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New insights on the role of hormonal therapy in ovarian cancer

Fiona Simpkins[1,2,3], **Arlene Garcia-Soto**[1], and **Joyce Slingerland**[1,2]

[1]Division of Gynecology Oncology, University of Miami, Miller School of Medicine, Miami, Florida

[2]Braman Family Breast Institute, University of Miami, Miller School of Medicine, Miami, Florida

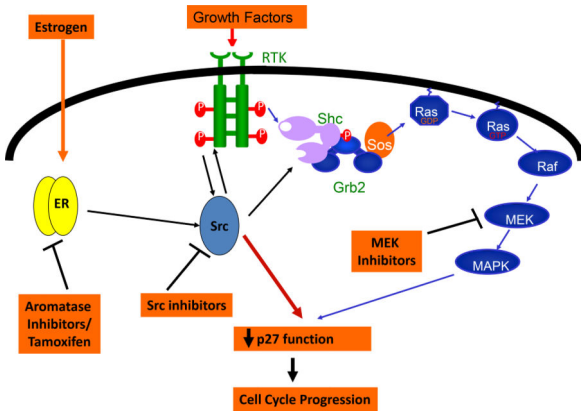
Abstract

Ovarian cancer (OVCA) is the most lethal gynecological malignancy. It is often diagnosed in advanced stages and despite therapy, 70% relapse within 2 years with incurable disease. Regimens with clinical benefit and minimal toxicity are urgently needed. More effective hormonal therapies would be appealing in this setting.

Estrogens (E2) are implicated in the etiology of OVCA. Estrogens drive proliferation and anti-estrogens inhibit ovarian cancer growth *in vitro* and *in vivo*. Despite estrogen receptor (ER) expression in 67% of OVCAs, small anti-estrogen therapy trials have been disappointing and the benefit of hormonal therapy has not been systematically studied in large well-designed trials. OVCAs often manifest de novo anti-estrogen resistance and those that initially respond invariably develop resistance. Estrogens stimulate ovarian cancer progression by transcriptional activation and cross talk between liganded ER and mitogenic pathways, both of which drive cell cycle progression. Estrogen deprivation and estrogen receptor (ER) blockade cause cell cycle arrest in susceptible OVCAs by increasing the cell cycle inhibitor, p27. This review summarizes and discusses scientific and epidemiological evidence supporting estrogen's role in ovarian carcinogenesis, provides an overview of clinical trials of ER blockade and aromatase inhibitors in OVCA and reviews potential causes of antiestrogen resistance. Anti-estrogen resistance was recently shown to be reversed by dual ER and Src signaling blockade. Blocking cross-talk between ER and constitutively activated kinase pathways may improve anti-estrogen therapeutic efficacy in OVCA, as has been demonstrated in other cancers. Novel strategies to improve benefit from anti-estrogens by combining them with targeted therapies are reviewed.

Graphical abstract

[3]Corresponding author: Fiona Simpkins, Division of Gynecology Oncology, Department of Obstetrics & Gynecology, Miami, Florida, fsimpkins@med.miami.edu.



Keywords

ovarian cancer; estrogen receptor; antiestrogen-resistance

Clinical impact of ovarian cancer

Ovarian cancer is the most lethal gynecological cancer in the United States and the fourth leading cause of cancer death in women. In 2011, approximately 21,990 women were diagnosed and over 15,000 women died from ovarian cancer (American Cancer Society, 2011). Above 70% of women are diagnosed with late stage III and IV disease [1]. Despite aggressive surgery to remove the bulk of the tumor at diagnosis and post-surgical treatment with platinum/ taxane-based chemotherapy, about 70% of ovarian cancers relapse within 2 years [2]. Recurrent disease has a poor prognosis, with a 5 year survival of 23% and 14% for stage III and IV disease, respectively [3]. Survival has minimally improved over the past decade for advanced stages and clearly new therapies are needed. The goals of salvage therapy are to palliate symptoms and to maximize quality of life. A less toxic regimen, such as hormonal therapy, is particularly appealing in this setting. Thus, convenient regimens that have clinical benefit with minimal toxicity are essential for this population.

Hormone replacement therapy and ovarian cancer risk

Although the etiologic origins of ovarian cancer are poorly understood, most tumors are thought to arise in the surface epithelium of the ovary itself or the fallopian tubes, influenced by changes in the hormonal environment of ovulation and pregnancy, as well as use of exogenous estrogen supplementation. Ovarian cancer increases dramatically in peri- and post-menopausal women. The age-specific incidence increases from 13/100,000 at age 45 to 43/100,000 at age 60. Compared to earlier reproductive years, circulating peri-menopausal estrogen levels are higher, coincident with the time period when ovarian cancer risk rises sharply [4]. Thus, adrenal pre-estrogenic hormones are likely important in ovarian carcinogenesis [5].

Increasing epidemiologic data implicate estrogen in the etiology of ovarian cancer. These data come from studies of hormone replacement therapy (HRT) in post-menopausal women. A meta-analysis of nine studies including the Million Women Study and the Women’s

Health Initiative, showed the risk of ovarian cancer increased by 1.28 (1.20–1.36) in women who used hormonal replacement therapy compared to never users [6]. A recent meta-analysis of 14 studies revealed effects of formulation and duration of hormone replacement [estrogen alone (ET) or estrogen plus progesterone (EPP)] and risk of ovarian cancer [7]. Eight population-based case-control studies, five cohort studies, and 1 clinical trial, showed ovarian cancer risk was increased among ET users (RR per 5 years of use, RR=1.22 (95% CI, 1.18–1.27; P < .0001), and a lower but still statistically significant increased risk was seen with EPP use (RR= 1.10; 95% CI, 1.04–1.16; P = 0.001). The increased risk in ET users was statistically significantly greater than the risk in EPT users (P = 0.004) [7]. The duration and cumulative estrogen dose contributed most importantly to ovarian cancer risk. Twelve of thirteen studies showed an effect of ET duration on ovarian cancer risk [7]. Notably, estrogen use over 10 years increased ovarian cancer risk (RR= 1.45– 2.2) [8–10]. A cumulative estrogen dose of one gram increased ovarian cancer risk 1.056 fold, but the risk rose by 1.31 fold with 5 g cumulative estrogen intake (95% CI 1.003–1.112 and 1.01–1.7, respectively) [11]. These data support a moderate risk increase for ovarian cancer with hormone replacement therapy.

Expression and activity of estrogen receptors ERα and ERβ in ovarian cancer

There is increasing evidence that estrogens drive proliferation in a subset of ovarian cancer lines in cell culture and in xenograft models [12–15]. Moreover, anti-estrogens can inhibit proliferation of estrogen receptor positive OVCA cells *in vitro* and *in vivo* [13;15]. There are two types of estrogen receptor (ER): ERα and ERβ. The former is expressed in up to 60% of ovarian cancers (reviewed below); the latter is found in normal ovaries [16]. ERα activates expression of genes involved in cell survival and proliferation, thus promoting tumor growth and progression, while the function of ERβ has been found to be anti-proliferative and pro-apoptotic [17]. Growth response to estrogen in hormone responsive ovarian cancer cell lines was shown to be mediated by ERα and not by ERβ [15;18], since treatment with 17-β estradiol or an ERα specific agonist (PTT,4', 4', 4" –(4-Propyl-[1H]-pyrazole-1,2,5-tryl) trisphenol) induced cell proliferation [15]. This effect was not elicited by DPN (2,3-bis (4-hydroxyphenyl)-propionitrile), an ERβ selective agonist. When ERβ is coexpressed with ERα it may act as a brake on ERα-mediated effects, including cell proliferation [19].

Different roles in carcinogenesis have been proposed for ERβ. ERβ is encoded by *ESR2* gene, which is expressed in different splice variants (ER β1–5). ERβ mRNA levels and protein levels are decreased in ovarian cancer samples compared to normal ovarian tissues [16;20–25], while ERα mRNA levels are similar or slightly higher in cancer compared to normal ovarian tissue. ERβ expression declines during tumorigenesis of breast, colon and prostate cancer [26–30]. In addition to its anti-proliferative role, exogenous expression of ERβ increased apoptosis in ovarian cancer cells [17]. In breast, prostate and ovarian cancer cell lines, transfection of *ESR2* inhibited cell motility and invasion in a ligand independent fashion [17;31–33]. Antitumor effects of ERβ have been linked to its inhibition of cyclin A2 and cyclin D1 expression and upregulation of growth inhibitory p21 (WAF1) [33–37]. The ERβ expression has been inversely associated with stage of disease and positively associated

with disease free (DFS) and overall survival (OS) in a recent RT-PCR based study of 161 malignant ovarian tissue samples [38]. In a study of 58 ovarian cancers and 12 normal ovaries, nuclear ERβ localization was seen in normal cells, while ERβ was shifted to the cytoplasm in tumor cells and cytoplasmic ERβ expression was associated with decreased DFS and OS [39].

There are several splice variants of ERβ (or ERβ1) that appear to have distinct levels and functions in cancers [23;40;41]. These ERβ splice variants are characterized by alternative 3'-exons (ERβ2, ERβ3, ERβ4, ERβ5) or by deletion of single or multiple exons (ie ERβΔ2, ERβΔ5/6). Promoter hypermethylation decreased ERβ1, ERβ2 and ERβ4 mRNAexpression in ovarian cancer lines and tissues compared to their normal counterparts. However, that of ERβ5 mRNA was significantly elevated in all ovarian cancers compared to normal ovary, and particularly so in clear cell adenocarcinoma [42]. ERβ5 has been shown to heterodimerize with ERβ1, and enhance its overall activity in a ligand-dependent manner [43]. However, little is known currently about the function of ERβ5 in ovarian cancer. All in all, this suggests that ERβ isoforms may be involved in the development and progression of ovarian cancer. ERβ1 may be more important as a tumor suppressor in ovarian cancer because ERβ1 is more comprehensively repressed in ovarian cancers compared to other ERβ isoforms. The identification of ERβ regulated specific genes involved in epithelial proliferation and apoptosis may advance our understanding of the progression of ovarian cancer and aid in the design of new targeted therapies. A similar decrease in ERβ1, ERβ2 and ERβ4 has also been reported in breast and prostate cancers [42;44;45].-. Given the current data available regarding the antitumor effects of ERβ, strategies to restore or increase its expression may have potential in cancer therapy.

ERα Expression and prognostic importance of Erα protein in ovarian cancer

ERα (hereafter ER) is a nuclear hormone receptor superfamily member traditionally classified as a ligand activated transcription factor [46]. Upon ligand binding, ER undergoes conformational changes to form an "activated ER", involving by dissociation of heat shock proteins (hsp) 90, and hsp70 [47] and other proteins so it can dimerize and bind to specific DNA sequences, estrogen response elements (EREs) and interact with a complex array of potential co-regulators to modulate the transcription of ER target genes. In addition, other mechanisms of estrogen-regulated transcription involve indirect non-genomic actions of ER via cross talk with signaling kinase pathways that ultimately lead to changes in estrogen-regulated genes. There is also evidence that the unliganded ER may become transcriptionally activated by selected posttranslational modifications [48]. Estrogen receptor expression has been reported in 36–77% of ovarian cancers in several small studies [49]. A review of 45 studies, including 2508 ovarian cancers, reported that 67% expressed ER and 47% PR, proportions similar to those reported for breast cancer [49]. Most retrospective studies have evaluated small tumor numbers, used archive specimens with prolonged storage and different immunohistochemical methods, giving rise to inconsistent reports. Most recently, we assayed 338 primary ovarian cancer samples from The Cancer Genome Atlas (TCGA) project by reverse phase protein array and found that ER was

expressed in 67% of high grade serous ovarian cancers. We also found *ESR1* mRNA and ER protein levels were highly correlated [15].

While reports of the prognostic importance of ER status have been inconsistent, the largest study to date (n=582 patients), using tissue array and immunohistochemistry (IHC), showed ER correlated with better outcome. Multivariate analysis showed that ER and progesterone receptor (PR) expression > 10% was of independent prognostic value for improved disease specific survival [ER: hazard ratio (HR) 0.80; 95% confidence interval (CI), 0.63–0.99; PR: HR 0.69; 95% CI, 0.51–0.94]. The prognostic value of ER and PR expression was additive, with a HR for recurrence of 0.48 (95% CI, 0.13–0.74) [50].

In breast and endometrial carcinoma, the expression of certain estrogen-regulated target genes has been shown to have prognostic importance. Detection of estrogen-regulated gene expression may also prove to have utility for ovarian cancer patients. Despite the correlation of ER expression with improved patient outcome in the studies reviewed above, a recent study in 83 advanced stage ovarian/primary peritoneal high-grade serous carcinomas evaluated expression of ERα by IHC and expression of six genes known to be induced by estrogen in the female reproductive tract by qRT-PCR. ERα expression correlated with poor prognosis [51]. High expression of *ER*α and estrogen-induced genes was associated with worse overall survival and it was a negative prognostic factor independent of other patient-dependent covariates such as age, race, and BMI. The conflicting findings with regard to ER as a prognostic factor may be a result of various factors, including differences in the method of receptor detection, the lack of standardization of the scoring system, and differences in patient stage and sizes of cohorts analyzed. Further studies are needed to identify the best method to evaluate ER expression (immunohistochemistry or gene expression analysis) as a biomarker for prognosis and to identify which patients may benefit from antiestrogen therapies.

Estrogen receptor driven gene expression in ovarian cancer

Several studies have identified ERα-target genes in ovarian cancer cells. These show some overlap with estrogen response genes in breast cancer cells, but also reveal unique targets. The biological effects of estrogens are classically mediated by ER which functions as a hormone inducible transcription factor that binds to the estrogen-responsive element (ERE) located often in regions far from the transcription start site of target genes thereby involving distal enhancer elements, that function to tether the ER complex to the target gene promoters [48]. In breast cancer cells, ERα is thought to mediate the mitogenic actions of estrogen by inducing expression of genes involved in cell proliferation. Estrogen-induced genes identified in ERα positive breast cancer cell lines include the progesterone receptor (PR), cathepsin D, c-fos, and pS2 [52;53] and studies in primary breast cancers have suggested these may have prognostic utility for predicting whether a tumor is estrogen sensitive and will respond to antiestrogen therapy [53;54]. In ovarian cancers, however, there is a notable lack of expression of many the classical estrogen-responsive genes (PR, c-fos, pS2) identified in breast models. Early studies have shown ER-responsive genes involved in ovarian cancer cell proliferation include: cathepsin D [55], c-fos [56], TGFα [57], stromal cell-derived factor 1 (SDF-1) [58], *c-myc* [59], and PR [56]. ER target genes in ovarian

cancer associated with invasion include fibulin-1C [60;61], and cell cycle regulation include, cyclins D1, A and E [56]. The effects of E2 on gene expression in an ER+ ovarian cancer cell line, PEO1, were evaluated using DNA microarray containing 1200 cancer-related genes [18]. This study showed five transcripts had at least a 3-fold increase and 23 transcripts at least a 3-fold decrease in expression in E2 treated PEO1 compared to untreated cells. These ER targets were verified by real-time quantitative PCR. Gene up-regulated by E2, such as *TNFDF1*, *FOSLI*, *TRAP1*, *CTSD* (Cathepsin D) and *TFAP4*, are known to promote cell proliferation. Of particular note, however, was the number of down-regulated genes, especially those involved in maintenance of the cytoskeleton, suggesting a role for E2 signaling in ovarian cancer invasion and metastasis [18]. A limitation of this study is that expression changes were measured 24 hrs after E2 treatment, and thus genes affected may not be directed ER-targets. Further studies are warranted to better define direct ER targets in OVCA.

Only one study has described estrogen-mediated, promoter-specific and ER-α-dependent repression of target genes in ovarian cancer cells. This study showed the folate receptor (FR) α gene promoter is repressed in the presence of 17β-estradiol and derepressed by the antiestrogens tamoxifen and ICI 182,780. The ER corepressor, SMRT, enhanced the repression by 17β-estradiol/ER, but ER coactivators, including SRC family members, did not appreciably impact the ER ligand response [62].

Use of estrogen receptor blockers for ovarian cancer

While adjuvant hormonal therapy prevents disease recurrence and reduces mortality from ER positive breast cancer, the response to anti-estrogens in ovarian cancer is more limited and less encouraging. The potential impact of adjuvant hormonal therapy in ovarian cancer and the predictive value of hormonal receptors have not been studied in well-designed trials. Tamoxifen, an estrogen antagonist, and fulvestrant, a newer ER blocker,, have both been used primarily for recurrent ovarian cancer. Our review of twenty published trials of tamoxifen for recurrent ovarian cancer (total=695 pts, none of which required knowledge of ER status) showed an overall response rate (ORR) of only 13%. Interestingly, 35% of these patients showed stable disease (SD), defined as a lack of disease progression assessed by radiological imaging or CA-125 serum tumor marker level (Table 1). Among these studies, that of Hatch et al. [63] is the largest (n=105) and included patients that progressed after first line therapy and were thus not so heavily pretreated. Their ORR was 17% [9.5% complete response (CR); with 7.6% showing partial response (PR)] with a median complete response duration of 7.5 months (max 17 months). The remainder of the twenty trials in Table 1 included patients that were heavily pretreated, some of them resistant to chemotherapy. However, it is not possible to determine the platinum sensitivity status in these trials. If we select those trials in which at least 50% had not received more than 1 prior treatment (n=240) [63–67], OR rate doubles to 26% with a 9% CR rate. In addition, patients were not selected for tamoxifen therapy by their receptor status. Response rates for tamoxifen in breast cancer whenever receptor status was not routinely employed was around 30% which is lower than for patients with positive receptor status [68]. The majority, 13/19 trials, did not report if receptor status correlated to response. In Hatch et al, the patients with ER+ tumors had higher response rates to tamoxifen than ER- tumors [63]. In Swartz et al, all SD

patients were ER+ [69]. In Shirey and Weiner et al., ER status did not correlate with response, but ER status was known in only 25–30% of patients enrolled [70;71]. No study was specifically designed to test if ER status correlated with response to tamoxifen. To conclude, tamoxifen has been studied primarily in retrospective studies, involving recurrent, heavily pretreated, platinum resistant ovarian cancers, treated irrespective of ER status. Tamoxifen activity in advanced ovarian cancer has not been systematically evaluated and its role may have been underestimated because the target responsive population has not been defined.

Tamoxifen has been studied in a limited manner when used as first line treatment after surgery for advanced disease or to augment effects of post-surgical chemotherapy (called “consolidation”) for advanced ovarian cancer. A randomized prospective trial (n=100) of stage III/IV patients treated with first line chemotherapy including cisplatin and doxorubicin with or without tamoxifen, found no difference between PFS and OS between both groups [69]. Limitations to this trial are that the majority of patients (54%) had residual disease (≥2cm) and tamoxifen was given only with chemotherapy for only 36 weeks which is much shorter than that recommended for breast cancer use in this setting. Tamoxifen was recently evaluated in the “consolidation” setting in a phase III randomized trial investigating thalidomide vs tamoxifen in patients with biochemical recurrence (where the tumor marker, CA-125, increased by two-fold but there was no radiographical evidence of disease) after first-line chemotherapy. Thalidomide effects were similar to the tamoxifen treated group in terms of progression free survival (PFS) but the thalidomide group had a worse median and overall survival with a higher risk of death (HR=1.76, 95% CI=1.16–2.68) and it was significantly more toxic [72]. Unfortunately, there was no control group without either drug, thus it was not clear if either drug gave benefit over no additional therapy. Markman et al retrospectively reviewed 56 women with asymptomatic recurrent ovarian cancer treated with tamoxifen prior to initiation of cytotoxic chemotherapy [73]. The median treatment duration on tamoxifen was 3 months, but 42% of patients were on tamoxifen for ≥ 6 months and 19% for ≥ 12 months. Reasons for discontinuation of tamoxifen were development of symptoms, radiographical evidence of disease, or continuing rise in CA-125 tumor marker. No standard of care exists for management of asymptomatic recurrent disease. Clinical trials investigating hormonal therapy in this setting are warranted. In summary, antiestrogens have not been thoroughly evaluated in the adjuvant or consolidation setting for early or advanced ovarian cancer with low volume disease.

The pure ER antagonist, Fulvestrant, has also shown activity in recurrent ovarian cancer. Recently, a small phase II trial for 31 heavily pretreated ER+ (preselected) recurrent ovarian cancer patients showed a 38% clinical benefit for fulvestrant (1 CR, 1 PR, 11 pt or 35% SD at 90 days) with no grade 2, 3 or 4 toxicities and quality of life scores improved [74]. Well designed prospective trials are needed to carefully evaluate the role of anti-estrogens and the predictive role of receptor status in ovarian cancer.

Aromatase expression & effects of aromatase inhibitors in ovarian cancer

Aromatase, expressed in fat, liver, muscle, brain, normal breast tissue, and breast and ovarian cancers [75], converts adrenal androstenedione to estrogen and is the predominate

source of estrogen in postmenopausal women. There is increasing data that intra-tumoral estrogens, derived from in situ aromatization, function as autocrine growth factors that prompt cancer cell proliferation independently of circulating estrogen [76]. Aromatase inhibitors (AI) reduce estrogen production in post menopausal women by more than 90%. Aromatase expression, analyzed as either aromatase activity, mRNA expression or protein levels, has been found in 33–81% of ovarian cancers [77;78] This wide variability in aromatase detection results from small study size (average 20–40 specimens per study) and different methods used to measure activity (activity assays and mRNA). Aromatase is expressed in ovarian cancer epithelial cells, and in nearby stroma where there is frank ovarian cancer invasion [78;79].

AIs have shown some therapeutic activity against recurrent ovarian cancers, with modest response rates, and they may also stabilize disease. AIs have been shown to be superior to tamoxifen when used as adjuvant therapy for breast cancer [80]. *In vitro* studies demonstrated anti-tumor effects of AI on ovarian cancer cells which correlated with aromatase activity and ER expression [81]. In nine clinical trials (6 of letrozole, 2 of anastrozole and 1 of exemestane) totaling 300 patients, AIs for recurrent ovarian cancer have produced overall response rates of 8% (CR 1%, PR 7% and SD rates of 33%) (See Table 2). Few of these studies preselected patients based on hormone receptor or aromatase expression. One study by Smyth et al. recently showed that preselecting patients for study enrollment based on ER expression improved response to letrozole for recurrent ovarian cancer. In a study of 42 patients, overall response increased from 9% to 17% when patients were preselected for ER, and disease stabilization improved from 25 to 36%. These response rates approach that of salvage chemotherapy but with far less toxicity [82;83].

Biomarkers such as ER, PR, EGFR and HER-2 have been investigated as predictors of AI response for ovarian cancer. Results are encouraging but inconsistent. Three of nine trials using AIs for recurrent disease, showed biomarker levels in the diagnostic tumor correlated with response [82–84]. One study of 41 patients and another of 42 treated with letrozole showed elevated (pre-treatment) levels of ER, PR, EGFR and decreased HER-2 expression significantly correlated with better response. Another small study also showed ER/PR correlated with response. However, three studies (n=96 pts) showed no correlation between ER/PR or HER2 levels in the tumor at diagnosis and response. This discrepancy may be due to differences in ER assays, study size, or prior exposure to hormonal agents. Since not all patients will benefit from AIs it is important to develop molecular identifiers to predict response in ovarian cancer. In recurrent ovarian cancer, AIs appear to yield a similar clinical benefit (disease stabilization plus partial response) to tamoxifen (48% vs 41%). Given their favorable safety profiles, convenient use and moderate efficacy in the recurrent setting, AIs are a rational treatment option for ovarian cancer.

Mechanisms of growth arrest by aromatase inhibitors and anti-estrogens

Estrogen deprivation and ER blockade cause breast and ovarian cancer cells to arrest in the G1 phase of the cell cycle [15;85]. G1 cell cycle progression is governed by a family of cyclin-dependent kinases (cdks) that are activated by binding of different cyclins and inhibited by cdk inhibitors, such as p21 and p27. ER blockade by tamoxifen, fulvestrant or

estrogen withdrawal arrests cells in G1 by stabilizing p27 [15;85]. In normal rhesus ovarian surface epithelium, low dose estrogen, tamoxifen or fulvestrant all caused G1 arrest by induction of p53 and p21 [86]. Our work and that of others has shown that cell cycle regulation and in particular the mechanisms of G1 arrest mediated by anti-estrogens in ovarian cancer are similar to that in breast cancer [12;13;15;85;87].

Mechanism of resistance to anti-estrogens in ovarian cancer

Although hormonal therapies as single agents are well tolerated and show modest activity in recurrent ovarian cancer, the benefit is of short duration with an average of 3–4 months. In both breast and ovarian cancer, many patients manifest initial de novo resistance and those that do initially respond, often develop resistance to hormonal agents. In breast cancer, resistance can arise through cross-talk between ER and constitutively activated receptor tyrosine kinase (RTK) pathways [88]. Until recently, ligand activated ER transcriptional activity was thought to be the major mechanism whereby ER regulates cell behavior. Cross talk between estrogen bound ER and signal transduction may account for more ER-mediated functions than previously recognized. These effects do not initially affect estrogen dependent transcription and have been termed non-genomic actions of the ER. In breast cancer, it has been shown that estrogen stimulates breast cancer proliferation by rapid estrogen-stimulated ER-dependent activation of cSrc and of MEK/MAPK pathways, leading to p27 degradation and G1 progression in breast cancer cells [87;89–91].

The Src, Ras/Raf/MAPK and PI3K/AKT pathways have all been implicated in ovarian cancer proliferation, invasion, metastasis and survival [92;93]. cSrc can activate both Ras/Raf/MAPK and PI3K/AKT pathways downstream of RTKs (EGFR/HER2, PDGFR), and is over-expressed and activated in ovarian cancer cell lines and tumors compared to normal ovarian epithelium [94]. Src directly associates with EGFR and HER2, both of which are involved in ovarian tumorigenesis. Src inhibition reverses resistance to platinums and taxanes in ovarian cancer cells [95]. There is evidence for cross-talk between HER2/MAPK and estrogen signaling in ovarian cancer [96]. Recent pre-clinical data showed that a MEK inhibitor combined with fulvestrant additively decreased ovarian cancer cell growth via increased p21 and p53 in vitro and decreased endometrial cancer in vivo [86]. We recently found that Src inhibition with saracatinib reverses fulvestrant resistance in ER+ ovarian cancer cell lines and in an ovarian cancer xenograft model. Estrogen activated Src promoted Src binding to the ER in the cytoplasm and ER translocation to the nucleus. Src inhibition together with ER blockade more effectively arrested cell cycle progression and inhibited transcription of ER target genes such as Myc and FOSL1 [15]. A better understanding of ER signaling in ovarian cancer will permit refinement of combinations of targeted therapy with standard hormonal agents to improve treatment.

There is also evidence that ERα may be activated by kinase pathways in a ligand independent manner in ovarian cancer. One study showed ERK2 mediated phosphorylation of ERα in response to CD44's [a major hyaluronan (HA)1 receptor] interaction with hyaluronan and IQGAP1, independent of estrogen in ovarian cancer cells [97]. In addition, there is evidence for crosstalk between ERα and leptin signaling [98]. Leptin promotes ovarian cancer cell proliferation, at least in part, by ER transcriptional activation via the

STAT-3 signaling pathway mediated by ERK and PI3K pathways independent of estrogen [98]. Thus targeting crosstalk between liganded and/or un-liganded ER and kinase signaling pathways may have potential to overcome anti-estrogen resistance.

CONCLUSION

Ovarian cancer arises from surface epithelium which expresses ERα receptors. The observation that more than 60% of primary ovarian and breast tumors express epithelial ERα suggests there could be parallels between estrogen action in ovarian and breast cancer cells [15;49;54]. The ERs (ERα and ERβ) belong to the nuclear receptor family and function as hormone-inducible transcription factors in target cells [99]. Growth response to estrogens promote proliferation in ovarian cancer cell lines by ERα and not by ERβ [15;18]. Despite the majority of ovarian cancers expressing the ER, antiestrogens have shown disappointing therapeutic efficacy in part due to lack of verification of ER target expression and also due to drug resistance. It is unclear whether ER expression is a predictor of response to antiestrogens since most trials failed to preselect patients based on ER and did not correlate response with ER status. Molecular analysis of gene expression or pharmacogenomics may help identify new markers that are more predictive of response. There may prove to be a role for anti-estrogens in the post-operative (adjuvant) setting in OVCA to prevent or reduce cancer recurrence as is the case for breast cancer. Unfortunately, trials evaluating anti-estrogens in ovarian cancer patients in a true adjuvant setting have never been initiated. The trials that have compared chemotherapy with and without hormonal therapy for recurrent disease are inconclusive due to small sample size, inadequate treatment design and lack of ER ascertainment. Patients most likely to benefit would likely be those with optimally debulked ER positive tumors after post-operative chemotherapy. Such an adjuvant therapy study would require a cooperative group effort to permit randomization of sufficient patients to placebo vs anti-estrogen in this context.

Preclinical models demonstrate that targeting estrogen activated kinase pathways in combination with ER blockade reverses anti-estrogen resistance in ovarian cancer [15]. Given the preclinical and early clinical data, combinations of hormonal and molecular targeted therapies warrant further investigation in clinical trials for ovarian cancer. Although significant advances have been made in our understanding of ER action in breast cancer, the molecular pathways involved in hormone-stimulated proliferation in the ovary remain less clear. Defining ER-stimulated pathways that mediate proliferation in response to hormone will clarify the role of the receptor and its target genes in the onset and progression of ER+ ovarian cancers. This type of research may yield much needed new diagnostic or prognostic markers for clinical use. Such investigations may also reveal whether the mitogenic actions of estrogen in the ovary and breast occur through common mechanisms and ultimately provide avenues for development of improved ER-targeted therapeutics.

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Highlights

- Most OVCAs express estrogen receptor and estrogens drive ovarian carcinogenesis
- Anti-estrogen therapies are well tolerated in recurrent OVCA with minimal toxicity
- Efficacy of Anti-estrogen therapies is limited by resistance
- Targeting kinase pathways with ER blockade is a mechanism to reverse anti-estrogen resistance

Table 1

Tamoxifen in treatment or recurrent or resistant EOC

Study	N	Tamoxifen dose	CR	PR	SD	PD	Median survival (months)	Mean response duration (months)	ER +status
Karagol et at (2007) [100]	29	20 mg BID	1 (3)	2 (7)	6 (21)	20 (69)	3 (SD +PD) vs 15 (CR + PR)	NS	NS
Hatch et al (2006) [63]	105	20 mg BID	10 (10)	8 (8)	40 (38)	47 (45)	NS	3 (for PR and SD) vs 7.5 (CR)	62/105
Rolski et al (1998) [101]	47	40 mg daily	1 (2)	2 (4)	22(47)	NA	NA	6.9	NS
Marth et al (1997) [102]	65	30–40 mg daily	2 (3)	2 (3)	50 (77)	11 (17)	5.5 (SD +PD) vs 6.2 (CR+ PR)	NS	NS
Gennatas et al (1996) [64]	50	40 mg daily	2 (4)	26 (52)	NS	NS	NS	18	NS
Van Der Velden et al (1995) [66]	30	20 mg BID	2 (7)	0	10 (33)	NS	NS	11.5	NS
Jager et al (1995) [103]	33	30 mg daily	0	0	2 (6)	NS	NS	NS	NS
Van der Vange et al (1995) [104]	6	20 mg BID	0	1 (17)	1 (17)	NS	NS	NS	NS
Losa et al (1993) [105]	NA	40 mg daily	0	1	22	32	NS	NS	NS
Ahlgren et al (1993) [67]	29	80 mg qd × 30 days, f/u by 40 mg daily	2 (7)	7 (24)	18 (62)	6 (21)	5 (NR) vs 36 (R)	2 (NR) vs 24 (R)	NS
Osborne et al (1988) [106]	51	100 mg/m^2 in 24 hrs, f/u by 20 mg BID	1 (2)	0	0	50 (98)	NS	2	NS
Weiner et al (1987) [71]	31	40 mg/m^2 qd × 7, f/u by 10 mg bid	1 (3)	2 (6)	6 (19)	22 (71)	7 (NR) vs 16 (R)	14	4/11
Quinn et al (1987) [65]	40	20 mg BID	5 (13)	4 (10)	12 (30)	NS	NS	NS	NS
Slevin et al (1986) [107]	22	20 mg daily	0	0	1(5)	21 (95)	3.5 (SD +PD)	3	NS
Landoni et al (1985) [108]	55	40 mg daily	0	0	19 (35)	NS	NS	NS	NS
Shirey et al (1985) [70]	23	20–40 mg daily	0	0	19 (83)	NS	NS	2.5	6/23
Hamerlynck et al (1985) [109]	36	40 mg daily	0	2 (6)	7 (19)	NS	NS	NS	NS
Rowland et al (1985) [110]	9	20 mg daily	0	0	NS	NS	NS	NS	5/9
Pagel et al (1983) [111]	21	NS	1 (5)	7 (3)	12 (57)	NS	NS	NS	10/12
Schwartz et al (1982) [112]	13	20 mg daily, increased to 40 mg for progression	0	1 (8)	4 (31)	8 (62)	NS	NS	4/13
Total	**695**		**28 (4)**	**65 (9)**	**251 (35)**	**217 (36)**	**6.2–36 (R)**	**2–24**	**91/173**

CR: complete response, PR: partial response, SD stable disease, PD: progressive disease, R: responders, NR: non responder, NS: not stated, NA: not available

Table 2

Aromatase inhibitors in persistent or recurrent EOC

Study	N	Drug	CR	PR	SD	PD	Median Survival (months)	Median time to progression(months)	ER + status
Ramirez et al (2008) [113]	33	Letrozole	0	1 (3)	7 (21)	23 (70)	5.6 (NR) vs 10.9 (PR +SD)	2 (SD) vs 4 (PR)	33/33 (all platinum resistent)
Smyth et al (2007) [114]	42	Letrozole	0	7 (17)	11 (26)	NS	11 (26) PFS >6mo, 2(5) PFS >2 yrs	NS	42/42
Kavanagh et al (2007) [84]	13	Letrozole	2 (15)	2 (15)	5 (38)	4 (31)	NS	NS	13/13
Gourley et al (2006) [115]	33	Letrozole	0	3 (9)	14 (42)	16 (49)	NS	NS	NS
Papadimitriou et al (2004) [116]	27	Letrozole	1 (4)	3 (11)	5 (18)	18 (67)	26.5 (NR) vs not reached for R +SD	2.4 (NR) vs 17.6 (R+SD)	20/27
Bowman et al (2002) [82]	54	Letrozole	0	5 (9)	14 (26)	30 (56)	14	NS	Mixed ER−/ER+
Krasner et al (2005) [117]	23	Anastrozole	1 (4)	0	14 (61)	NS	NS	NS	23/23
Del Carmen et al (2003) [118]	53	Anastrozole	0	1 (2)	22 (42)	30 (57)	NS	2.8	Mixed ER−/ER+
Verma et al (2006) [119]	22	Exemestane	0	0	8 (36)	NS	NS	2.2	16/22
Total	**300**		**4 (1)**	**22 (7)**	**100(33)**	**121 (40)**			**147/160**

CR: complete response, PR: partial response, SD stable disease, PD: progressive disease, R: responders, NR: non responder, NS: not stated, ER: estrogen receptor