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Estrogen receptors and human disease: an update

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Abstract

A myriad of physiological processes in mammals are influenced by estrogens and the estrogen receptors (ERs), ER α and ER β . As we reviewed previously, given the widespread role for estrogen in normal human physiology, it is not surprising that estrogen is implicated in the development or progression of a number of diseases. In this review, we are giving a 5-year update of the literature regarding the influence of estrogens on a number of human cancers (breast, ovarian, colorectal, prostate, and endometrial), endometriosis, fibroids, and cardiovascular disease. A large number of sophisticated experimental studies have provided insights into human disease, but for this review, the literature citations were limited to articles published after our previous review (Deroo and Korach in *J Clin Invest* 116(3):561–570, 2006) and will focus in most cases on human data and clinical trials. We will describe the influence in which estrogen's action, through one of or both of the ERs, mediates the aforementioned human disease states.

Keywords

Estrogen; Estrogen receptors; Human disease; Cancer; Endometriosis; Fibroids; Ovary

Estrogen receptors

Elucidating the functions of the estrogen receptors (ER) in normal and diseased states is important for the development of relevant therapeutic strategies. Two main forms of ER exist, ER α and ER β , which are encoded by separate genes, *Esr1* and *Esr2*, respectively. They are transcribed from different chromosomal locations and multiple splice variants exist for these receptors. Each receptor has distinct tissue expression patterns, post-translational modifications, and cellular localization in normal and disease states. The ERs are classical hormone nuclear receptors and members of the nuclear receptor super family having the functional structural domains A-F (Mangelsdorf et al. 1995; Hewitt et al. 2009; Burns et al. 2011). The A/B-domain contains the activation function 1 (AF-1), which is hormone-independent. The C-domain holds the DNA-binding domain, the D-domain or hinge region has nuclear localization sequences and interacts with AP-1, and the E/F-domain is the

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ligand-binding domain with the ligand-dependent activation function, AF-2. Over the last 5 years, great strides have been made to understand the post-translational modifications, polymorphisms, methylation status, and localization of ER. Most notably and much beyond the scope of this review, sequencing of chromatin immunoprecipitation enriched chromatin fragments (ChIP-seq) has addressed the relationship between ER chromatin interactions and responses to estradiol (Fullwood et al. 2009; Welboren et al. 2009a, b; Grober et al. 2011; Hewitt et al. 2012). The aforementioned studies reveal significant ER binding to chromatin without ligand, increased binding of ER with ligand and binding of ER quite distal to the promoter start sight or in intronic regions. These detailed studies are providing a vast amount of data that will be a part of the continued elucidation of the various mechanisms and function of the ERs, which are critical in the development of therapeutics. In this review, we will focus on the alterations of the ERs in human disease.

Breast cancer and ER

A plethora of clinical and experimental data is available regarding the ERs and breast cancer; therefore, this review will focus on the literature pertaining to human disease and clinical data. Most notably, breast cancer incidence has decreased in recent years, most likely as a result of the decline in the number of women receiving hormone replacement therapy due to negative health findings from the Women's Health Initiative (Chlebowski et al. 2009). The localization of hormone nuclear receptors in normal breast tissue has not been well studied; consequently, Li et al. studied the localization of ER α , ER β , progesterone receptor (PR)-A and PR-B, and androgen receptor (AR) in normal human mammary gland tissue. Samples from premenopausal women show that ER α , PR-A, PR-B, and AR localize mostly to the inner layer of epithelial cells lining acini and intralobular ducts and to myoepithelial cells in the external layer of interlobular ducts (Li et al. 2010). ER β was found to be more widespread, having staining of stromal, epithelial, and myoepithelial cells in acini and ducts. Many studies have correlated the nuclear receptor status of the tumor to treatment regimens and survival outcomes.

Breast cancer survival and ER α

Estrogens play a central role in breast cancer development with ER α status being the most important predictor of breast cancer prognosis. ER α has long been determined to be a prognostic marker for breast cancer and increased survival is seen with ER α -positive status as these tumors respond to anti-estrogen therapy. The exception, however, is tumors which overexpress a 36-kDa variant of ER α , termed ER α -36. ER α -36 has no intrinsic transcription activity, but localizes predominantly to the plasma membrane and cytoplasm of cells and mediates the membrane-initiated non-genomic signaling pathway. The overexpression of ER α -36 is associated with poor disease-free survival, and patients are less likely to benefit from tamoxifen treatment (Shi et al. 2009; Lin et al. 2010; Vranic et al. 2011). Current studies associating breast cancer with ER α -positive status focus on post-translational modifications to ER α in hopes to find better therapies by understanding the ER α responsiveness. Multiple phosphorylation sites in ER α can be detected in breast tumor biopsy samples. The relationship of ER α phosphorylation (pS-104/106-ER α , p-S118-ER α , p-S167-ER α , p-S282-ER α , p-S294-ER α , p-T311-ER α , and p-S559-ER α) to clinical

outcome after tamoxifen therapy suggests high phosphorylation status is associated with increased mortality (Skliris et al. 2010; Murphy et al. 2011). ER α -S305 phosphorylation positive breast cancers are resistant to adjuvant tamoxifen treatment, while ER α -S305 phosphorylation negative tumors have improved recurrence-free survival with tamoxifen treatment (Holm et al. 2009; Kok et al. 2011). Consequently, blocking ER α -S305 phosphorylation may represent a new therapy strategy (Barone et al. 2010). ER α status and decreased p44/42 mitogen-activated protein kinase (MAPK)/ERK1/2 activity are also factors that suggest a successful response to treatment (Generali et al. 2009). More specifically, ER α low phosphorylation at S118 and high phosphorylation of S167 are associated with improved disease-free survival (Yamashita et al. 2008; Motomura et al. 2010). A phosphorylated form of membrane ER α is proposed to characterize an invasive cancer state and suggests transcription-independent cellular responses to estrogen are involved in disease progression (Mintz et al. 2008). The interplay of ER α and MAPK to integrate signaling inputs occurs by estrogen-occupied ER α activating and interacting with ERK2 which colocalizes ERK2 and ER α at chromatin-binding sites (Madak-Erdogan et al. 2011). Phosphorylation modifications of ER α affect survival in ER α -positive breast cancer and could be used to distinguish patients who are more likely to benefit from endocrine therapy alone from those who may be resistant.

In breast cancer, ER, PR, human epidermal growth factor receptor 2 (HER2) and Ki67 are biological makers for predicting prognosis and treatment decisions, but other nuclear receptors/transcription factors also play a role in breast cancer progression. The expression of ER α and PR in normal mammary tissue adjacent to the pathological tissue compared to women with benign breast disease shows that the overexpression of ER α and PR is associated with reduced breast cancer risk, but increased age at the diagnosis of hormone receptor-positive tumors is associated with higher disease-specific mortality (Lagiou et al. 2009; van de Water et al. 2012). In HER2-positive tumors, ER α and PR are associated with AR co-expression and lower proliferative activity, while AR-negative/ER α -negative tumors were associated with highest proliferative activity and histological grade (Lin Fde et al. 2012). Suggesting that co-expression of AR and ER α provides a protective effect. Tumors with high ER α expression and low Ki67 labeling are associated with tamoxifen and aromatase inhibitor treatment as a first-line endocrine therapy; however, low levels of ER α are a determinant of tamoxifen resistance in ER α -positive cancers (Endo et al. 2011; Kim et al. 2011).

Breast cancer survival and ER β

Both ER α and ER β are normally present in the mammary gland. ER α is a prognostic marker in breast cancer, but the role of ER β is less clear. ER β is regulated by transcriptional and post-transcriptional modifications; ER β mRNAs are transcribed from three promoters and variants of ER β 1, ER β 2 and ER β 5 play a role in breast cancer (Smith et al. 2010). Immunohistochemical expression of ER α and ER β in a breast cancer tumor tissue array demonstrated that 78 % of tumors are ER α -positive and 50 % of tumors are ER β -positive. In the 512 tumors analyzed, the ER α -positive status correlates with survival and treatment responses, but no overall prognostic significance was demonstrated for ER β (Borgquist et al. 2008). Although in a separate study, ER β expression was found associated with ER α

expression (Marotti et al. 2010). In contrast, a more detailed study of ER β status examining nuclear and cytoplasmic expression of ER β 1, ER β 2, and ER β 5 suggests that the cellular localization of these isoforms differentially affects patient outcome (Chen et al. 2007; Mandusic et al. 2007; Shaaban et al. 2008; Yan et al. 2011). Examination of ER β isoforms from laser microdissected human breast cancers show that the levels of the ER β isoform expression are cell type and cellular compartment-dependent (Cummings et al. 2009). Cytoplasmic ER β 2 expression predicts worse overall survival, but positive staining for ER β 1 nuclear is associated with better survival (Lin et al. 2007; Sugiura et al. 2007; Honma et al. 2008; Shaaban et al. 2008). In ER α -positive/PR-positive tumors, patients with higher ER β levels had longer survival; however, no association of ER β levels and survival was found with ER α -negative/PR-negative tumors (Maehle et al. 2009). In contrast, Gruvberger-Saal et al. suggest from their study that in ER α -negative tumors, ER β expression responds to tamoxifen and increases overall survival (Gruvberger-Saal et al. 2007). In contrast, co-expression of ER β and HER2 associates with poorer prognosis in primary breast cancers (Qui et al. 2009). No correlation between ER β levels and classical prognosticators for breast cancers are found; however, in node-positive cancers, ER β -positive is related to the need for a more aggressive clinical course (Novelli et al. 2008). Similarly, in ER α -negative tumors, a correlation between ER β protein expression and Ki67 is seen (Rosa et al. 2008). One study has demonstrated that nuclear ER β -S105 phosphorylation is associated with better survival even in tamoxifen-resistant cases (Hamilton-Burke et al. 2010). Overall, the data suggest that ER β is playing some role in breast cancer that is independent of ER α . A more detailed characterization of ER β as well as that of other hormone receptors will be required to determine the role for ER β as a predictor for survival.

Breast cancer and ER's interaction with transcription factors

Endocrine resistance is a major hurdle to hormonal treatments for breast cancer, but recent studies have focused on finding ER-interacting proteins to potentially target as new therapeutic treatments. Tumors with higher IGF-1 and ER α take longer to develop tamoxifen resistance (Chong et al. 2011). In contrast, CUE domain-containing protein-2 (CUEDC2) expression and ER α expression are inversely correlated with high CUEDC2 expression being a predictor of poor responsiveness to tamoxifen treatment (Pan et al. 2011). Fork head proteins (FOX) belong to a group of pioneering transcription factors that interact with ER. FOXA1 and ER α predict favorable outcomes in breast cancer patients (Bernardo et al. 2010). FOXA1 influences genome-wide interactions between ER α and chromatin. In ER α -responsive breast cancer cells, response to tamoxifen depends on FOXA1 and ER α interaction, but in tamoxifen-resistant cells, ER α binding was ligand-independent but dependent on FOXA1 (Hurtado et al. 2011; Ross-Innes et al. 2012). FOXM1 has also been identified as a transcriptional target of ER α and may play a role in mitogenic function (Millour et al. 2010). Another genomic pioneering factor, pre-B cell leukemia homeobox 1 (PBX1) drives ER α signaling and underlies progression of breast cancer. PBX1-transcriptional program is associated with poor outcome in patients and a study in cells with PBX1 knockdown no longer proliferate after estrogen (Magnani et al. 2011). Future therapies may be aimed to target ER α -interacting partners.

Understanding the interplay of ER β and interacting partners is more in its infancy than ER α . Examination of interacting partners of ER β was done in MCF-7 cells, and the interactome revealed 303 proteins that co-purify with ER β nuclear extracts (Nassa et al. 2011). The identification of these interacting partners should pioneer a number of studies to more adequately understand the biological role of ER β in cancer. Important early studies show the presence of ER β attenuates the transcriptional activity of ER α (Matthews et al. 2006). Since that time, an interesting study with MCF-7 cells engineered to express ER α only, ER β only, or ER α and ER β examined ER-binding sites. The results reveal substantial binding site overlap when the ERs were expressed alone, with many fewer sites shared with both ERs present (Charn et al. 2010). Each ER restricts the binding of the other with ER α being more dominant to displace ER β to new sites less enriched for estrogen response elements (ERE) (Charn et al. 2010). Additionally, the knockdown of ER β in MCF-10 and MCF-7 cells results in increased growth in a ligand-independent manner while overexpression of ER β allows MCF-7 cells to respond to tamoxifen and inhibit proliferation (Hodges-Gallagher et al. 2008; Treeck et al. 2010). In a mouse model, over-expression of ER β in xenograft tumors from T47D cells reduced tumor growth and angiogenesis (Williams et al. 2008). These results regarding ER β suggest this ER exerts anti-proliferative effects on breast cancer.

Breast cancer and miRNA association with ER

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression in different physiological and pathological process often negatively by hybridizing to complementary sites of target transcripts. Many miRNAs are implicated in several human cancers, including breast cancer, associated with the loss of tumor suppressor miRNAs or the overexpression of oncogenic miRNAs (O'Day and Lal 2010). Here, we discuss the association of ERs and miRNAs in breast cancer. miR-22 represses ER α expression by directly targeting its 3' untranslated region (UTR), which induces mRNA degradation (Pandey and Picard 2009). ER β 1 is often down-regulated in breast cancers, and analysis of primary breast tumors demonstrates this may be due to a negative correlation between miR-92 and ER β 1 mRNA and protein (Al-Nakhle et al. 2010). In vitro experiments confirm this finding by showing that overexpression of miR-92 decreases ER β 1 via direct targeting of the ER β 3' UTR (Al-Nakhle et al. 2010).

Distinct expression of miRNAs is found between primary ER α -positive and ER α -negative breast cancer tumors and cell lines. Cells transfected with miRNA-221 and miRNA-222 have decreased ER α expression and increased resistance to tamoxifen treatment (Zhao et al. 2008). Acquired resistance to therapy occurs in a majority of breast cancer patients. Rao et al. show that prolonged fulvestrant (a selective estrogen receptor downregulator) therapy increases miR-221 and -222 expression, which results in the dysregulation of multiple oncogenic pathways associated with drug resistance (Rao et al. 2011). miR-221 and -222 are negatively modulated by ER α . A negative feedback loop may contribute to the proliferative advantage and migratory activity of breast cancer cells, which may promote the ER α -positive to ER α -negative tumor status transition (Di Leva et al. 2010). A microarray analysis for estrogen-regulated miRNAs in MCF-7 cells found that estrogen induces 21 miRNAs and represses seven of them, together potentially regulate 420 estradiol-regulated and 753 non-estradiol-regulated genes at the post-transcriptional level (Bhat-Nakshatri et al. 2009). A

similar study in MCF-7 cells also found a subset of miRNAs regulated by estrogen and further demonstrates clinical relevance as pre-miR18a is upregulated in ER α -positive compared to ER α -negative breast cancers (Castellano et al. 2009). These studies suggest roles for miRNAs in the regulation of ER activity and consequently in the development and progression of breast cancers.

Breast cancer and ER single-nucleotide polymorphisms (SNPs)

Studies have examined single-nucleotide polymorphisms (SNPs) for ER α and ER β to determine whether they confer risks for breast cancer development. Women with sporadic breast cancer more frequently (odds ratio (OR) = 1.99) carry the CC genotype of ER β promoter SNP rs2987983 (Treeck et al. 2009). A large cohort examining four htSNPs that tag the six major haplotypes of ER β demonstrated that the inherited variants in ER β are not associated with an appreciable (OR > 1.2) change in breast cancer risk in Caucasian women (Cox et al. 2008). In contrast, in sporadic breast cancer, decreased risk is associated with the LL and the SL genotypes in c. 1092 + 3607(CA)(10–26) in ER β (OR = 0.013) (Tsezou et al. 2008). The rs1801132 and rs2234693 ER α polymorphisms confer a slight decreased breast cancer risk for CC and CC/CT carriers (Li et al. 2010). C325G SNP in ER α is associated with increased cancer risk (OR = 2.28) in women 50 years and younger; however, overall susceptibility to breast cancer was not found (Siddig et al. 2008). SNP rs2046210 at 6q25.1 in the ER α promoter only shows a weak association with breast cancer in Chinese and European ancestry women (Zheng et al. 2009). In a study of more than 55,000 breast cancer patients to look at SNP rs3020314 in ER α intron 4 found no large risks for increased breast cancer susceptibility in European populations (Dunning et al. 2009). The expansive number of patients analyzed for ER SNPs suggests different SNPs may alter a woman's risk for breast cancer.

Ovarian cancer and ER

Ovarian cancer has one of the highest rates of mortality of the gynecological malignancies, and female oncogenesis is most likely attributed to the asymptomatic nature of the disease and inadequate treatment strategies. Ovarian cancer is often not detected until the disease is of a late stage and symptoms of abdominal pressure, pelvic pain, persistent indigestion, and/or loss of appetite are recognized (Zahedi et al. 2012). The standard of care includes surgery and chemotherapy, but this often results in toxicities and disease relapse; therefore, it is of importance to find methods to detect this disease earlier. Many human studies over the last few years have focused on both ERs in the understanding of survival outcomes, associations with SNPs and molecular responses by utilizing ovarian cancer cell models.

In reproductive age women, ER α is present in the ovarian stroma and thecal cells, ovarian surface epithelium and in corpus luteum; however, the localization of ER α in the ovaries of postmenopausal women was unknown (Brodowska et al. 2007). In contrast, ER β is localized predominately to the granulosa cells of the ovary (Brandenberger et al. 1998). In order to make hormone treatments of ovarian cancer more effective, the normal localization of ER α in the ovary of postmenopausal women was examined. ER α is found in the ovarian surface epithelium, in epithelial inclusion cysts and stroma of women who had their last

menstruation less than 5 years before the study, while women who had their last menstruation more than 5 years before the study had decreasing levels of ER α in the ovary.

Ovarian cancer and survival

The levels of ER α and ER β and their relationship in expression levels to other hormone receptors have been widely studied recently. Epithelial cells in advanced serious ovarian cancer tissue have lower levels of ER β and PR, but not ER α when compared to normal ovarian tissue (Issa et al. 2009; De Stefano et al. 2011). ER α expression is associated with progression-free survival and cause-specific survival as these patients can be selected for specific anti-hormonal therapy similar to hormone-responsive breast cancers (Burgess et al. 2010). The Nurses' Health Study reported that in epithelial ovarian tumors, PR expression is less likely to be invasive, of a lower grade and stage than PR-negative tumors, while ER α status in these tumors did not associate with any pathologic features of the tumor (Hecht et al. 2009). Experimental models designed to study the mechanism of action of ER α in ovarian cancer suggest roles for leptin as an induced signal transducer and activator of transcription 3 (STAT-3) binding to ER α . Down-regulation of E-cadherin by the ER α regulation of Snail and Slug, as well as reciprocal roles of estrogen, interleukin-6 (IL-6), and IL-8 are all being considered as cellular actions (Park et al. 2008; Salonen et al. 2009; Yang et al. 2009; Choi et al. 2011).

On the other hand, loss of ER β expression correlates with shorter overall survival of ovarian cancer and may be a feature of malignant transformation as the expression of ER β decreases with cancer progression (Chan et al. 2008; Halon et al. 2011). A reason for this transformation may be that ER β expression is predominately nuclear in normal ovarian tissue, but often ovarian cancers exhibit cytoplasmic ER β immunopositivity. ER β levels are inversely correlated with metastasis-associated gene 1 (MTA1) expression and in an in vitro cell model, overexpressing MTA1 reduces ER β levels (Dannenmann et al. 2008). Re-expression of ER β in an ER β -null ovarian clear cell adenocarcinoma cell line inhibits proliferation, migration, and motility (Zhu et al. 2011). The increased loss of ER β with ovarian cancer progression suggests a protective role for ER β in the ovary.

Ovarian cancer and SNPs and methylation

SNPs and methylation have been examined to determine whether they may be risk factors for ovarian cancer. A comprehensive study of epithelial ovarian cancer in American white women examined 13 different SNPs in ER α and found the strongest association of rs2295190 for the mucinous subtype of ovarian cancer (OR = 1.32) (Doherty et al. 2010). The ER β rs1271572 polymorphism has an OR = 1.35 for the risk of development of invasive ovarian carcinoma in women <50 years and was strongest among women who had never used contraceptive steroids (Lurie et al. 2009, 2011). A study to characterize the role of haplotype diversity in ER β with the risk of ovarian cancer found five haplotypes with a frequency of >5 % in white subjects, but no association was observed for the risk of ovarian cancer (Leigh Pearce et al. 2008). Promoter methylation analysis of ER β from treatment insensitive ovarian cancer cell lines revealed that promoter methylation is cell type-specific and that the loss of ER β isoform expression and inactivation correlates with aberrant

promoter methylation (Suzuki et al. 2008; Yap et al. 2009). Overall, a slight increase in ovarian cancer risk may be attributed to SNPs or altered methylation status of *ER α* or *ER β* .

Non-target tissue cancers and ER

Colon cancer

Clinical and animal studies show that hormone replacement therapy reduces the risk of colon tumor formation. Research in the last 5 years has focused on the roles of *ER α* and *ER β* in the development of colon cancer, but *ER β* is denoted as the principal mediator in the colon (Giroux et al. 2011). *ER β* and associated splice variants (*ER β 1*, *ER β 2*, and *ER β 5*) are highly expressed in normal colon tissue with less expression in early disease states and the lowest *ER β* expression in colon adenocarcinomas (Castiglione et al. 2008). In familial adenomatous polyposis, decreased *ER β* expression is related to the severity of disease and a mouse model of disease, *Apc*(Min/+), given an *ER β* -selective agonist, diarylpropionitrile (DPN), results in a significant reduction in polyp multiplicity in both male and female experimental groups (Barone et al. 2010; Giroux et al. 2011). As prognostic markers in rodents and humans, *ER β* knockout mice have increased the presence of mucin-depleted foci, an early event in colon cancer (Saleiro et al. 2010). Estradiol influences the physiology of non-cancerous colonocytes experimentally through *ER β* during the initiation/promotion stage of disease development, which results in fewer pre-neoplastic lesions (Weige et al. 2009). In human colon cancer, *ER β* along with other associated transcription factors are being studied to analyze *ER β* 's role. Subsite-specific localization differences of *ER β* expression in colonic epithelium have implications for the epidemiology of colon cancer (Papaxoinis et al. 2010). Low *ER β* and high matrix metalloproteinases (MMP) 7 expressions are a risk factor in colon cancer. MMP7 is consistently expressed throughout cancer progression, but patients with higher *ER β* nuclear expression have a higher 5-year survival rate (Fang et al. 2010). The co-expression of *ER β* and proline, glutamate- and leucine-rich protein 1 (PELP1/MNAR) in epithelial cells of carcinomas is a favorable prognostic factor (Grivas et al. 2009). In insulin-resistant syndrome, a combined effect of insulin-like growth factor 1 (IGF1) and estrogens is correlated with colon cancers as a gradual increase in IGF-1 receptor expression and gradual decrease in *ER β* expression is observed (Papaxoinis et al. 2007). These studies support a role for *ER β* as a relevant biomarker of tumor progression and possible chemopreventive target in patients at risk for colonic neoplasia.

Even though *ER α* expression is extremely rare in colorectal tissue and its expression appears not to be associated with colon cancer, studies have addressed *ER α* (Grivas et al. 2009). Experimental studies of *Apc*(Min/+) mice lacking *ER α* showed an increased colon tumor burden and multiplicity compared to wild-type mice resulting in an elevated Wnt- β -catenin signaling pathway and resulting tumorigenesis (Cleveland et al. 2009). These studies suggest that estrogen's protective action may be to suppress rather than stimulate the Wnt- β -catenin pathway in the colon. Decreased *ER β* is observed in colonic polyps and colon cancer. *ER α* expression does not change in patients with colonic polyps; however, in colon cancer, *ER α* levels increase in men and not in women (Di Leo et al. 2008; Nussler et al. 2008). These data suggest sex-specific effects related to the *ER α* . In contrast, decreased levels of the *ER α* splice variants, *ER α -36* and *ER α -46*, correlate with tumor stage and lymph node metastasis

(Jiang et al. 2008). Examination of ER α promoter methylation status in sporadic colorectal cancer is found to be altered in normal background mucosa in association with vitamin B-12 status (Al-Ghnam et al. 2007; Hiraoka et al. 2010). Both ER α and ER β are implicated in colon cancer, where ER β is most likely a critical mediator and can be a target for mitigating cancer preventative effects.

Prostate cancer

Since our previous review, little research has been published regarding ERs and prostate cancer. Rodent studies show that estrogen signaling through ER α or ER β is not needed for dioxin to inhibit prostatic epithelial budding, but a diet rich in sesame pericarp increases ER β expression in the prostate and has a beneficial effect on the healthy status of the animal (Allgeier et al. 2009; Anagnostis and Papadopoulos 2009). In contrast, an ER β antagonist selectively induced apoptosis in experimental castrate-resistant CD133+ basal cells and suggests a role for ER β in prostatic stem cells and in prostate cancer. Estrogens are known to play a role in prostate carcinogenesis, but the expression of ERs throughout prostate carcinogenesis is unknown (Ellem and Risbridger 2007; McPherson et al. 2010; Risbridger et al. 2010). In general, low expression of ER α is detected in prostatic epithelial cells while ER β is predominantly expressed in prostatic epithelial cells, but the ER α expression is highly variable in human tissues depending on disease status (Leav et al. 2001). Human studies have focused on SNPs of ER α and ER β . ER α (rs1801132, rs2077647, rs746432, rs2273206, rs851982, and rs2228480) and ER β (rs4986938, rs928554, rs8018687, and rs number not available for ESR2 5696 bp 3' of STP A >G) SNPs from multiple cohorts with large study participation observed little evidence for any association of ER α or ER β polymorphisms with prostate cancer risk (Chen et al. 2007; Chae et al. 2009). Clinical and basic science evidence linking estrogen and estrogen receptors to prostate cancer still remains an area of study.

Endometrial cancer

Endometrial cancer is the most common gynecological malignancy with risk factors being exposure to estrogens and having high body mass index (Collins et al. 2009). Recent human studies have focused on survival rates relative to hormone receptor status, association with other transcription factors and receptor SNPs. Examination of endometrial carcinomas by tissue microarray, fluorescence in situ hybridization (FISH), and immunohistochemistry demonstrates that the amplification of ER α is related to early-stage cancer, but in contrast, the absence of ER α correlates to death from disease (Lebeau et al. 2008; Jongen et al. 2009). Expression of ER α , PR-A, and PR-B is associated with lower-grade tumors, but patients with lower ratios of ER α /ER β or PR-A/PR-B exhibit shorter disease-free survival (Jongen et al. 2009). A similar immunohistochemical analysis also demonstrates the loss of ER α , PR-A, and PR-B results in poorer survival, but the expression of ER β does not correlate with survival (Shabani et al. 2007). Experimental studies show a similar correlation since mouse models of endometrial cancers show different severities of tumorigenicity when hormone receptors are lacking (reviewed in Yang et al. 2011a, b). ER α levels measured in metastatic endometrial carcinoma prior to hormonal treatment correlate with clinical response to tamoxifen and medroxyprogesterone acetate (Singh et al. 2007). Patient survival is

associated primarily with ER α expression as these tumors are able to respond to anti-hormonal therapy.

In uterine carcinosarcoma, a rare and highly aggressive form of endometrial cancer, ER α and PR receptor expression are suppressed while ER β expression is elevated and continues to increase with disease progression (Huang et al. 2009). In this cancer relative to normal endometrium, IGF-1 expression is reduced and HER2 increases, which supports a potential role for ER β via crosstalk with HER2 in disease progression (Huang et al. 2009). Additionally, crosstalk may occur with G-coupled protein receptor 30 (GPR30) and ER β as they are coordinately overexpressed and expression increases in advanced-stage disease (Huang et al. 2010). In endometrial cancers, crosstalk also occurs between steroid and prostaglandin pathways as cyclooxygenase 2 (COX-2) expression is higher in ER α -negative/low tumors and full length ER β (ER β 1) and two ER β variants (ER β 2 and ER β 5) are expressed regardless of tumor grade with most of the cells of these poorly differentiated cancers being ER β -positive/ER α -negative (Collins et al. 2009). An inverse relationship between ER α and ER β in endometrial cancers suggests ER β antagonists may be useful therapeutics for ER β -positive/ER α -negative/low cancers.

SNP analysis is commonly being used to analyze common genetic variations in patients with endometrial cancer. A positive association for the risk of cancer is seen in women who express ER α and CYP1B1 L432 V (Zhu et al. 2011). In a Swedish population, analysis of ER α gene promoter SNPs found five adjacent tagSNPs covering a 15-kb region at the 5' end that associates with decreased risk for endometrial cancer; however, the variants did not associate with myometrial invasion or cancer survival rates (Einarsdottir et al. 2009). Polymorphic variations of ER α (rs2234670, rs2234693, and rs9340799) suggest decreased endometrial cancer risk most strongly with rs9340799 (OR = 0.75 for heterozygous and OR = 0.53 for homozygous) (Wedren et al. 2008). These results suggest that intronic variation in ER α , depending on the SNP, confers risk or protection to endometrial cancer.

Endometriosis and ER

Endometriosis affects 10–14 % of reproductive-aged women with symptoms such as dysmenorrhea, dyspareunia, and infertility. This number increases to 35–50 % in women with pelvic pain, infertility, or both (Galle 1989; Rawson 1991). Endometriosis is hypothesized to occur via retrograde menstruation, but because this occurs in greater than 90 % women, the lower incidence (10–14 %) of endometriosis suggests additional elements impact its etiology (Giudice and Kao 2004; Bulun et al. 2005). Endometriosis is hormonally responsive, and therapies for endometriosis aim to decrease ovarian estrogen production and/or counteract estrogen effects with the use of gonadotropin-releasing hormone (GnRH) agonists, progestins (including oral contraceptives), and androgens (Giudice and Kao 2004). Endometriotic lesions are found throughout the peritoneal cavity attached to the ovaries, fallopian tubes, anterior and posterior cul-de-sac of the uterus, and surrounding ligaments (Giudice and Kao 2004). A definitive diagnosis of endometriosis is only made by positive histological evaluation of endometriotic lesions after laproscopic surgery and treatments only suppress disease symptoms; consequently, elucidating the cause of endometriosis is of critical importance. Current hypotheses regarding disease pathogenesis and pathophysiology

suggest inherent defects in the immune system, the uterus, the endometrium, or even the peritoneal environment of women with endometriosis (Taylor et al. 1999; Sharpe-Timms 2001; Bischoff and Simpson 2004; Capellino et al. 2006; Bukulmez et al. 2008; Weiss et al. 2009; Kulak et al. 2011).

Peritoneal macrophages from women with endometriosis have increased inflammatory cytokines, which are associated with increased ER α expression (Montagna et al. 2008). Conversely, ER β expression correlates with an increase of inflammatory cytokines in women with and without endometriosis (Montagna et al. 2008). Along with the altered ratio of ER β to ER α mRNA, the inflammatory status in women with endometriosis also affects the aromatase levels in eutopic and ectopic endometrium (Bukulmez et al. 2008; Juhasz-Boss et al. 2011). The aforementioned studies suggest that paracrine factors are involved in disease regulation; therefore, a baboon model of endometriosis was used to address this hypothesis. In the baboon, aberrant distribution of ER α , ER β , PR, and FKBP52 is seen in the eutopic endometrium and in the stromal cells, ER β decreases in both glandular epithelium and stromal cells (Jackson et al. 2007). Further studies need to be done to determine the impact of paracrine signaling and if the signaling occurs from both eutopic and ectopic tissue or if one tissue type elicits stronger paracrine signals in the pathogenesis of endometriosis.

Ovarian endometriosis is found on the ovarian fossa, and studies have focused on alterations in ovarian function and infertility. Decreased fertility rates seen in women with endometriosis may relate to endometriosis found on the ovarian fossa. Granulosa cells from women with ovarian endometriosis have higher PR-A and ER α gene expression, lower-quality embryos, and decreased pregnancy rates than women with tubal infertility (Karita et al. 2011). A prospective study of ovarian endometriosis found increased levels of ER β are associated with reductions in ectopic tissue expression of ER α , estrogen-related receptor α (ERR α) and ets-related gene (Erg) (Cavallini et al. 2011). They suggest from their findings that the up-regulation of ER β is the principal ER involved in the progression of endometriosis. Another study focused on ovarian endometrioma samples find enzymes involved in estradiol formation and in progesterone inactivation are up-regulated, potentially resulting in increased local levels of mitogenic estradiol and decreased levels of protective progesterone (Smuc et al. 2009). Additionally, baboons with spontaneous endometriosis exhibit progesterone resistance, and the normal antagonism of progesterone on ER α is absent in animals with endometriosis (Wang et al. 2009). To address the complex nature of ovarian endometriosis, low-density array analysis was done on ovarian endometriosis samples. The results revealed that a number of differentially regulated genes are estrogen related with a large proportion being in the “secreted” and “extracellular region” categories (Vouk et al. 2011). These studies indicate that both ERs and alterations in hormonal milieu alter the paracrine environment and play a role in endometriosis pathogenesis.

Endometriosis and SNPs and methylation

A number of research groups have evaluated ER α or ER β SNPs and the association with endometriosis. Examination of the RsaI polymorphism of the ER β gene found a nine times higher frequency for the AG polymorphism genotype in the patients with endometriosis

compared to controls (Silva et al. 2011). The ER β gene +1730 G/A polymorphism is associated with the risk of infertility and/or endometriosis-associated infertility and a predisposing factor to endometriosis (Bianco et al. 2009; Zulli et al. 2010). In a Korean population, the ER β gene +1730 G/A polymorphism was not associated with endometriosis (Lee et al. 2007). SNPs associated with ER α (rs2234693–T/C SNP, dinucleotide (TA)(n) repeat), and ER β (dinucleotide (CA)(n) repeat) revealed ER α longer (TA)(n) repeats correlated with susceptibility to stage I–II endometriosis, and ER β shorter (CA)(n) repeats were linked with endometriosis without infertility (Lamp et al. 2011). Two independent studies have confirmed that the ER α gene-397 (T/C) PvuII polymorphism predisposes women to approximately 2.6-fold increase in endometriosis (Hsieh et al. 2007; Govindan et al. 2009). Evaluation of intron 1 and exon 1 ER α gene polymorphisms was not associated with increased risk for endometriosis (Sato et al. 2008). Together, these data suggest that ER SNPs, specifically SNPs for ER β , are associated with increased susceptibility for endometriosis.

ER β promoter methylation in the CpG islands from –197 to +359 shows significantly higher methylation in primary endometrial cells versus endometriotic cells, suggesting that methylation status is responsible for differential expression of ER β in endometriosis and endometrium (Xue et al. 2007). The same group demonstrates increased ER β levels concomitant with lower ER α levels in endometriosis and experimentally demonstrates that knockdown of ER β increases ER α while overexpression of ER β decreases ER α levels (Trukhacheva et al. 2009). Thus, ER β may serve as a therapeutic target for the treatment for endometriosis.

Fibroids and ER

Uterine leiomyomas or fibroids are the most common uterine tumors in women and occur during childbearing years. Fortunately, fibroids rarely progress to leiomyosarcomas (Strissel et al. 2007). They are more common in African–American women than Caucasian women (Peddada et al. 2008). Fibroids are often asymptomatic, but symptoms can include bleeding between menstrual cycles, menorrhagia, pelvic cramping with menstruation, and/or sensations of fullness or pressure in the lower abdomen. Experimental studies are being done to determine what stimulates fibroid growth. Ishikawa et al. (2010) grafted human uterine leiomyomata tissue beneath the renal capsule of immunodeficient mice and found that the fibroid tissue increases in size with estrogen plus progesterone and estrogen alone, but decreases in size with anti-progestin and progesterone withdrawal. The cause of fibroids is unknown, but their growth coincides with hormones and menstruation. Fibroids within the same woman often have different growth rates despite being in the same hormonal milieu demonstrating the difficulty in the study of fibroids (Peddada et al. 2008).

Recent studies on ER α or ER β and fibroids have focused on receptor expression, SNPs, methylation, and phosphorylation. Fibroids express higher levels of ER α , ER β , and PR than control myometrium, but postmenopausal fibroids have 2.5-fold higher ER β expression with no difference in ER α or PR (Strissel et al. 2007; Bakas et al. 2008; Chakravarty et al. 2008). ER α is present in smooth muscle cells with a variation in subcellular localization, while ER β is widely distributed in smooth muscle, endothelial, and connective tissue cells with nuclear

location (Valladares et al. 2006). The link between uterine fibroids and increased ER expression compared to normal myometrium led to assessing polymorphisms and susceptibility to fibroids. ER α SNPs (rs9322331 and rs17847075) analyzed in Brazilian women do not differ in women with fibroids compared to controls (Villanova et al. 2006). In contrast, a study of Asian Indian women examining a T/C SNP in intron 1 and exon 2 boundary of ER α indicated a significant association of the C allele with endometriosis (OR = 2.66) and fibroids (OR = 2.08) (Govindan et al. 2009). Much more research is needed to understand the role ERs are playing in fibroids.

Phosphorylation and methylation status impacts ER α activity. The expression of ER α -phospho-S118 by p44/42 MAPK from fibroids taken during the proliferative phase is increased, and these fibroids exhibit higher PCNA expression compared to patient-matched myometria and secretory-phase fibroids (Hermon et al. 2008). Asada et al. investigated the DNA methylation status of ER α promoter region (–1188 to +229 bp) and indicate hypomethylation of the CpG sites in leiomyomas coincides with increased ER α mRNA levels (Asada et al. 2008). Further studies focusing on the hormonal responsivity, SNPs, and methylation status in fibroids are needed to draw full conclusions, but ER α appears to be a main factor in fibroids.

Cardiovascular disease and ER

Cardiovascular disease in women following menopause increases to the same levels found in men, suggesting a cardioprotective role for estrogens. However, hormone replacement therapy was found not to be cardioprotective in postmenopausal women (Rossouw et al. 2002, 2007; Farquhar et al. 2005; Manson et al. 2007). Much of the research published in the last 5 years regarding ERs and cardiovascular disease has been in animal models. We will first summarize the human studies and then focus on key animal data. Kjaergaard et al. examined whether the ER α IVS1-397T/C polymorphism affects high-density lipoprotein cholesterol response to hormone replacement therapy and the risk of cardiovascular disease, cancer of reproductive organs, and hip fracture (Kjaergaard et al. 2007). From 9,244 Danish individuals followed for 23–25 years, they concluded that the ER α IVS1-397T/C polymorphism does not contribute to disease. Both ER α and ER β are present in the vasculature and in the human heart. ER α and ER β mRNA expression from left ventricular specimens from patients with coronary heart disease and dilated cardiomyopathy are lower when compared to healthy heart donors (Leibetseder et al. 2010). Analysis of time dependency of receptor expression showed an 8-h period rhythm for ER β in patients with dilated cardiomyopathy that was not observed in coronary heart disease patients. The increased ER α and ER β mRNA expression in left ventricular specimens from patients with coronary heart disease and dilated cardiomyopathy may reflect a compensatory mechanism by the ERs to counteract the decline in ventricular function seen with these diseases (Leibetseder et al. 2010).

Animal studies for cardiovascular disease and ERs mainly focused on cardioprotection or ER's crosstalk with other transcription factors. Estrogen is known to confer cardioprotection, but this protective role has been challenged due to numerous clinical trials demonstrating that hormone replacement therapy has negative cardiovascular consequences

(as reviewed in our previous article Deroo and Korach 2006). Nevertheless, understanding the mechanistic role of ER in cardiovascular disease is important. Selectively, knocking out *ER α* reduces estrogen's protection by increasing atherosclerotic plaques and serum cholesterol levels in ApoE mice (reviewed in Mendelsohn 2000; Rossouw et al. 2007). Loss of *ER α* specifically in coronary endothelial cells abolishes the protective action of estrogen to limit infarct size and coronary endothelial function (Favre et al. 2010). The loss of endothelial *ER α* suggests a critical role for *ER α* in the estrogen-induced prevention of endothelial dysfunction after ischemia/reperfusion. Three studies demonstrate both ERs contribute to the pro-angiogenesis effects of estrogen replacement therapy and can promote the mobilization and homing of bone marrow stem cells into the myocardium to preserve cardiac function after myocardial infarction (Hamada et al. 2006; Chen et al. 2009; Bolego et al. 2010). The mode of estrogen's influences on vascular endothelial growth factor and its signaling machinery (VEGF receptors, Akt and eNOS) to affect the development of coronary microvasculature in the heart is via *ER α* , as wild type and *ER β* knockout mice do not have a marked decrease in coronary capillary density like the *ER α* knockout mice (Jesmin et al. 2010). In volume-overloaded hearts of ovariectomized rats, estrogen treatment improves the tissue inhibitor of metalloproteinases (TIMP-2)/MMP-2 and TIMP-1/MMP-9 protein balance, restores *ER α* (not *ER β*) expression, and prevents MMP-9 activation, perivascular collagen accumulation and development of heart failure (Voloshenyuk and Gardner 2010). In ovariectomized rats, estrogen replacement therapy increases *ER α* and *ER β* expression relative to controls (Chen et al. 2009). The *ER β* knockout mice have elevated blood pressure, and 8 β -VE2, an *ER β* selective ligand that does not promote uterine growth, lowers blood pressure in these mice superior to estradiol or the *ER α* selective agonist 16 α -LE2 (Jazbutyte et al. 2008). *ER β* 's involvement in myocardial infarction was demonstrated by treatment with DPN, an *ER β* selective ligand, which increased myocardial functional recovery (Vornehm et al. 2009). The aforementioned animal studies would support a protective role for the ERs and agonist treatment in cardiovascular disease. Based on experimental studies, estrogen's protection on neural ischemia and peripheral vascular disease is mediated through *ER α* while myocardial protection works through *ER β* . Due to the complexity of human disease, future studies will be needed in animal models to recapitulate the numerous aspects affecting cardiovascular disease.

Concluding remarks

The loss or overexpression of the ERs contributes to disease development and progression. The focus of research over the last 5 years has focused mostly on ERs and cancer, endometriosis, and fibroids. Less human research has been done with cardiovascular disease, stroke, and Alzheimer's disease due to the negative findings of the Women's Health Initiative (Rossouw et al. 2002). Nonetheless, in the clinical setting, endocrine therapy with ER agonists and antagonists is often used for treatment. ER antagonists are critical first-line treatments for hormone-positive cancers and hormonal control of the menstrual cycle often decreases the symptoms of endometriosis. Available ER antagonists often have off target effects; therefore, much work has been done and needs to be done to define tissue-specific selective estrogen receptor modulators (SERMs). More importantly, understanding the basic mechanisms of how SERM's work in relation to tissue selective actions and the responses of

estrogen and ER will be a benefit toward developing more effective therapeutics. Moreover, the further knowledge of the disease hormone receptor expression levels, localization, and post-translational modifications will allow for targeted therapies by SERMs. For instance, detailed hormone receptor status, interacting partners, and post-translational modification of breast cancer reveal survival outcomes and these cancer subtypes may someday be targeted specifically to increase disease survival. Increasing our understanding of the mechanisms of action of ER in normal and disease states will hopefully lead to further treatments and increased disease survival or treatment for symptoms.

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Abbreviations

ER	Estrogen receptor
PR	Progesterone receptor
AR	Androgen receptor
DPN	Diarylpropionitrile
MAPK	Mitogen-activated protein kinase
HER2	Human epidermal growth factor receptor 2
UTR	Untranslated region
SNP	Single-nucleotide polymorphism
miRNA	MicroRNA
FOX	Forkhead binding protein

References

1. Al-Ghnam R, Peters J, et al. Methylation of estrogen receptor alpha and mutL homolog 1 in normal colonic mucosa: association with folate and vitamin B-12 status in subjects with and without colorectal neoplasia. *Am J Clin Nutr.* 2007; 86(4):1064–1072. [PubMed: 17921385]
2. Allgeier SH, Vezina CM, et al. Estrogen signaling is not required for prostatic bud patterning or for its disruption by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol Appl Pharmacol.* 2009; 239(1):80–86. [PubMed: 19523480]
3. Al-Nakhle H, Burns PA, et al. Estrogen receptor {beta}1 expression is regulated by miR-92 in breast cancer. *Cancer Res.* 2010; 70(11):4778–4784. [PubMed: 20484043]
4. Anagnostis A, Papadopoulos AI. Effects of a diet rich in sesame (*Sesamum indicum*) pericarp on the expression of oestrogen receptor alpha and oestrogen receptor beta in rat prostate and uterus. *Br J Nutr.* 2009; 102(5):703–708. [PubMed: 19309532]
5. Asada H, Yamagata Y, et al. Potential link between estrogen receptor-alpha gene hypomethylation and uterine fibroid formation. *Mol Hum Reprod.* 2008; 14(9):539–545. [PubMed: 18701604]
6. Bakas P, Liapis A, et al. Estrogen receptor alpha and beta in uterine fibroids: a basis for altered estrogen responsiveness. *Fertil Steril.* 2008; 90(5):1878–1885. [PubMed: 18166184]

7. Barone I, Iacopetta D, et al. Phosphorylation of the mutant K303R estrogen receptor alpha at serine 305 affects aromatase inhibitor sensitivity. *Oncogene*. 2010a; 29(16):2404–2414. [PubMed: 20101208]
8. Barone M, Scavo MP, et al. ERbeta expression in normal, adenomatous and carcinomatous tissues of patients with familial adenomatous polyposis. *Scand J Gastroenterol*. 2010b; 45(11):1320–1328. [PubMed: 20446826]
9. Bernardo GM, Lozada KL, et al. FOXA1 is an essential determinant of ERalpha expression and mammary ductal morphogenesis. *Development*. 2010; 137(12):2045–2054. [PubMed: 20501593]
10. Bhat-Nakshatri P, Wang G, et al. Estradiol-regulated microRNAs control estradiol response in breast cancer cells. *Nucleic Acids Res*. 2009; 37(14):4850–4861. [PubMed: 19528081]
11. Bianco B, Christofolini DM, et al. +1730 G/A polymorphism of the estrogen receptor beta gene (ERbeta) may be an important genetic factor predisposing to endometriosis. *Acta Obstet Gynecol Scand*. 2009; 88(12):1397–1401. [PubMed: 19878085]
12. Bischoff F, Simpson JL. Genetic basis of endometriosis. *Ann N Y Acad Sci*. 2004; 1034:284–299. [PubMed: 15731320]
13. Bolego C, Rossoni G, et al. Selective estrogen receptor-alpha agonist provides widespread heart and vascular protection with enhanced endothelial progenitor cell mobilization in the absence of uterotrophic action. *FASEB J*. 2010; 24(7):2262–2272. [PubMed: 20203089]
14. Borgquist S, Holm C, et al. Oestrogen receptors alpha and beta show different associations to clinicopathological parameters and their co-expression might predict a better response to endocrine treatment in breast cancer. *J Clin Pathol*. 2008; 61(2):197–203. [PubMed: 18223096]
15. Brandenberger AW, Tee MK, et al. Estrogen receptor alpha (ER-alpha) and beta (ER-beta) mRNAs in normal ovary, ovarian serous cystadenocarcinoma and ovarian cancer cell lines: down-regulation of ER-beta in neoplastic tissues. *J Clin Endocrinol Metab*. 1998; 83(3):1025–1028. [PubMed: 9506768]
16. Brodowska A, Laszczynska M, et al. The localization of estrogen receptor alpha and its function in the ovaries of postmenopausal women. *Folia Histochem Cytobiol*. 2007; 45(4):325–330. [PubMed: 18165170]
17. Bukulmez O, Hardy DB, et al. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. *Endocrinology*. 2008; 149(3):1190–1204. [PubMed: 18048499]
18. Bulun SE, Imir G, et al. Aromatase in endometriosis and uterine leiomyomata. *J Steroid Biochem Mol Biol*. 2005; 95(1–5):57–62. [PubMed: 16024248]
19. Burges A, Bruning A, et al. Prognostic significance of estrogen receptor alpha and beta expression in human serous carcinomas of the ovary. *Arch Gynecol Obstet*. 2010; 281(3):511–517. [PubMed: 19639330]
20. Burns KA, Li Y, et al. Selective mutations in estrogen receptor alpha D-domain alters nuclear translocation and non-estrogen response element gene regulatory mechanisms. *J Biol Chem*. 2011; 286(14):12640–12649. [PubMed: 21285458]
21. Capellino S, Montagna P, et al. Role of estrogens in inflammatory response: expression of estrogen receptors in peritoneal fluid macrophages from endometriosis. *Ann N Y Acad Sci*. 2006; 1069:263–267. [PubMed: 16855153]
22. Castellano L, Giamas G, et al. The estrogen receptor-alpha-induced microRNA signature regulates itself and its transcriptional response. *Proc Natl Acad Sci USA*. 2009; 106(37):15732–15737. [PubMed: 19706389]
23. Castiglione F, Taddei A, et al. Expression of estrogen receptor beta in colon cancer progression. *Diagn Mol Pathol*. 2008; 17(4):231–236. [PubMed: 19034156]
24. Cavallini A, Resta L, et al. Involvement of estrogen receptor-related receptors in human ovarian endometriosis. *Fertil Steril*. 2011; 96(1):102–106. [PubMed: 21561608]
25. Chae YK, Huang HY, et al. Genetic polymorphisms of estrogen receptors alpha and beta and the risk of developing prostate cancer. *PLoS ONE*. 2009; 4(8):e6523. [PubMed: 19654868]
26. Chakravarty D, Srinivasan R, et al. Estrogen receptor beta (ERbeta) in endometrial simple hyperplasia and endometrioid carcinoma. *Appl Immunohistochem Mol Morphol*. 2008; 16(6):535–542. [PubMed: 18931615]

27. Chan KK, Wei N, et al. Estrogen receptor subtypes in ovarian cancer: a clinical correlation. *Obstet Gynecol.* 2008; 111(1):144–151. [PubMed: 18165403]
28. Charn TH, Liu ET, et al. Genome-wide dynamics of chromatin binding of estrogen receptors alpha and beta: mutual restriction and competitive site selection. *Mol Endocrinol.* 2010; 24(1):47–59. [PubMed: 19897598]
29. Chen JQ, Russo PA, et al. ERbeta shifts from mitochondria to nucleus during estrogen-induced neoplastic transformation of human breast epithelial cells and is involved in estrogen-induced synthesis of mitochondrial respiratory chain proteins. *Biochim Biophys Acta.* 2007a; 1773(12): 1732–1746. [PubMed: 17604135]
30. Chen YC, Kraft P, et al. Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiol Biomarkers Prev.* 2007b; 16(10):1973–1981. [PubMed: 17932344]
31. Chen Y, Jin X, et al. Estrogen-replacement therapy promotes angiogenesis after acute myocardial infarction by enhancing SDF-1 and estrogen receptor expression. *Microvasc Res.* 2009; 77(2):71–77. [PubMed: 19010336]
32. Chlebowski RT, Kuller LH, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med.* 2009; 360(6):573–587. [PubMed: 19196674]
33. Choi JH, Lee KT, et al. Estrogen receptor alpha pathway is involved in leptin-induced ovarian cancer cell growth. *Carcinogenesis.* 2011; 32(4):589–596. [PubMed: 21173433]
34. Chong K, Subramanian A, et al. Measuring IGF-1, ER-alpha and EGFR expression can predict tamoxifen-resistance in ER-positive breast cancer. *Anticancer Res.* 2011; 31(1):23–32. [PubMed: 21273576]
35. Cleveland AG, Oikarinen SI, et al. Disruption of estrogen receptor signaling enhances intestinal neoplasia in Apc(Min/+) mice. *Carcinogenesis.* 2009; 30(9):1581–1590. [PubMed: 19520794]
36. Collins F, MacPherson S, et al. Expression of oestrogen receptors, ERalpha, ERbeta, and ERbeta variants, in endometrial cancers and evidence that prostaglandin F may play a role in regulating expression of ERalpha. *BMC Cancer.* 2009; 9:330. [PubMed: 19758455]
37. Cox DG, Bretsky P, et al. Haplotypes of the estrogen receptor beta gene and breast cancer risk. *Int J Cancer.* 2008; 122(2):387–392. [PubMed: 17935138]
38. Cummings M, Iremonger J, et al. Gene expression of ERbeta isoforms in laser microdissected human breast cancers: implications for gene expression analyses. *Cell Oncol.* 2009; 31(6):467–473. [PubMed: 19940362]
39. Dannenmann C, Shabani N, et al. The metastasis-associated gene MTA1 is upregulated in advanced ovarian cancer, represses ERbeta, and enhances expression of oncogenic cytokine GRO. *Cancer Biol Ther.* 2008; 7(9):1460–1467. [PubMed: 18719363]
40. De Stefano I, Zannoni GF, et al. Cytoplasmic expression of estrogen receptor beta (ERbeta) predicts poor clinical outcome in advanced serous ovarian cancer. *Gynecol Oncol.* 2011; 122(3): 573–579. [PubMed: 21665249]
41. Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest.* 2006; 116(3):561–570. [PubMed: 16511588]
42. Di Leo A, Barone M, et al. ER-beta expression in large bowel adenomas: implications in colon carcinogenesis. *Dig Liver Dis.* 2008; 40(4):260–266. [PubMed: 18093886]
43. Di Leva G, Gasparini P, et al. MicroRNA cluster 221-222 and estrogen receptor alpha interactions in breast cancer. *J Natl Cancer Inst.* 2010; 102(10):706–721. [PubMed: 20388878]
44. Doherty JA, Rossing MA, et al. ESR1/SYNE1 polymorphism and invasive epithelial ovarian cancer risk: an Ovarian Cancer Association Consortium study. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(1):245–250. [PubMed: 20056644]
45. Dunning AM, Healey CS, et al. Association of ESR1 gene tagging SNPs with breast cancer risk. *Hum Mol Genet.* 2009; 18(6):1131–1139. [PubMed: 19126777]
46. Einarsdottir K, Darabi H, et al. Common genetic variability in ESR1 and EGF in relation to endometrial cancer risk and survival. *Br J Cancer.* 2009; 100(8):1358–1364. [PubMed: 19319135]
47. Ellem SJ, Risbridger GP. Treating prostate cancer: a rationale for targeting local oestrogens. *Nat Rev Cancer.* 2007; 7(8):621–627. [PubMed: 17611544]

48. Endo Y, Toyama T, et al. High estrogen receptor expression and low Ki67 expression are associated with improved time to progression during first-line endocrine therapy with aromatase inhibitors in breast cancer. *Int J Clin Oncol*. 2011; 16(5):512–518. [PubMed: 21431343]
49. Fang YJ, Lu ZH, et al. Prognostic impact of ERbeta and MMP7 expression on overall survival in colon cancer. *Tumour Biol*. 2010; 31(6):651–658. [PubMed: 20680712]
50. Farquhar CM, Marjoribanks J, et al. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2005; (3):CD004143. [PubMed: 16034922]
51. Favre J, Gao J, et al. Endothelial estrogen receptor {alpha} plays an essential role in the coronary and myocardial protective effects of estradiol in ischemia/reperfusion. *Arterioscler Thromb Vasc Biol*. 2010; 30(12):2562–2567. [PubMed: 20847304]
52. Fullwood MJ, Liu MH, et al. An oestrogen-receptor-alpha-bound human chromatin interactome. *Nature*. 2009; 462(7269):58–64. [PubMed: 19890323]
53. Galle PC. Clinical presentation and diagnosis of endometriosis. *Obstet Gynecol Clin North Am*. 1989; 16(1):29–42. [PubMed: 2664621]
54. Generali D, Buffa FM, et al. Phosphorylated ERalpha, HIF-1alpha, and MAPK signaling as predictors of primary endocrine treatment response and resistance in patients with breast cancer. *J Clin Oncol*. 2009; 27(2):227–234. [PubMed: 19064988]
55. Giroux V, Bernatchez G, et al. Chemopreventive effect of ERbeta-Selective agonist on intestinal tumorigenesis in Apc (Min/+) mice. *Mol Carcinog*. 2011; 50(5):359–369. [PubMed: 21480389]
56. Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004; 364(9447):1789–1799. [PubMed: 15541453]
57. Govindan S, Shaik NA, et al. Estrogen receptor-alpha gene (T/C) Pvu II polymorphism in endometriosis and uterine fibroids. *Dis Markers*. 2009; 26(4):149–154. [PubMed: 19729795]
58. Grivas PD, Tzelepi V, et al. Expression of ERalpha, ERbeta and co-regulator PELP1/MNAR in colorectal cancer: prognostic significance and clinicopathologic correlations. *Cell Oncol*. 2009; 31(3):235–247. [PubMed: 19478391]
59. Grober OM, Mutarelli M, et al. Global analysis of estrogen receptor beta binding to breast cancer cell genome reveals an extensive interplay with estrogen receptor alpha for target gene regulation. *BMC Genomics*. 2011; 12:36. [PubMed: 21235772]
60. Gruvberger-Saal SK, Bendahl PO, et al. Estrogen receptor beta expression is associated with tamoxifen response in ERalpha-negative breast carcinoma. *Clin Cancer Res*. 2007; 13(7):1987–1994. [PubMed: 17404078]
61. Halon A, Nowak-Markwitz E, et al. Loss of estrogen receptor beta expression correlates with shorter overall survival and lack of clinical response to chemotherapy in ovarian cancer patients. *Anticancer Res*. 2011; 31(2):711–718. [PubMed: 21378361]
62. Hamada H, Kim MK, et al. Estrogen receptors alpha and beta mediate contribution of bone marrow-derived endothelial progenitor cells to functional recovery after myocardial infarction. *Circulation*. 2006; 114(21):2261–2270. [PubMed: 17088460]
63. Hamilton-Burke W, Coleman L, et al. Phosphorylation of estrogen receptor beta at serine 105 is associated with good prognosis in breast cancer. *Am J Pathol*. 2010; 177(3):1079–1086. [PubMed: 20696772]
64. Hecht JL, Kotsopoulos J, et al. Relationship between epidemiologic risk factors and hormone receptor expression in ovarian cancer: results from the nurses' health study. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(5):1624–1630. [PubMed: 19383883]
65. Hermon TL, Moore AB, et al. Estrogen receptor alpha (ERalpha) phospho-serine-118 is highly expressed in human uterine leiomyomas compared to matched myometrium. *Virchows Arch*. 2008; 453(6):557–569. [PubMed: 18853184]
66. Hewitt SC, O'Brien JE, et al. Selective disruption of ER{alpha} DNA-binding activity alters uterine responsiveness to estradiol. *Mol Endocrinol*. 2009; 23(12):2111–2116. [PubMed: 19812388]
67. Hewitt SC, Li L, et al. Research resource: whole-genome estrogen receptor alpha binding in mouse uterine tissue revealed by ChIP-Seq. *Mol Endocrinol*. 2012; 26(5):887–898. [PubMed: 22446102]
68. Hiraoka S, Kato J, et al. Methylation status of normal background mucosa is correlated with occurrence and development of neoplasia in the distal colon. *Hum Pathol*. 2010; 41(1):38–47. [PubMed: 19733896]

69. Hodges-Gallagher L, Valentine CD, et al. Estrogen receptor beta increases the efficacy of antiestrogens by effects on apoptosis and cell cycling in breast cancer cells. *Breast Cancer Res Treat.* 2008; 109(2):241–250. [PubMed: 17638070]
70. Holm C, Kok M, et al. Phosphorylation of the oestrogen receptor alpha at serine 305 and prediction of tamoxifen resistance in breast cancer. *J Pathol.* 2009; 217(3):372–379. [PubMed: 18991335]
71. Honma N, Horii R, et al. Clinical importance of estrogen receptor-beta evaluation in breast cancer patients treated with adjuvant tamoxifen therapy. *J Clin Oncol.* 2008; 26(22):3727–3734. [PubMed: 18669459]
72. Hsieh YY, Wang YK, et al. Estrogen receptor alpha-351 XbaI*G and -397 PvuII*C-related genotypes and alleles are associated with higher susceptibilities of endometriosis and leiomyoma. *Mol Hum Reprod.* 2007; 13(2):117–122. [PubMed: 17121748]
73. Huang GS, Arend RC, et al. Tissue microarray analysis of hormonal signaling pathways in uterine carcinosarcoma. *Am J Obstet Gynecol.* 2009; 200(4):457.e451–457.e455. [PubMed: 19200930]
74. Huang GS, Gunter MJ, et al. Co-expression of GPR30 and ERbeta and their association with disease progression in uterine carcinosarcoma. *Am J Obstet Gynecol.* 2010; 203(3):242.e241–242.e245. [PubMed: 20605134]
75. Hurtado A, Holmes KA, et al. FOXA1 is a key determinant of estrogen receptor function and endocrine response. *Nat Genet.* 2011; 43(1):27–33. [PubMed: 21151129]
76. Ishikawa H, Ishi K, et al. Progesterone is essential for maintenance and growth of uterine leiomyoma. *Endocrinology.* 2010; 151(6):2433–2442. [PubMed: 20375184]
77. Issa RM, Lebeau A, et al. Estrogen receptor gene amplification occurs rarely in ovarian cancer. *Mod Pathol.* 2009; 22(2):191–196. [PubMed: 18690166]
78. Jackson KS, Brudney A, et al. The altered distribution of the steroid hormone receptors and the chaperone immunophilin FKBP52 in a baboon model of endometriosis is associated with progesterone resistance during the window of uterine receptivity. *Reprod Sci.* 2007; 14(2):137–150. [PubMed: 17636225]
79. Jazbutyte V, Arias-Loza PA, et al. Ligand-dependent activation of ER{beta} lowers blood pressure and attenuates cardiac hypertrophy in ovariectomized spontaneously hypertensive rats. *Cardiovasc Res.* 2008; 77(4):774–781. [PubMed: 18056768]
80. Jesmin S, Mowa CN, et al. VEGF signaling is disrupted in the hearts of mice lacking estrogen receptor alpha. *Eur J Pharmacol.* 2010; 641(2–3):168–178. [PubMed: 20639141]
81. Jiang H, Teng R, et al. Transcriptional analysis of estrogen receptor alpha variant mRNAs in colorectal cancers and their matched normal colorectal tissues. *J Steroid Biochem Mol Biol.* 2008; 112(1–3):20–24. [PubMed: 18703141]
82. Jongen V, Briet J, et al. Expression of estrogen receptor-alpha and -beta and progesterone receptor-A and -B in a large cohort of patients with endometrioid endometrial cancer. *Gynecol Oncol.* 2009; 112(3):537–542. [PubMed: 19108875]
83. Juhasz-Boss I, Fischer C, et al. Endometrial expression of estrogen receptor beta and its splice variants in patients with and without endometriosis. *Arch Gynecol Obstet.* 2011; 284(4):885–891. [PubMed: 21110202]
84. Karita M, Yamashita Y, et al. Does advanced-stage endometriosis affect the gene expression of estrogen and progesterone receptors in granulosa cells? *Fertil Steril.* 2011; 95(3):889–894. [PubMed: 21269613]
85. Kim C, Tang G, et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. *J Clin Oncol.* 2011; 29(31):4160–4167. [PubMed: 21947828]
86. Kjaergaard AD, Ellervik C, et al. Estrogen receptor alpha polymorphism and risk of cardiovascular disease, cancer, and hip fracture: cross-sectional, cohort, and case-control studies and a meta-analysis. *Circulation.* 2007; 115(7):861–871. [PubMed: 17309937]
87. Kok M, Zwart W, et al. PKA-induced phosphorylation of ERalpha at serine 305 and high PAK1 levels is associated with sensitivity to tamoxifen in ER-positive breast cancer. *Breast Cancer Res Treat.* 2011; 125(1):1–12. [PubMed: 20213082]

88. Kulak J Jr, Fischer C, et al. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. *Endocrinology*. 2011; 152(8):3226–3232. [PubMed: 21586552]
89. Lagiou P, Georgila C, et al. Estrogen alpha and progesterone receptor expression in the normal mammary epithelium in relation to breast cancer risk. *Int J Cancer*. 2009; 124(2):440–442. [PubMed: 18798271]
90. Lamp M, Peters M, et al. Polymorphisms in ESR1, ESR2 and HSD17B1 genes are associated with fertility status in endometriosis. *Gynecol Endocrinol*. 2011; 27(6):425–433. [PubMed: 20586553]
91. Leav I, Lau KM, et al. Comparative studies of the estrogen receptors beta and alpha and the androgen receptor in normal human prostate glands, dysplasia, and in primary and metastatic carcinoma. *Am J Pathol*. 2001; 159(1):79–92. [PubMed: 11438457]
92. Lebeau A, Grob T, et al. Oestrogen receptor gene (ESR1) amplification is frequent in endometrial carcinoma and its precursor lesions. *J Pathol*. 2008; 216(2):151–157. [PubMed: 18720455]
93. Lee GH, Kim SH, et al. Estrogen receptor beta gene +1730 G/A polymorphism in women with endometriosis. *Fertil Steril*. 2007; 88(4):785–788. [PubMed: 17336962]
94. Leibetseder V, Humpeler S, et al. Time dependence of estrogen receptor expression in human hearts. *Biomed Pharmacother*. 2010; 64(3):154–159. [PubMed: 19944560]
95. Leigh Pearce C, Near AM, et al. Comprehensive evaluation of ESR2 variation and ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2008; 17(2):393–396. [PubMed: 18268123]
96. Li N, Dong J, et al. Potentially functional polymorphisms in ESR1 and breast cancer risk: a meta-analysis. *Breast Cancer Res Treat*. 2010a; 121(1):177–184. [PubMed: 19760036]
97. Li S, Han B, et al. Immunocytochemical localization of sex steroid hormone receptors in normal human mammary gland. *J Histochem Cytochem*. 2010b; 58(6):509–515. [PubMed: 20026671]
98. Lin Fde M, Pincerato KM, et al. Coordinated expression of oestrogen and androgen receptors in HER2-positive breast carcinomas: impact on proliferative activity. *J Clin Pathol*. 2012; 65(1):64–68. [PubMed: 22039288]
99. Lin CY, Strom A, et al. Inhibitory effects of estrogen receptor beta on specific hormone-responsive gene expression and association with disease outcome in primary breast cancer. *Breast Cancer Res*. 2007; 9(2):R25. [PubMed: 17428314]
100. Lin SL, Yan LY, et al. ER-alpha36, a variant of ER-alpha, promotes tamoxifen agonist action in endometrial cancer cells via the MAPK/ERK and PI3K/Akt pathways. *PLoS ONE*. 2010; 5(2):e9013. [PubMed: 20126312]
101. Lurie G, Wilkens LR, et al. Genetic polymorphisms in the estrogen receptor beta (ESR2) gene and the risk of epithelial ovarian carcinoma. *Cancer Causes Control*. 2009; 20(1):47–55. [PubMed: 18704709]
102. Lurie G, Wilkens LR, et al. Estrogen receptor beta rs1271572 polymorphism and invasive ovarian carcinoma risk: pooled analysis within the Ovarian Cancer Association Consortium. *PLoS ONE*. 2011; 6(6):e20703. [PubMed: 21673961]
103. Madak-Erdogan Z, Lupien M, et al. Genomic collaboration of estrogen receptor alpha and extracellular signal-regulated kinase 2 in regulating gene and proliferation programs. *Mol Cell Biol*. 2011; 31(1):226–236. [PubMed: 20956553]
104. Maehle BO, Collett K, et al. Estrogen receptor beta—an independent prognostic marker in estrogen receptor alpha and progesterone receptor-positive breast cancer? *APMIS*. 2009; 117(9):644–650. [PubMed: 19703124]
105. Magnani L, Ballantyne EB, et al. PBX1 genomic pioneer function drives ERalpha signaling underlying progression in breast cancer. *PLoS Genet*. 2011; 7(11):e1002368. [PubMed: 22125492]
106. Mandusic V, Nikolic-Vukosavljevic D, et al. Expression of estrogen receptor beta wt isoform (ERbeta1) and ERbetaDelta5 splice variant mRNAs in sporadic breast cancer. *J Cancer Res Clin Oncol*. 2007; 133(8):571–579. [PubMed: 17457609]
107. Mangelsdorf DJ, Thummel C, et al. The nuclear receptor superfamily: the second decade. *Cell*. 1995; 83(6):835–839. [PubMed: 8521507]
108. Manson JE, Allison MA, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007; 356(25):2591–2602. [PubMed: 17582069]

109. Marotti JD, Collins LC, et al. Estrogen receptor-beta expression in invasive breast cancer in relation to molecular phenotype: results from the nurses' health study. *Mod Pathol.* 2010; 23(2): 197–204. [PubMed: 19898422]
110. Matthews J, Wihlen B, et al. Estrogen receptor (ER) beta modulates ERalpha-mediated transcriptional activation by altering the recruitment of c-Fos and c-Jun to estrogen-responsive promoters. *Mol Endocrinol.* 2006; 20(3):534–543. [PubMed: 16293641]
111. McPherson SJ, Hussain S, et al. Estrogen receptor-beta activated apoptosis in benign hyperplasia and cancer of the prostate is androgen independent and TNFalpha mediated. *Proc Natl Acad Sci USA.* 2010; 107(7):3123–3128. [PubMed: 20133657]
112. Mendelsohn ME. Mechanisms of estrogen action in the cardiovascular system. *J Steroid Biochem Mol Biol.* 2000; 74(5):337–343. [PubMed: 11162942]
113. Millour J, Constantinidou D, et al. FOXM1 is a transcriptional target of ERalpha and has a critical role in breast cancer endocrine sensitivity and resistance. *Oncogene.* 2010; 29(20):2983–2995. [PubMed: 20208560]
114. Mintz PJ, Habib NA, et al. The phosphorylated membrane estrogen receptor and cytoplasmic signaling and apoptosis proteins in human breast cancer. *Cancer.* 2008; 113(6):1489–1495. [PubMed: 18615623]
115. Montagna P, Capellino S, et al. Peritoneal fluid macrophages in endometriosis: correlation between the expression of estrogen receptors and inflammation. *Fertil Steril.* 2008; 90(1):156–164. [PubMed: 17548071]
116. Motomura K, Ishitobi M, et al. Expression of estrogen receptor beta and phosphorylation of estrogen receptor alpha serine 167 correlate with progression-free survival in patients with metastatic breast cancer treated with aromatase inhibitors. *Oncology.* 2010; 79(1–2):55–61. [PubMed: 21071990]
117. Murphy LC, Seekallu SV, et al. Clinical significance of estrogen receptor phosphorylation. *Endocr Relat Cancer.* 2011; 18(1):R1–R14. [PubMed: 21149515]
118. Nassa G, Tarallo R, et al. A large set of estrogen receptor beta-interacting proteins identified by tandem affinity purification in hormone-responsive human breast cancer cell nuclei. *Proteomics.* 2011; 11(1):159–165. [PubMed: 21182203]
119. Novelli F, Milella M, et al. A divergent role for estrogen receptor-beta in node-positive and node-negative breast cancer classified according to molecular subtypes: an observational prospective study. *Breast Cancer Res.* 2008; 10(5):R74. [PubMed: 18771580]
120. Nussler NC, Reinbacher K, et al. Sex-specific differences in the expression levels of estrogen receptor subtypes in colorectal cancer. *Gend Med.* 2008; 5(3):209–217. [PubMed: 18727987]
121. O'Day E, Lal A. MicroRNAs and their target gene networks in breast cancer. *Breast Cancer Res.* 2010; 12(2):201. [PubMed: 20346098]
122. Pan X, Zhou T, et al. Elevated expression of CUEDC2 protein confers endocrine resistance in breast cancer. *Nat Med.* 2011; 17(6):708–714. [PubMed: 21572428]
123. Pandey DP, Picard D. miR-22 inhibits estrogen signaling by directly targeting the estrogen receptor alpha mRNA. *Mol Cell Biol.* 2009; 29(13):3783–3790. [PubMed: 19414598]
124. Papaxoinis K, Patsouris E, et al. Insulinlike growth factor I receptor and estrogen receptor beta expressions are inversely correlated in colorectal neoplasms and affected by the insulin resistance syndrome. *Hum Pathol.* 2007; 38(7):1037–1046. [PubMed: 17442373]
125. Papaxoinis K, Triantafyllou K, et al. Subsite-specific differences of estrogen receptor beta expression in the normal colonic epithelium: implications for carcinogenesis and colorectal cancer epidemiology. *Eur J Gastroenterol Hepatol.* 2010; 22(5):614–619. [PubMed: 20173645]
126. Park SH, Cheung LW, et al. Estrogen regulates snail and slug in the down-regulation of E-cadherin and induces metastatic potential of ovarian cancer cells through estrogen receptor alpha. *Mol Endocrinol.* 2008; 22(9):2085–2098. [PubMed: 18550773]
127. Peddada SD, Laughlin SK, et al. Growth of uterine leiomyomata among premenopausal black and white women. *Proc Natl Acad Sci USA.* 2008; 105(50):19887–19892. [PubMed: 19047643]
128. Qui WS, Yue L, et al. Co-expression of ER-beta and HER2 associated with poorer prognosis in primary breast cancer. *Clin Invest Med.* 2009; 32(3):E250–E260. [PubMed: 19480740]

129. Rao X, Di Leva G, et al. MicroRNA-221/222 confers breast cancer fulvestrant resistance by regulating multiple signaling pathways. *Oncogene*. 2011; 30(9):1082–1097. [PubMed: 21057537]
130. Rawson JM. Prevalence of endometriosis in asymptomatic women. *J Reprod Med*. 1991; 36(7): 513–515. [PubMed: 1834839]
131. Risbridger GP, Davis ID, et al. Breast and prostate cancer: more similar than different. *Nat Rev Cancer*. 2010; 10(3):205–212. [PubMed: 20147902]
132. Rosa FE, Caldeira JR, et al. Evaluation of estrogen receptor alpha and beta and progesterone receptor expression and correlation with clinicopathologic factors and proliferative marker Ki-67 in breast cancers. *Hum Pathol*. 2008; 39(5):720–730. [PubMed: 18234277]
133. Ross-Innes CS, Stark R, et al. Differential oestrogen receptor binding is associated with clinical outcome in breast cancer. *Nature*. 2012; 481(7381):389–393. [PubMed: 22217937]
134. Rossouw JE, Anderson GL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA*. 2002; 288(3):321–333. [PubMed: 12117397]
135. Rossouw JE, Prentice RL, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007; 297(13):1465–1477. [PubMed: 17405972]
136. Saleiro D, Murillo G, et al. Enhanced induction of mucin-depleted foci in estrogen receptor {beta} knockout mice. *Cancer Prev Res (Phila)*. 2010; 3(9):1198–1204. [PubMed: 20716634]
137. Salonen J, Butzow R, et al. Oestrogen receptors and small nuclear ring finger protein 4 (RNF4) in malignant ovarian germ cell tumours. *Mol Cell Endocrinol*. 2009; 307(1–2):205–210. [PubMed: 19524139]
138. Sato H, Nogueira-de-Souza NC, et al. Intron 1 and exon 1 alpha estrogen receptor gene polymorphisms in women with endometriosis. *Fertil Steril*. 2008; 90(6):2086–2090. [PubMed: 18178192]
139. Shaaban AM, Green AR, et al. Nuclear and cytoplasmic expression of ERbeta1, ERbeta2, and ERbeta5 identifies distinct prognostic outcome for breast cancer patients. *Clin Cancer Res*. 2008; 14(16):5228–5235. [PubMed: 18698041]
140. Shabani N, Kuhn C, et al. Prognostic significance of oestrogen receptor alpha (ERalpha) and beta (ERbeta), progesterone receptor A (PR-A) and B (PR-B) in endometrial carcinomas. *Eur J Cancer*. 2007; 43(16):2434–2444. [PubMed: 17911007]
141. Sharpe-Timms KL. Endometrial anomalies in women with endometriosis. *Ann N Y Acad Sci*. 2001; 943:131–147. [PubMed: 11594534]
142. Shi L, Dong B, et al. Expression of ER-{alpha}36, a novel variant of estrogen receptor {alpha}, and resistance to tamoxifen treatment in breast cancer. *J Clin Oncol*. 2009; 27(21):3423–3429. [PubMed: 19487384]
143. Siddig A, Mohamed AO, et al. Estrogen receptor alpha gene polymorphism and breast cancer. *Ann N Y Acad Sci*. 2008; 1138:95–107. [PubMed: 18837889]
144. Silva RC, Costa IR, et al. RsaI polymorphism of the ERbeta gene in women with endometriosis. *Genet Mol Res*. 2011; 10(1):465–470. [PubMed: 21476192]
145. Singh M, Zaino RJ, et al. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a gynecologic oncology group study. *Gynecol Oncol*. 2007; 106(2):325–333. [PubMed: 17532033]
146. Skliris GP, Nugent ZJ, et al. A phosphorylation code for oestrogen receptor-alpha predicts clinical outcome to endocrine therapy in breast cancer. *Endocr Relat Cancer*. 2010; 17(3):589–597. [PubMed: 20418363]
147. Smith L, Coleman LJ, et al. Expression of oestrogen receptor beta isoforms is regulated by transcriptional and post-transcriptional mechanisms. *Biochem J*. 2010; 429(2):283–290. [PubMed: 20462399]
148. Smuc T, Hevir N, et al. Disturbed estrogen and progesterone action in ovarian endometriosis. *Mol Cell Endocrinol*. 2009; 301(1–2):59–64. [PubMed: 18762229]

149. Strissel PL, Swiatek J, et al. Transcriptional analysis of steroid hormone receptors in smooth muscle uterine leiomyoma tumors of postmenopausal patients. *J Steroid Biochem Mol Biol.* 2007; 107(1–2):42–47. [PubMed: 17646097]
150. Sugiura H, Toyama T, et al. Expression of estrogen receptor beta wild-type and its variant ERbetacx/beta2 is correlated with better prognosis in breast cancer. *Jpn J Clin Oncol.* 2007; 37(11):820–828. [PubMed: 17932113]
151. Suzuki F, Akahira J, et al. Loss of estrogen receptor beta isoform expression and its correlation with aberrant DNA methylation of the 5'-untranslated region in human epithelial ovarian carcinoma. *Cancer Sci.* 2008; 99(12):2365–2372. [PubMed: 19032364]
152. Taylor HS, Bagot C, et al. HOX gene expression is altered in the endometrium of women with endometriosis. *Hum Reprod.* 1999; 14(5):1328–1331. [PubMed: 10325287]
153. Treeck O, Elemenler E, et al. Polymorphisms in the promoter region of ESR2 gene and breast cancer susceptibility. *J Steroid Biochem Mol Biol.* 2009; 114(3–5):207–211. [PubMed: 19429453]
154. Treeck O, Lattrich C, et al. Estrogen receptor beta exerts growth-inhibitory effects on human mammary epithelial cells. *Breast Cancer Res Treat.* 2010; 120(3):557–565. [PubMed: 19434490]
155. Trukhacheva E, Lin Z, et al. Estrogen receptor (ER) beta regulates ERalpha expression in stromal cells derived from ovarian endometriosis. *J Clin Endocrinol Metab.* 2009; 94(2):615–622. [PubMed: 19001520]
156. Tsezou A, Tzetis M, et al. Association of repeat polymorphisms in the estrogen receptors alpha, beta (ESR1, ESR2) and androgen receptor (AR) genes with the occurrence of breast cancer. *Breast.* 2008; 17(2):159–166. [PubMed: 17904846]
157. Valladares F, Frias I, et al. Characterization of estrogen receptors alpha and beta in uterine leiomyoma cells. *Fertil Steril.* 2006; 86(6):1736–1743. [PubMed: 17011556]
158. van de Water W, Markopoulos C, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA.* 2012; 307(6):590–597. [PubMed: 22318280]
159. Villanova FE, Andrade PM, et al. Estrogen receptor alpha polymorphism and susceptibility to uterine leiomyoma. *Steroids.* 2006; 71(11–12):960–965. [PubMed: 16935316]
160. Voloshenyuk TG, Gardner JD. Estrogen improves TIMP-MMP balance and collagen distribution in volume-overloaded hearts of ovariectomized females. *Am J Physiol Regul Integr Comp Physiol.* 2010; 299(2):R683–R693. [PubMed: 20504902]
161. Vornehm ND, Wang M, et al. Acute postischemic treatment with estrogen receptor-alpha agonist or estrogen receptor-beta agonist improves myocardial recovery. *Surgery.* 2009; 146(2):145–154. [PubMed: 19628068]
162. Vouk K, Smuc T, et al. Novel estrogen-related genes and potential biomarkers of ovarian endometriosis identified by differential expression analysis. *J Steroid Biochem Mol Biol.* 2011; 125(3–5):231–242. [PubMed: 21397694]
163. Vranic S, Gatalica Z, et al. ER-alpha36, a novel isoform of ER-alpha66, is commonly over-expressed in apocrine and adenoid cystic carcinomas of the breast. *J Clin Pathol.* 2011; 64(1):54–57. [PubMed: 21045236]
164. Wang C, Mavrogianis PA, et al. Endometriosis is associated with progesterone resistance in the baboon (*Papio anubis*) oviduct: evidence based on the localization of oviductal glycoprotein 1 (OVGP1). *Biol Reprod.* 2009; 80(2):272–278. [PubMed: 18923157]
165. Wedren S, Lovmar L, et al. Estrogen receptor alpha gene polymorphism and endometrial cancer risk—a case-control study. *BMC Cancer.* 2008; 8:322. [PubMed: 18990228]
166. Weige CC, Allred KF, et al. Estradiol alters cell growth in nonmalignant colonocytes and reduces the formation of preneoplastic lesions in the colon. *Cancer Res.* 2009; 69(23):9118–9124. [PubMed: 19903848]
167. Weiss G, Goldsmith LT, et al. Inflammation in reproductive disorders. *Reprod Sci.* 2009; 16(2):216–229. [PubMed: 19208790]
168. Welboren WJ, Sweep FC, et al. Genomic actions of estrogen receptor alpha: what are the targets and how are they regulated? *Endocr Relat Cancer.* 2009a; 16(4):1073–1089. [PubMed: 19628648]

169. Welboren WJ, van Driel MA, et al. ChIP-Seq of ERalpha and RNA polymerase II defines genes differentially responding to ligands. *EMBO J*. 2009b; 28(10):1418–1428. [PubMed: 19339991]
170. Williams C, Edvardsson K, et al. A genome-wide study of the repressive effects of estrogen receptor beta on estrogen receptor alpha signaling in breast cancer cells. *Oncogene*. 2008; 27(7):1019–1032. [PubMed: 17700529]
171. Xue Q, Lin Z, et al. Promoter methylation regulates estrogen receptor 2 in human endometrium and endometriosis. *Biol Reprod*. 2007; 77(4):681–687. [PubMed: 17625110]
172. Yamashita H, Nishio M, et al. Low phosphorylation of estrogen receptor alpha (ERalpha) serine 118 and high phosphorylation of ERalpha serine 167 improve survival in ER-positive breast cancer. *Endocr Relat Cancer*. 2008; 15(3):755–763. [PubMed: 18550720]
173. Yan M, Rayoo M, et al. Nuclear and cytoplasmic expressions of ERbeta1 and ERbeta2 are predictive of response to therapy and alters prognosis in familial breast cancers. *Breast Cancer Res Treat*. 2011; 126(2):395–405. [PubMed: 20490651]
174. Yang J, Wang Y, et al. Reciprocal regulation of 17beta-estradiol, interleukin-6 and interleukin-8 during growth and progression of epithelial ovarian cancer. *Cytokine*. 2009; 46(3):382–391. [PubMed: 19401270]
175. Yang S, Thiel KW, et al. Endometrial cancer: reviving progesterone therapy in the molecular age. *Discov Med*. 2011a; 12(64):205–212. [PubMed: 21955848]
176. Yang S, Thiel KW, et al. Progesterone: the ultimate endometrial tumor suppressor. *Trends Endocrinol Metab*. 2011b; 22(4):145–152. [PubMed: 21353793]
177. Yap OW, Bhat G, et al. Epigenetic modifications of the Estrogen receptor beta gene in epithelial ovarian cancer cells. *Anticancer Res*. 2009; 29(1):139–144. [PubMed: 19331143]
178. Zahedi P, Yoganathan R, et al. Recent advances in drug delivery strategies for treatment of ovarian cancer. *Expert Opin Drug Deliv*. 2012; 9(5):567–583. [PubMed: 22452661]
179. Zhao JJ, Lin J, et al. MicroRNA-221/222 negatively regulates estrogen receptor alpha and is associated with tamoxifen resistance in breast cancer. *J Biol Chem*. 2008; 283(45):31079–31086. [PubMed: 18790736]
180. Zheng W, Long J, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nat Genet*. 2009; 41(3):324–328. [PubMed: 19219042]
181. Zhu J, Hua K, et al. Re-expression of estrogen receptor beta inhibits the proliferation and migration of ovarian clear cell adenocarcinoma cells. *Oncol Rep*. 2011a; 26(6):1497–1503. [PubMed: 21874257]
182. Zhu ZY, Mu YQ, et al. Association of CYP1B1 gene polymorphisms and the positive expression of estrogen alpha and estrogen beta with endometrial cancer risk. *Eur J Gynaecol Oncol*. 2011b; 32(2):188–191. [PubMed: 21614911]
183. Zulli K, Bianco B, et al. Polymorphism of the estrogen receptor beta gene is related to infertility and infertility-associated endometriosis. *Arq Bras Endocrinol Metabol*. 2010; 54(6):567–571. [PubMed: 20857063]