ovarian growths exhibited aberrant AKT-MAPK1-ERK signaling that correlated strongly with features of ovarian cancer [33]. Lenhard et al assessed expression of ERα/β and PR-A/-B in ovarian cancer tissue, finding positive expression rates of 31.4% and 60.1% for ERα/β and 36.2% and 33.8% for PR-A/-B, respectively. In that series ERα was associated with ovarian cancer cell proliferation while ERβ showed antiproliferative effects, and PR-B emerged as an independent prognostic marker that correlated positively with ERα and PR-A, suggesting a complex interaction between these receptors [34]. In contrast, a study by Ciucci et al on adult granulosa cell tumor (AGCT), a rare sex-cord stromal ovarian tumor, found predominant expression of ERβ forms (ERβ1, ERβ2, and ERβ5) (Fig. 1). The study showed that ERβ2 prevented apoptosis by localizing to the mitochondria of granulosa cancer cells and interacting with B-cell lymphoma 2 (Bcl-2) family proteins such as Bad, implicating ERβ2 in tumor cell survival [35]. This dual behavior of ERβ—support-

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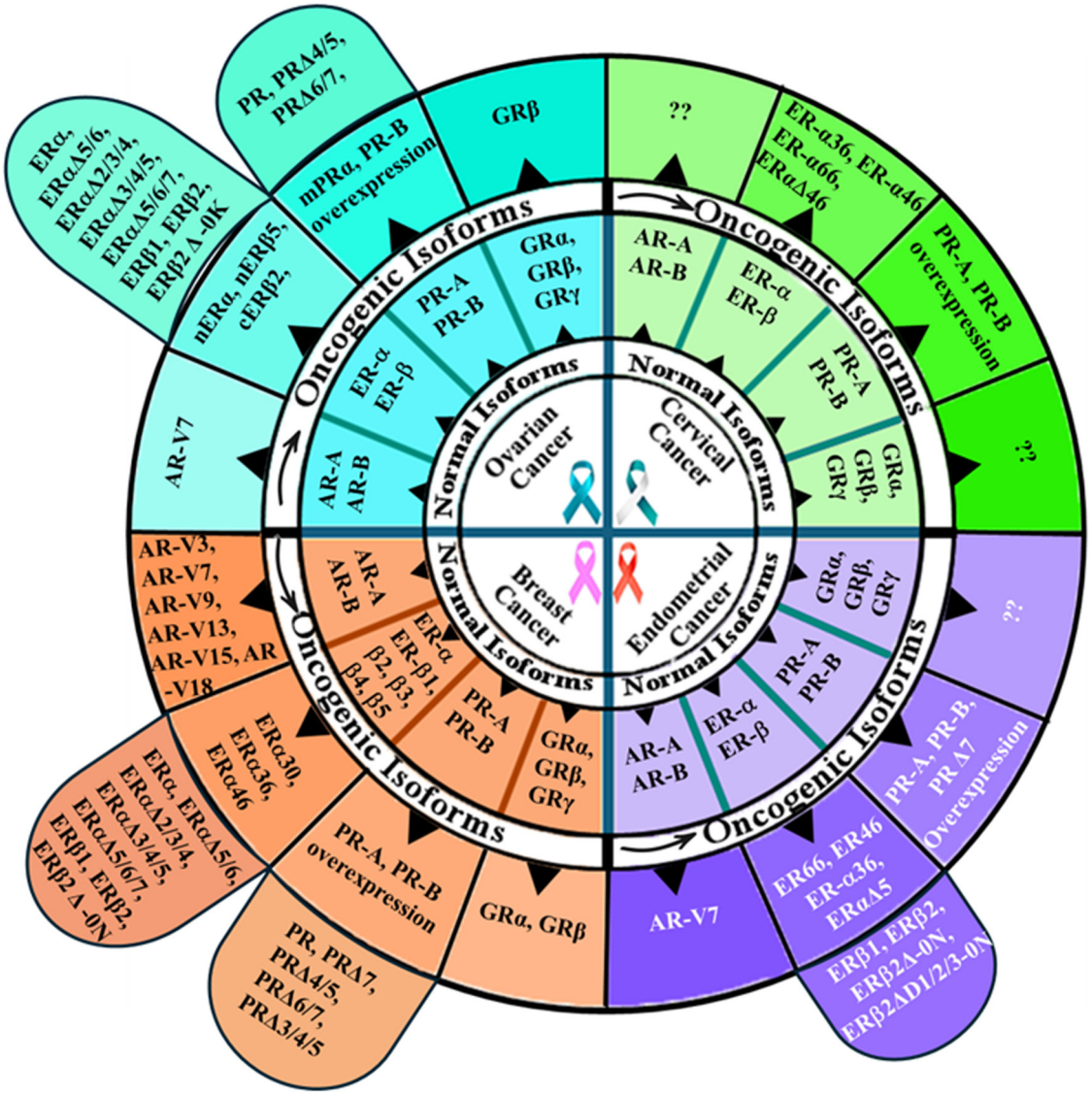


Figure 1. Steroid hormone receptor forms in gynecologic cancers, grouped by molecular origin. Forms generated by authentic alternative splicing (e.g., ERα46, ERβ2/ERβ5, ER E5SV, AR-V7) are distinguished from those arising through alternative promoter usage and/or alternative translation initiation (e.g., PR-A/PR-B, ERα36). ERα and ERβ are receptor subtypes encoded by separate genes (ESR1 and ESR2) and are not splice variants of one another.

ing survival in AGCT while exerting antiproliferative effects in other contexts—complicates any single interpretation of ERβ's impact on tumor behavior.

Isoforms in EC

The majority of endometrial malignancies occur in women after menopause, and approximately 80% of patients are diagnosed while the tumor is still confined to the uterus (stage I disease) [36, 37]. Endometrial carcinomas express enzymes involved in local estrogen metabolism, including CYP19A1 (aromatase) and 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2), which have distinct roles in estrogen synthesis and inactivation [38, 39]. In both pre- and post-menopausal women, intratumoral estradiol (E2) concentrations have been positively correlated with clinical stage and with the extent of tumor invasion [40]. Against this background of locally elevated estrogen exposure, stage I endometrioid adenocarcinomas have been examined for differential expression of ERα, full-length ERβ1, and the truncated ERβ forms ERβ2 and ERβ5 (Fig. 1).

Other studies have identified several ERα forms with distinct roles in cancer biology. ERα66 is the classic full-length receptor, and ERα46 is generated by alternative splicing [20] (Fig. 1). ERα36, first cloned in 2005, lacks both transcriptional activation functions (activation function 1 (AF-1) and activation function 2 (AF-2)) but retains the DNA-binding domain and a truncated ligand-binding region [41]. In endometrial carcinoma,

total ERα36 expression has been reported to be significantly lower than in normal endometrial tissue, while correlating with cervical stromal invasion. This is not necessarily inconsistent with the pro-proliferative signaling described above: reduced overall abundance in bulk tissue does not preclude potent non-genomic signaling in the subset of cells that retain expression, and differences in cohort composition and detection method may also contribute. Resolving the question will require isoform-specific quantification in stage- and grade-matched series. Given its distinct structure and signaling output, ERα36 nonetheless remains a candidate molecular target and prognostic biomarker in EC, warranting further investigation [42].

Isoforms in cervical cancer

ERα is known to contribute to cervical carcinogenesis. Three ERα protein forms are commonly distinguished—full-length ERα66 and the N-terminally truncated forms ERα46 and ERα36—which arise through different molecular mechanisms rather than through a single splicing event. Wang et al examined ERα36 over-expression in cervical cancer tissue. High ERα36 expression promoted estrogen-mediated proliferation, invasion, and metastasis of cervical cancer cells, whereas silencing ERα36 had the opposite effect. High mobility group AT-hook 2 (HMGA2) was subsequently identified as a downstream target of ERα36 in these cells, and the oncogenic effect of ERα36 was attenuated after HMGA2 knockdown, identifying ERα36 as a candidate therapeutic target in cervical cancer [31] (Fig. 1).

Kumar et al hypothesized that ERα may play an important role in cervical cancer-associated fibroblasts (C-CAFs). They found that the ER antagonist methyl-piperidino-pyrazole (MPP) significantly down-regulated ERα target genes linked to proliferation and angiogenesis, including fibroblast growth factor 1 (FGF1), platelet-derived growth factor C (PDGF-C), vascular endothelial growth factor A (VEGF-A), VEGF-C, matrix metalloproteinase 1 (MMP-1), angiopoietin 1 (ANGPT1), and epiregulin (EREG), as well as genes associated with epithelial-mesenchymal transition (EMT) such as connective tissue growth factor (CTGF), collagen type VI alpha 1 chain (COL6A1), serpin family E member 1 (SERPINE1), cadherin-2 (CDH2), thrombospondin-1 (THBS1), and insulin-like growth factor binding protein 3 (IGFBP3), suggesting that ERα signaling in C-CAFs promotes cancer progression [43]. In a separate study, Lopez-Romero et al reported that expression of the transcription factor BORIS (brother of the regulator of imprinted sites) was detectable in low-grade cervical lesions and increased in high-grade lesions and invasive carcinoma, and examined its association with ERβ, suggesting a role in cervical carcinogenesis [44].

Isoforms in vulvar and other gynecologic cancers

Evidence in vulvar cancer is limited but internally consistent. In a study of 33 patients with vulvar squamous cell carcinoma assessed by immunohistochemistry, high cytoplasmic ERβ expression was associated with shorter disease-free survival (DFS) and overall survival (OS) than low cytoplasmic ERβ, and was also related to tumor grade; on multivariate analysis, high cytoplasmic ERβ and larger tumor size were independent negative prognostic factors for both DFS and OS [45]. As this is a single small retrospective series, cytoplasmic ERβ should be regarded as a candidate prognostic marker requiring independent validation. For fallopian tube and vaginal carcinomas, isoform-resolved data are currently too sparse to support tumor-specific conclusions, and these sites represent a clear evidence gap.

Cross-cancer comparison

Taken together, the tumor-specific data summarized above illustrate why a receptor form cannot be assigned a uniform direction of effect across sites. Progesterone signaling is broadly antiproliferative in the endometrium, where loss of PR-B is associated with progestin resistance and where progestins are used therapeutically; yet constitutive PR-B activity is tumorigenic in the ovary, and in the breast progestins can be growth-promoting such that an antiprogestin rather than a progestin is the rational agent. ERβ is antiproliferative in ovarian cancer models but anti-apoptotic in AGCTs and adverse in vulvar carcinoma, while ERα36 is over-expressed in cervical cancer yet reduced overall in endometrial carcinoma relative to normal endometrium. The direction of effect is therefore a property of the receptor form within a given tissue context, not of the receptor form alone. Any isoform-based biomarker or therapeutic strategy must accordingly be developed and validated within a defined tumor type before cross-cancer inference is attempted.

Clinical Implications and Therapeutic Targeting of SHR Isoforms

Interpretive framework: associations in retrospective tissue cohorts are considered candidate prognostic or predictive signals; cell-line, animal, *in silico*, and other mechanistic studies are considered preclinical; and a strategy is described as clinically actionable only when supported by appropriate prospective clinical validation. This distinction is applied to avoid overstating therapeutic conclusions.

Prognostic and predictive value of SHR isoforms

The prognostic and predictive value of SHR forms in gynecologic cancers is increasingly recognized. In cervical cancer, Ke et al reported that ERα positivity, particularly in tumors with squamous cell carcinoma histology, predicts a lower risk of lymph node metastasis (LNM) in patients with stage IA2–IIA2 disease, suggesting that ERα may serve as an independent marker for identifying patients who do not require radical surgery [46]. In endometrial carcinoma, PR-B was identified as an independent prognostic factor, whereas ERα and PR-A were associated with tumor grade and histological subtype but did not independently predict survival [47]. Saito et al assessed PR forms in 103 endometrioid endometrial carcinomas and found PR-A and PR-B present in 48.5% and 76.7% of cases,

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respectively; lower PR expression correlated with higher tumor grade, shorter disease-free survival, and poorer OS [48].

Expanding the discussion of ERα in EC, another study explored its potential as a clinical biomarker. Absence of ERα was associated with more advanced stage, higher tumor grade, and increased lymph node involvement; although ERα did not strongly predict recurrence-free or disease-specific survival, the authors suggest that preoperative ERα expression, considered alongside intraoperative findings, could help guide surgical decisions regarding lymphadenectomy [49]. PR-A has been investigated in cervical adenocarcinoma, where univariate analysis identified it as a negative prognostic factor; on multivariate analysis, co-expression of RIP140 and PR-A predicted the worst survival, whereas PR-A in the absence of RIP140 was linked to improved survival, indicating that the prognostic value of PR-A is modulated by RIP140 [50]. Conversely, a meta-analysis by Zhang et al found that elevated ERα or ERβ levels individually did not significantly predict favorable survival relative to non-distinguished ER expression in EC [51]. As comparative mechanistic context from breast cancer, Dhimolea et al showed that lower ERβ1 and higher ERβ2 expression identify ERα-positive patients at higher risk of relapse, with ERβ1 linked to better early outcomes and ERβ2 to relapse after 4 years of adjuvant endocrine therapy (AET) [52]; whether this holds in gynecologic tumors is untested.

Isoform-directed treatment remains an investigational concept in gynecologic oncology. For example, an *in silico* study designed an RNA aptamer against the DNA-binding domain of GRα (GR-DBD) by virtual screening, intended to block its interaction with the glucocorticoid response element (GRE) upstream of S100A8 and thereby inactivate S100A8 transcription; this constitutes computational and preclinical evidence rather than a clinically validated cervical-cancer therapy [53]. Similarly, experimental manipulation of PR-B or ER-related receptor forms may identify mechanistic vulnerabilities, but therapeutic relevance requires validation in appropriate *in vivo* models and prospective patient studies. Consequently, the studies below are described according to their experimental level and should not be interpreted as established treatment recommendations.

Loss of PR-B activity removes progesterone's antagonism of estrogen signaling, permitting estrogen-driven proliferation and survival and thereby contributing to progression; strategies aimed at restoring PR-B levels have accordingly been proposed for EC, although this remains a preclinical concept [54]. A separate preclinical strategy targeted estrogen-related receptor α (ERRα) in endometrial carcinoma using the inverse agonist XCT790 combined with siRNA knockdown [55]. As comparative context from breast cancer, Almeida et al reported that tetrahydrocannabinol (THC) may bind ERβ and thereby contribute to pro-apoptotic antitumor effects [56], and Acconcia found that cardiac glycosides (CGs), particularly ouabain (OU), can degrade ERα and restrain tumor cell growth, with high expression of the ATP1B3 Na/K-ATPase subunit in ERα-positive breast cancer correlating with OU sensitivity and representing a possible biomarker; combination with agents such as gefitinib was proposed to enhance efficacy [57]. Both are cell-line studies and neither has been evaluated in gynecologic disease.

Numerous studies highlight the importance of ERβ, particularly ERβ1, in ovarian cancer. Pharmacological inhibition of lysine-specific histone demethylase 1A (KDM1A) increases ERβ expression and enhances activation of its target genes, and synergizes with the ERβ agonist LY500307, which targets ovarian cancer stem cells by promoting apoptosis and reducing tumor-initiating capacity [58, 59]. In a doctoral dissertation, Campion reported that ligand-activated PR-B induced cellular senescence in ovarian cancer cells through a forkhead box protein O1 (FOXO1)-dependent mechanism, with both PR-B and FOXO1 required to activate the p21 gene, and further proposed that FOXO1 can act as a cofactor enabling PR-A to regulate genes normally activated by PR-B [60].

Resistance to hormone therapy and SHR isoforms

In breast cancer, Wargon et al [61] showed that carcinomas responsive to therapy had high PR-A/PR-B ratios, while resistant ones had low ratios. Two resistant phenotypes were identified: constitutive and acquired. In constitutive resistance, PR-A promoter methylation suppressed PR-A expression and was reversible by demethylation, restoring antiprogestin sensitivity [62]. In acquired resistance, prolonged antiprogestin treatment reduced PR-A expression, but estrogen or tamoxifen restored sensitivity by increasing PR-A levels and altering the PR-A/PR-B ratio [63]. In EC, Kruppel-like factor 12 (KLF12) down-regulates PGR expression, particularly affecting PR-B, the form that confers progestin sensitivity, whereas PR-A acts predominantly as a repressor of steroid receptor activity. KLF12 overexpression reduces PR-B levels, decreasing progestin sensitivity and contributing to resistance, whereas lowering KLF12 increases PR-B and improves hormone-therapy response. KLF12 also activates the PI3K-AKT pathway, further driving resistance. Targeting KLF12 could therefore help overcome progestin resistance in EC by restoring PR-B levels and inhibiting PI3K-AKT signaling [54].

AET is commonly used to treat early-stage ERα-positive breast cancer, but a substantial proportion of patients (~40%) do not fully respond to tamoxifen. This led Meligova et al to examine other factors affecting treatment outcome, including the ERβ forms ERβ1 and ERβ2. MCF7 cells expressing ERβ1 became more sensitive to the antiproliferative effects of these drugs, whereas MCF7 cells expressing ERβ2 became more resistant. Analysis of global transcriptional changes indicated that ERβ1 may mark drug responsiveness while ERβ2 may indicate resistance, suggesting that the two forms play different roles in the response of breast cancer cells to therapy [64]. Whether the same relationship applies in gynecologic tumors has not been tested.

Emerging Research and Future Directions

Novel discoveries in SHR isoform functionality

Myocardial infarction-associated transcript (MIAT) is overexpressed in ERα-positive breast cancer cells. Estrogen signaling induces MIAT expression in an ERα-dependent manner, promoting proliferation and EMT. MIAT acts as a competing

endogenous RNA that sponges miR-155-5p and thereby alters dual specificity phosphatase 7 (DUSP7) levels, and has been linked to tumor growth and progression through estrogen signaling [65–67]. PR forms differentially regulate key components of cell migration in breast cancer, including urokinase plasminogen activator (uPA), the uPA receptor (uPAR), β1-integrin, and focal adhesion kinase (FAK) signaling. Unliganded PR-B, but not PR-A, promoted FAK Tyr397 phosphorylation and co-localized with activated FAK in cell protrusions, suggesting that nucleocytoplasmic trafficking of PR-B enhances its interaction with FAK complexes [68]. Pateetin et al used a doxycycline-regulated system to stably express PR-A and PR-B in PR-null T47DC42 breast cancer cells, revealing distinct proteomic changes. PR-A expression was linked to metabolic shifts, with tricarboxylic acid (TCA) cycle enrichment in the absence of progestin and glycolysis in its presence, suggesting stem cell-like traits. PR-B expression, regardless of progestin, was associated with cell-cycle regulation and apoptosis. Liganded PR-A also up-regulated chromatin remodeling proteins (e.g., H1.2 histone) and cathepsin D (CTSD), both linked to poor prognosis and increased proliferation [69]. Metabolic programs downstream of hormone receptor signaling, such as *de novo* lipogenesis, are themselves being pursued therapeutically [70], though not yet in a receptor-form-specific manner.

A study by Salvati et al revealed cooperation between ERα and the chromatin modifier DOT1-like histone lysine methyltransferase (DOT1L), which enhances ovarian cancer cell growth and drug resistance. It controls the transcription of genes involved in key cancer cell features, such as the cell cycle, EMT, drug metabolism, and cell-to-cell signaling, as well as expression of the ERα gene itself [71]. Increased ERαD7 expression has been associated with improved outcomes in type 1 EC, as it reduces estrogen sensitivity and impairs ERα-mediated tumor progression. Interestingly, the balance between the splice factors HTRA2-BETA1 and HNRNPG influences ERα exon 7 splicing, with HNRNPG antagonizing HTRA2-BETA1's effect, promoting exon skipping, and impacting the expression of ERα isoforms. This altered splicing mechanism appears to correlate with disease prognosis, where higher HNRNPG levels are linked to better outcomes in EC patients [72].

Potential for isoform-specific biomarkers

Hormone receptor forms play a complex role in various cancers, influencing both prognosis and treatment response. In ovarian cancer, Jonsson et al found that neither ERα nor ERβ as a single marker significantly affected 5-year progression-free survival (PFS) or OS [73]. In breast cancer, ERα serves as a robust prognostic and predictive marker for tamoxifen response, but its relevance diminishes after 5 years and its loss can contribute to endocrine resistance. The role of ERβ remains contested; although some evidence suggests it may suppress ERα, studies yield conflicting results regarding its impact on therapy response and prognosis, highlighting the need for further investigation [74].

PR-A and PR-B are also key biomarkers in hormone-dependent cancers. Fabris et al tested antibodies for detecting PR forms in formalin-fixed paraffin-embedded (FFPE) tissue. Most antibodies recognized both forms, except Ab-6, which was specific to PR-B. Their results emphasize the need for careful validation of PR-A-specific antibodies, since the PR-A/PR-B ratio may carry prognostic information in breast cancer [75]. In another study, Singhal et al found that tumors expressing higher levels of PR-A correlate with poorer survival, while those with higher PR-B levels are associated with better outcomes, suggesting that the balance of PR forms could serve as a prognostic factor [76]. Together these findings underline the importance of reliable, form-specific detection methods before any PR-A/PR-B ratio can be used clinically.

Implications for personalized medicine

Cartwright et al examined the varying effects of different progestins on PR-A and PR-B in breast tissue. They found that co-expression of PR-A and PR-B significantly influenced the potency and efficacy of progestins, with some progestins, such as R5020 and P4, showing stronger transrepression when both forms were present. Their work emphasized the importance of studying progestins individually rather than as a class, especially in tissues where PR forms are not evenly expressed, and suggests that personalized approaches to hormone therapy may be necessary based on PR-form expression [77]. The MIPRA trial reported by Elia et al investigated the antiprogestin mifepristone (MFP) in breast cancer patients with a high PR-A/PR-B ratio. In this single-arm, open-label presurgical window-of-opportunity study, 20 postmenopausal patients with luminal tumors showing a PR-A/PR-B ratio > 1.5 and PR ≥ 50% received MFP (200 mg/day orally) for 14 days before surgery, with change in the proliferation marker Ki67 as the primary endpoint. A 49.62% decrease in Ki67 was observed in surgical specimens relative to baseline ($P = 0.0003$), and tumor volume decreased in the most responsive cases. The authors concluded that MFP may benefit patients with high PR-A/PR-B ratios, supporting the PR-form ratio as a selection biomarker [78]. This remains a small, single-arm breast-cancer study, and no equivalent trial has been conducted in gynecologic cancer.

Clinical trials show that some ovarian cancer patients benefit from endocrine therapy, but unlike breast cancer, tumor ERα status alone does not predict response in high-grade serous ovarian cancer (HGSOC). By identifying specific biomarkers, such as the ERα target IGFBP3, which are associated with clinical response, it may be possible to develop more personalized treatment strategies. The findings from Andersen et al suggest that fulvestrant could be more effective than tamoxifen for certain patients, allowing for tailored therapy choices based on individual tumor characteristics, thereby improving treatment outcomes and minimizing unnecessary treatments [79].

Conclusions

Summary of key findings

SHR diversity in gynecologic cancer is biologically important

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but mechanistically heterogeneous. The revised framework distinguishes true splice variants from receptor subtypes encoded by separate genes, alternative promoter/translation products, post-translational modifications, and polymorphisms. Across ovarian, endometrial, cervical, and vulvar cancers, the most substantial evidence concerns ER- and PR-related receptor forms, but their effects differ by tumor type and cellular context. AR-V7 provides emerging evidence that AR splicing can occur in gynecologic tumors, whereas gynecologic evidence for GR and particularly MR variants remains limited. Most isoform-specific therapeutic observations are preclinical or exploratory; therefore, they should be viewed as hypothesis-generating until analytical validity, prognostic or predictive value, and clinical utility are established in independent patient cohorts and prospective studies.

Across the gynecologic sites reviewed, PR forms influence key cell-cycle programs in ovarian cancer, and ERβ shows dual behavior—antiproliferative in some contexts, yet supporting tumor cell survival in others, notably in AGCTs. ERα36 has been implicated in non-genomic, EGFR- and PKCδ/ERK-linked signaling in endometrial and cervical cancer, further complicating the therapeutic landscape. Clinically, ERα positivity has been associated with a lower risk of LNM in cervical cancer, which may help select patients for less radical surgery; PR-B has been identified as an independent prognostic factor in endometrial carcinoma; absence of ERα in EC is associated with more advanced stage; PR-A expression, modulated by RIP140, is a negative prognostic factor in cervical adenocarcinoma; and high cytoplasmic ERβ correlates with poor prognosis in vulvar squamous cell carcinoma. Breast-cancer studies of PR-A/PR-B ratios and of the ERβ1/ERβ2 balance provide comparative mechanistic context but cannot be transferred directly to gynecologic disease. Each of these associations derives from retrospective cohorts and should be regarded as a candidate marker pending independent validation.

Isoform-directed therapy remains at an early stage. *In silico* and cell-based studies have explored RNA aptamers directed against GRα, ERRα inhibition, cannabinoid binding to ERβ, and cardiac glycoside-mediated ERα degradation, while work on hormone-therapy resistance has implicated PR-A/PR-B ratios, KLF12, and estrogen-regulated long non-coding RNAs (lncRNAs). None of these approaches has yet been evaluated prospectively in gynecologic cancer, and the supporting data are predominantly preclinical. They are therefore best regarded as hypothesis-generating directions requiring pharmacologic validation and, where justified, prospective clinical evaluation before any claim of clinical utility is made.

Future research priorities

Future studies should prioritize tumor-specific, isoform-resolved analyses using RNA sequencing or validated isoform-specific assays; explicitly identify whether each receptor form results from splicing, promoter usage, translation initiation, or another mechanism; and validate findings in independent gynecologic patient cohorts. Studies should also distinguish tumor-cell from stromal and immune-cell receptor expression, because compartment-specific signaling may produce different biological effects. For candidate biomarkers, analytical validation should precede assessment of prognostic or predictive performance. For therapeutic targets, mechanistic cell and animal data should be followed by pharmacologic validation and, where justified, prospective clinical evaluation. AR, GR, and MR diversity represents an important evidence gap, with current gynecologic data insufficient for strong isoform-specific clinical conclusions.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

AP participated in the study concept and design, the literature review and analysis, and drafting of the manuscript. CKR participated in conceptualization, study design, supervision, and critical review and editing of the manuscript. Both authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

17β-HSD: 17β-hydroxysteroid dehydrogenase; AET: adjuvant endocrine therapy; AF-1/AF-2: activation function 1/2; AGCT: adult granulosa cell tumor; ANGPT1: angiopoietin 1; AR: androgen receptor; AR-V7: androgen receptor splice variant 7; ATP1B3: Na/K-ATPase subunit beta-3; Bcl-2: B-cell lymphoma 2 protein family; BORIS: brother of the regulator of imprinted sites; C-CAF: cervical cancer-associated fibroblast; CCNB1: cyclin B1; CCND1: cyclin D1; CDC25C: cell division cycle 25C; CDH2: cadherin-2; CDK1: cyclin-dependent

kinase 1; CG: cardiac glycoside; COL6A1: collagen type VI alpha 1 chain; CTGF: connective tissue growth factor; CTSD: cathepsin D; CYP19A1: cytochrome P450 family 19 subfamily A member 1 (aromatase gene); DFS: disease-free survival; DOT1L: DOT1-like histone lysine methyltransferase; DUSP7: dual specificity phosphatase 7; E2: estradiol; EC: endometrial cancer; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; ER: estrogen receptor; ER E5SV: estrogen receptor exon 5 splicing variant; EREG: epiregulin; ERK: extracellular signal-regulated kinase; ERRα: estrogen-related receptor α; ESR1: estrogen receptor 1 gene (encodes ERα); ESR2: estrogen receptor 2 gene (encodes ERβ); FAK: focal adhesion kinase; FFPE: formalin-fixed paraffin-embedded; FGF1: fibroblast growth factor 1; FOXM1: forkhead box protein M1; FOXO1: forkhead box protein O1; GLOBOCAN: Global Cancer Observatory incidence and mortality database; GR: glucocorticoid receptor; GR-DBD: glucocorticoid receptor DNA-binding domain; GRE: glucocorticoid response element; HGSOC: high-grade serous ovarian cancer; HMGA2: high mobility group AT-hook 2; HNRNPG: heterogeneous nuclear ribonucleoprotein G; HTRA2-BETA1: transformer-2 beta splicing factor (SRFS10/HTRA2-beta1); IGFBP3: insulin-like growth factor binding protein 3; KDM1A: lysine-specific histone demethylase 1A; Ki67: marker of proliferation Ki-67; KLF12: Kruppel-like factor 12; lncRNA: long non-coding RNA; LNM: lymph node metastasis; MAPK: mitogen-activated protein kinase; MFP: mifepristone; MIAT: myocardial infarction-associated transcript; MMP-1: matrix metalloproteinase 1; MPP: methyl-piperidino-pyrazole; MR: mineralocorticoid receptor; NR3C1: nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor gene); NR3C2: nuclear receptor subfamily 3 group C member 2 (mineralocorticoid receptor gene); OS: overall survival; OU: ouabain; PDGF-C: platelet-derived growth factor C; PFS: progression-free survival; PGR: progesterone receptor gene; PI3K/AKT: phosphoinositide 3-kinase/protein kinase B; PKCδ: protein kinase C delta; PLK1: Polo-like kinase 1; PR: progesterone receptor; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RIP140: receptor-interacting protein 140; S100A8: S100 calcium-binding protein A8; SERPINE1: Serpin family E member 1 (plasminogen activator inhibitor-1); SHR: steroid hormone receptor; TCA: tricarboxylic acid (cycle); THBS1: thrombospondin-1; THC: tetrahydrocannabinol; uPA: urokinase plasminogen activator; uPAR: urokinase plasminogen activator receptor; VEGF-A: vascular endothelial growth factor A; VEGF-C: vascular endothelial growth factor C

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